World Health Organization

Department of Immunization, Vaccines and Biologicals (IVB)

SAGE

October 2015

Strategic Advisory Group of Experts on Immunization
20-22 October 2015

Executive Boardroom
WHO HQ, Geneva

World Health Organization

SAGE October 2015

This booklet contains key background documents for the meeting of the
Strategic Advisory Group of Experts (SAGE) on immunization
20-22 October 2015

Further documents can be found online at the SAGE work space web site:

http://apps.who.int/immunization/sage/meetings/2015/october/en/

For password, please send an e-mail to: *sageexecsec@who.int*

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World Health Organization

Draft Agenda
Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)
20 – 22 October 2015
EB Room, WHO, HQ, Geneva

Tuesday, 20 Oct 2015

Time	Session	Purpose of session, target outcomes and questions for SAGE	
8:30	**Welcome – introduction of participants** J. Abramson, Chair of SAGE		20 min.
8:50	**Report from Director, IVB - Session 1** Global report including key updates and challenges from regions, J.-M. Okwo-Bele, WHO, 30 min. Discussion: 1h	**FOR INFORMATION**	1h 30 min.
10:20	**Coffee/tea break**	**Break**	**30 min.**
10:50	**Ebola vaccines - Session 2** Introduction, F Were, SAGE member, 5 min. Summary of key data reviewed by SAGE WG a. Epidemiology and risk factors for EVD, B. Aylward and C. Dye, WHO, 15 min. b. Status of vaccine development , preliminary results from clinical trials, modelled projections of impact and deployment plans, V. Moorthy, AM. Henao Restrepo, M.P Preziosi, WHO, 35 min. c. Projections of impact of vaccination under different epidemiological scenarios , J Edmunds, LSHTM, 15 min. Blueprint for R&D during emergencies, M-P. Kieny, WHO, 10 min. Conclusions and draft recommendations from the WG, H. Rees, Co-chair Ebola WG, 10 min.	**FOR DISCUSSION** SAGE will be presented with the key data reviewed by the Working Group in formulating its draft conclusions and recommendations. The presentations will cover epidemiological issues, the status of vaccine development (including a summary of preliminary data from clinical trials), and projections on the impact of vaccination, using different vaccination strategies and in different epidemiological scenarios. In addition, SAGE will be presented with a proposed blueprint for R&D during public health emergencies. Finally, SAGE will be presented with the conclusions and draft recommendations for post-licensure vaccine use, for review	2h 30 min.

	Discussion: 1h		
13:20	**Lunch**	**Break**	**1h 10 min.**
14:30	**Report from Gavi – Session 3** Report from the GAVI Alliance, S. Berkley, Gavi, 20 min. Discussion: 20 min.	**FOR INFORMATION**	40 min.
15:10	**Global Polio Eradication Initiative - Session 4** Objective of the session; overview of Global Polio Eradication Initiative, H. Jafari, WHO, 15 min. Updates on preparation for OPV2 withdrawal (e.g. IPV introduction, operationalizing OPV2 withdrawal, bOPV licensures and containment), M. Zaffran, WHO, 30 min.	**FOR INFORMATION AND DECISION** **<u>For decision</u>** · Reaffirm the OPV2 withdrawal date of April 2016, after careful assessment of progress toward the following: · Elimination of all persistent cVDPV2 · Preparedness for OPV2 withdrawal · Endorse the specific switch dates in April 2016 and the framework for monitoring tOPV withdrawal **<u>For information</u>** · To update SAGE on: . the current status of the polio eradication program · the contingency planning for vaccine supply · the status of polio legacy planning	3h
15:55	**Coffee/tea break**	**Break**	**30 min.**

16:25	**Global Polio Eradication Initiative - Session 4 (Contd.)** Report from SAGE WG, Y. AL-Mazrou, Chair of the Polio Working Group, 30 min. Discussion: 70 min. Updates on legacy planning, P. Rutter, WHO, 15 min. Discussion: 20 min.		
18:40	**Cocktail**		

Wednesday, 21 Oct 2015

09:00	**Measles and rubella vaccines - Session 5** Update on global measles and rubella control and regional elimination, P. Strebel, WHO, 15 min. Refinements to the vaccination strategies for measles and rubella control and elimination (i.e., use of a supplemental dose of measles containing vaccine (MCV) among infants <9 months of age, determining the target age range for M and MR SIA), P. Figueroa, Member and previous Chair of the SAGE Working Group on measles and rubella vaccines, 30 min. Measles revaccination of HIV-infected children on anti-retroviral therapy, W. Moss, Member of the SAGE Working Group on measles and rubella vaccines, 15 min. Discussion: 60 min	**FOR DISCUSSION AND DECISION** **<u>For discussion</u>** · To review the current status of global measles and rubella control and regional elimination · To review the plans for a Midterm Review of the Measles and Rubella Strategic plan · To review how existing data can be used to determine the target age range for M and MR SIAs **<u>For decision</u>** · Epidemiological settings in which a supplemental dose of MCV is recommended for infants aged <9 months · Measles revaccination of HIV-infected children on anti-retroviral therapy	2h
11:00	**Coffee/tea break**	**Break**	**30 min.**
11:30	**Reports from other Advisory Committees on Immunization - Session 6** Report of the Global Advisory Committee on Vaccine Safety (GACVS), M. Wharton, Chair of GACVS, 10 min. Discussion: 10 min. Report of the Product Development for Vaccines Advisory Committee (PDVAC), D. Kaslow, Chair of PDVAC, 10 min. Discussion: 10 min. Report of the Immunization Practices Advisory Committee (IPAC), C. Morgan, Chair of IPAC. 10 min. Discussion: 10 min. Report of the Immunization and vaccines related implementation research advisory committee (IVIR-AC), G. Kang, Member of IVIR-AC, 10 min. Discussion: 10 min. Report of the Expert Committee on Biological Standardization (ECBS), E. Griffiths, Chair of ECBS, 10 min. Discussion: 10 min.	**FOR INFORMATION**	1h 40 min.

13:10	**Lunch**	**Break**	**1h**
14:10	**Malaria Vaccine** **Jointly Co-Chaired Malaria Policy Advisory Committee (MPAC)/SAGE - Session 7** Opening comments to session. F. Binka, Acting Chair of MPAC, and J. Abramson, Chair of SAGE, 10 min. Malaria disease burden, epidemiology, status of malaria control and surveillance, and the need for new interventions. K. Marsh, African Academy of Sciences, 20 min. Review of RTS,S clinical trial results. P. Smith, Chair of JTEG, 30 min. Discussion: 30 min.	**FOR DECISION** Present SAGE and MPAC with the report of the Joint Technical Expert Group (JTEG) on the RTS,S malaria vaccine and request SAGE/MPAC's consideration of the proposed recommendations. SAGE/MPAC recommendations on vaccine use will then be used to write the first WHO position paper on the use of a malaria vaccine.	3h 30 min
15:40	**Coffee/tea break**		**30 min.**
16:10	**Malaria Vaccine** **Jointly Co-Chaired Malaria Policy Advisory Committee (MPAC)/SAGE meeting- Session 7 (Contd.)** JTEG assessment and proposed recommendations. P. Smith, Chair of JTEG, 20 min. Discussion: 80 min. Wrap-up of discussion and agreed SAGE/MPAC recommendations. F. Binka, Acting Chair of MPAC, 20 min.		
18:10	**End of day**		

Thursday, 22 Oct 2015

08:30	**Global Vaccine Action Plan: progress report - Session 8** The GVAP Secretariat Report 2015: Update on process, new indicators, actions taken by the secretariat in response to previous reports, T. Cherian (on behalf of the Secretariat of the Decade of Vaccines Working Group), WHO, 15 min. Summary of GVAP implementation progress review and recommendations for corrective actions, N. Arora, Chair of the SAGE Decade of Vaccines Working Group, 30 min. Discussion: 1h 45 min	**FOR DISCUSSION AND DECISION** SAGE will be expected to produce an independent annual report on progress with the Decade of Vaccines Global Vaccine Action Plan. Specially, SAGE will be asked to: • Review the DoV WG "Assessment report on DoV progress 2015" based on the "GVAP Secretariat report 2015" and some Independent stakeholder submissions. • Make recommendations on any necessary changes to the formulation of the indicators, operational definitions and/or the processes for data collection. • Identify successes, challenges and areas where additional efforts or corrective actions by countries, regions, partners, donor agencies or other parties, are needed. • Provide recommendations and corrective actions for Members States, regions, partners, donor agencies "SAGE Assessment report on the Decade of Vaccines progress" which will be the basis of the "progress report" for the WHO Executive Board and World Health Assembly.	2h 30 min
11:00	**Coffee/tea break**	**Break**	**30 min.**
11:30	**Report on activities from international immunization partners – Session 9** Presentation by UNICEF, H. Deehan, UNICEF, 20min. Discussion: 20min Presentation by MSF, A. Juan-Giner, Médecins Sans Frontières (MSF), 20min. Discussion: 20min	**FOR INFORMATION** This will be the launch of the series of presentations to be held at future SAGE meetings on the immunization-related activities of partners working in the field of immunization.	1h 20 min.
12:50	**Closing**		20 min.
13:10	**End of meeting**		

World Health Organization

Meeting of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization
14-16 April 2015
Geneva, Switzerland

SAGE members

Professor Jon S. Abramson (Chair) Department of Pediatrics **Wake Forest University Baptist Medical Centre** Medical Center Blvd Winston-Salem 27157 NC **United States of America**
Dr Yagob Yousef Al-Mazrou Secretary General **Council of Health Services** Riyadh 12628 **Saudi Arabia**
Professor Narendra Kumar Arora (Vice-Chair) Executive Director **The INCLEN Trust International** Second Floor, F-1/5 Okhla Industrial Area Phase 1 New Delhi 110020 **India**
Dr Alejandro Cravioto Senior Epidemiologist **Global Evaluative Sciences USA, Inc.** 98109 Seattle United States of America
Professor Juhani Eskola Director General, THL Health Protection **National Institute for Health and Welfare** Mannerheimintie 166 P.O. Box 30 00271 Helsinki **Finland**
Dr Ilesh Jani Director General **Instituto Nacional de Saúde (INS)** Ministry of Health PO Box 264 Maputo **Mozambique**
Dr Jaleela Jawad Head, Immunization Group and EPI Manager Public Health Directorate **Ministry of Health** Manama **Bahrain**
Dr Kari Johansen Expert Influenza and other Vaccine Preventable Diseases Surveillance and Response Support Unit **European Centre for Disease Prevention and Control** Tomtebodavägen 11A 171 83 Stockholm **Sweden**

Professor Terence Nolan
Head, Department of Public Health
Melbourne School of Population Health
The University of Melbourne
Level 5
207 Bouverie Street
Carlton Victoria 3010
Australia

Dr Katherine L. O'Brien
Associate Professor
Department of International Health
John Hopkins Bloomberg School of Public Health
Centre for American Indian Health & International Vaccine Access Center
615 North Wolfe Street
Baltimore 21205 MD
United States of America

Professor Claire-Anne Siegrist
Head, WHO Collaborating Centre for Neonatal Vaccinology
Department of Pediatrics & Pathology-Immunology
Centre Médical Universitaire
1 rue Michel Servet
1211 Genève 4
Switzerland

Dr Piyanit Tharmaphornpilas
Senior Medical Officer
Ministry of Public Health
Tiwanon Road
Taladkwan
Muang
Nonthaburi 11000
Thailand

Dr Nikki Turner
Associate Professor, Director Immunisation Advisory Centre
Department of General Practice and Primary Health Care
The University of Auckland
PO Box 17360, Greenlane,
Auckland 1051
New Zealand

Professor Fredrick Were
Professor of Pediatrics
University of Nairobi
P.O. Box 30588
Nairobi
Kenya

Dr Charles Shey Wiysonge
Professor & Deputy Director
Centre for Evidence-based Health Care
Stellenbosch University
7460 Cape Town
South Africa

Strategic Advisory Group of Experts (SAGE)
Terms of reference

Functions

SAGE is the principal advisory group to WHO for vaccines and immunization. It is charged with advising WHO on overall global policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions. SAGE is concerned not just with childhood vaccines and immunization, but all vaccine-preventable diseases.

SAGE advises the WHO Director-General specifically on the:

1. adequacy of progress towards the achievement of the goals of the Decade of Vaccines (DoV) Collaboration and Global Vaccine Action Plan (GVAP);
2. major issues and challenges to be addressed with respect to achieving the goals of the DoV and GVAP;
3. immunization programme response to current public health priorities;
4. major general policies, goals and targets including those related to vaccine research and development;
5. adequacy of WHO's strategic plan and priority activities to achieve the DoV and GVAP goals consistent with its mandate and considering the comparative advantages and the respective roles of partner organizations;
6. cross-departmental activities and initiatives related to vaccine and immunization technologies and strategies and linkages with other health interventions;
7. engagement of WHO in partnerships that will enhance achievement of global immunization goals.

Membership

The SAGE comprises 15 members, who shall serve in their personal capacity and represent a broad range of disciplines encompassing many aspects of immunization and vaccines.

SAGE members are recruited and selected as acknowledged experts from around the world in the fields of epidemiology, public health, vaccinology, paediatrics, internal medicine, infectious diseases, immunology, drug regulation, programme management, immunization delivery, health-care administration, health economics, and vaccine safety.

The membership of SAGE shall seek to reflect a representation of:

1. professional affiliation (e.g., academia, medical profession, clinical practice, research institutes, and governmental bodies including national immunization programmes, public health departments and regulatory authorities);
2. major areas of expertise (e.g., influenza control, diarrhoeal diseases, respiratory diseases, research, biologics, immunization safety); and
3. the three major strategic areas of WHO's work relating to immunization (i.e., accelerating innovation, ensuring quality and safety, and maximizing access and links with other health interventions).

SAGE members, including the Chairperson, shall be nominated by the WHO IVB Director in consultation with WHO Regional Offices and other relevant WHO departments upon the proposal of an independent selection panel including representatives of key partner organizations. A public call for nominations is issued. After determination of eligibility, nominations are submitted to the selection panel. Members will be selected on the basis of their qualifications and ability to contribute to the accomplishment of SAGE's objectives.

SAGE members are appointed by the WHO Director-General; all nominations for new SAGE members, as well as renewals and discontinuation of appointments to SAGE, must be approved by the WHO Director-General. Consideration will be given to ensuring appropriate geographic representation and gender balance.

Members of SAGE shall be appointed to serve for an initial term of three years. Such three-year terms may only be renewed once. To allow for continuity and efficiency the Chairperson of SAGE is expected to act as Chairperson for a minimum of three years, not taking into account if he/she has already served three years or has been renewed for a further three years as a member of SAGE. He/she needs however, to be a member of SAGE for a minimum of one year before taking up Chairmanship.

Prior to being appointed as SAGE members and prior to renewal of term, nominees and current SAGE members shall be required to complete a WHO Declaration of Interests as per the attached form (Annex 1).

In addition, prior to confirmation by WHO of their appointment as SAGE members, SAGE nominees shall be required to sign a Confidentiality Undertaking (Annex 2). All papers presented to SAGE, which may include pre-publication copies of research reports or documents of commercial significance, shall be treated as confidential. SAGE deliberations are confidential and may not be publicly disclosed by SAGE members.

A register of members' interests and signed confidentiality agreements shall be maintained by WHO.

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Membership in SAGE may be terminated for any of the following reasons:

(1) failure to attend two consecutive SAGE meetings;
(2) change in affiliation resulting in a conflict of interest; and
(3) a lack of professionalism involving, for example, a breach of confidentiality.

Roles and responsibilities of SAGE members

Members of SAGE have a responsibility to provide WHO with high quality, well considered advice and recommendations on matters described in this SAGE terms of reference. Members play a critical role in ensuring the reputation of SAGE as an internationally recognized advisory group in the field of immunization. In keeping with SAGE's mandate to provide strategic advice rather than technical input, members will be committed to the development and improvement of public health policies. Focused technical input will be solicited from identified experts and advisory scientific groups.

The Committee has no executive or regulatory function. Its role is solely to provide advice and recommendations to the Director-General of WHO, and includes providing advice and recommendations on urgent matters as needed.

SAGE members may be approached by non-WHO sources for their views, comments and statements on particular matters of public health concern and asked to state the views of SAGE. SAGE members shall refer such enquiries to WHO.

Meetings and operational procedures

SAGE will normally meet biannually. The frequency of meetings may, however, be adjusted as necessary. Decisions or recommendations will, as a rule, be taken by consensus.

SAGE members are asked to update their declared interests before each meeting. SAGE members with potentially conflicting interests will not participate in deliberations on the specific topic(s) for which they would have a conflict of interest. SAGE member's relevant interests will be made publically available along with the meeting documentation on the SAGE website after the meeting.

UNICEF, the Secretariat of the Global Alliance for Vaccines and Immunization (GAVI), and WHO Regional Offices will participate as observers in SAGE meetings and deliberations.

WHO may also invite other observers to SAGE meetings, including representatives from WHO regional technical advisory groups, non-governmental organizations (NGO), international professional organizations, technical agencies, donor organizations and associations of manufacturers of vaccines and immunization technologies.

Additional experts may be invited to meetings, as appropriate, to further contribute to specific agenda items.

SAGE will work with WHO to develop its priorities of work and meeting agendas.

SAGE will be kept informed by WHO and partner agencies of progress in implementation of strategies and the attainment of objectives at country and regional level. SAGE will also be informed of policies and recommendations set by the WHO regional technical advisory groups. WHO, with advice from SAGE, will determine which policy recommendation issues and information from other WHO technical advisory groups should be brought to the attention of SAGE.

SAGE Working Groups are established as resources intended to increase the effectiveness of SAGE deliberations by reviewing and providing evidence-based information and options for recommendations together with implications of the various options to be discussed by the full SAGE in an open public forum. These Working Groups are established on a time-limited basis to help address specific questions identified by SAGE when the issue is particularly complicated and could not be addressed by an existing standing WHO advisory committees. The need and charge for a Working Group is discussed and agreed during SAGE meetings. The purpose, structure and functioning of the Working Groups is described in detail in Annex 3.

In addition to attendance of meetings, active participation will be expected from all SAGE members throughout the year, including participation in SAGE Working Groups, video and telephone conferences as well as frequent interactions via e-mail. Review of documents may also be solicited. SAGE members may be requested to participate as observers in other important WHO departmental or cross-departmental meetings.

SAGE members will not be remunerated for their participation in SAGE; however, reasonable expenses such as travel expenses incurred by attendance at SAGE or related meetings will be compensated by WHO.

SAGE reports to the WHO Director-General (or designee(s)). The SAGE Chairperson will debrief the Director-General (or designee) and the IVB Director following each SAGE meeting. Minutes of SAGE meetings will be taken and circulated among SAGE members. The recommendations/conclusions of SAGE meeting shall be published, with the prior approval of WHO, in the Weekly Epidemiological Record and posted on the IVB Departmental website within two months of each SAGE meeting. In addition, these recommendations and conclusions will be translated into all the WHO headquarters official languages and posted on the IVB Departmental website.

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Purpose, structure and functioning of the Strategic Advisory Group of Experts on Immunization (SAGE) Working Groups

Purpose and decision to establish a SAGE Working Group
SAGE Working Groups are established as resources intended to increase the effectiveness of SAGE deliberations by reviewing and providing evidence-based information and options for recommendations together with implications of the various options to be discussed by the full SAGE in an open public forum.

These Working Groups are normally established on a time limited basis to help address specific questions identified by SAGE when the issue cannot be addressed by existing standing WHO advisory committees. Some Working Groups such as that on polio eradication or the Decade of Vaccines Working Group can be established for a number of years.

The need for and creation of a Working Group is discussed and agreed during SAGE meetings, preparatory teleconferences for SAGE meetings, or in case of urgency via email interaction .

Terms of reference of the Working Groups and identification of needed expertise to serve on the Working Group
Each Working Group operates under specific terms of reference (TORs). These TORs are defined within 30 days of the SAGE decision to establish the Working Group.

Proposed TORs and related expertise to serve on the Working Group are developed jointly by the SAGE member serving as Working Group Chair, the Lead WHO technical staff and SAGE Executive Secretary. Draft TORs and related expertise are reviewed by SAGE members. Final decision is taken jointly by the SAGE Chair, Working Group Chair, SAGE Executive Secretary, and the Director of the Department of Immunization, Vaccines and Biologicals.

Working Group composition and selection of membership
Each Working Group should include two or more SAGE members (one of whom functions as Chair), and additional subject matter experts serving in their own individual capacity and with a view to meet the identified needed expertise for the group. SAGE members and other experts who have identified conflicts of interest cannot serve on the Working Group charged with responsibility in the identified areas of conflict. WHO staff (one of whom functions as the Working Group technical lead serve as secretariat to the Working Group. In some instances other UN or non UN agencies can be co-opted as part of the secretariat. For Working Groups which terms of reference require proceedings over a number of years, if a SAGE member rotates out of SAGE while the Working Group is still active, then he/she remains on the Working Group but a new SAGE member should be enrolled to serve on the group. A new SAGE member should be appointed as Working Group Chair when the previous Chair rotates out of SAGE. For Working Groups having proceedings spanning over a number of years, the same rotation process as applied to SAGE membership should be applied i.e. two 3–year terms, the renewal being determined by the Working Group Chair, Lead WHO technical staff and SAGE Executive secretary based on the contribution of the member to the group. If some members resign for personal reasons, are no longer eligible to serve on the group, or are unable to meaningfully contribute to the proceedings of the group, given their expertise would be lacking the group, they can be replaced with first considering an appointment from the list of initial candidates to join the group. The decision will be made as for the selection of candidates (see below). If no one from this list is suitable then another expert could be solicited and co-opted without resourcing to an open call for nomination.

The size of the Working Group should not exceed 10-12 members and will be adjusted based on the need for expertise and representation.

A public call for nomination for Working Group members will be posted on the SAGE website together with the relevant TORs of the Working Group and indication of the desirable expertise. SAGE members, regional offices, diplomatic missions, WHO staff and key partner organizations will also be approached for potential nominations. Nominees will be requested to provide both a Curriculum Vitae and a completed Declaration of Interests form prior to being considered for membership on the Working Group. From the pool of nominees, the Working Group Chair, SAGE Executive Secretary and Lead WHO staff will propose a Working Group composition for endorsement by the SAGE Chair and the Director of the Department of Immunization, Vaccines and Biologicals. The proposed list should be accompanied by the rationale for the proposed selection. In addition to meeting the required expertise, attention will be given to ensure proper diversity including geographic and gender representation.

On rare occasions joint reviews of evidence by SAGE and another area/Department's advisory committee with expertise in the topic being considered may have to be organized for the two groups to jointly issue recommendations. As a result a SAGE Working Group may be formed in conjunction with this other solicited advisory committee. In this instance members of the solicited advisory committee might also be co-opted on the Working Group and a Working Group co-Chair may be appointed from among members of this other advisory committee. In this case, the selection of Working Group members will equally involve the Chair and secretariat of the solicited advisory committee.

Working Group members will not be remunerated for their participation in the Working Group; however, reasonable expenses such as travel expenses incurred by attendance at Working Group meetings, SAGE meetings or related meetings will be compensated by WHO.

Working Group Process

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WHO secretariat will perform or coordinate, systematic assessment of the evidence such as analysis of data addressing efficacy, effectiveness, safety, feasibility, and economic aspects of immunization policy to address questions developed by the Working Group in order to propose appropriate vaccine policy recommendations. This is done in accordance with the process for evidence –review and development of recommendations by SAGE as available at http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf?ua=1. SAGE uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process for the review of evidence. The Working Group will be expected to define the questions to inform the recommendations. It should identify critical questions for which an in-depth review/systematic review of the evidence is needed and determine important outcomes. In developing proposed recommendations the Working Group should use the GRADE-DECIDE Framework and systematically consider the following: balance of benefits and harms, resource use and value for money, equity impacts, feasibility, acceptability, values and preferences, and other relevant considerations.
Issues and recommendations should always be based on GRADing of evidence. Only when not appropriate (and as per criteria stated in Guidance for the development of evidence-based vaccine related recommendations) the Group may opt to develop Good Practice Statements.
All proposed recommendation and comprehensive evidence in support of recommendations including GRADE tables and evidence to decision tables (if relevant) should be presented to SAGE.

SAGE Working Groups are not allowed to render consensus advice or recommendations directly to the WHO Director-General. SAGE Working Group Chairs, other Working Group representatives, or the Working Groups per se are not empowered to speak on behalf of SAGE. Rather, they are utilized by SAGE to gather and organize information upon which SAGE can deliberate and act. Thus, while SAGE Working Groups can and should examine an area in detail and define the issues, including developing options for recommendations, the actual processes of group deliberation terminating in development of group consensus and recommendations must occur in the public forum of SAGE meetings by SAGE. If the Working Group cannot reach consensus then the diverging views will be reflected in the background document or Working Group Report presented to SAGE. Such documents will be publicly posted on the SAGE website as soon as the SAGE meeting is over.

Effective communication and a strong working collaboration between the Working Group Chair, Lead WHO staff and the Working Group members are significant determinants of the effectiveness of a Working Group. Draft minutes of Working Group in person meetings or conference calls are produced. As soon as the minutes are approved by the Working Group, they are made available to SAGE members on a protected web workspace. Depending on the Working Group, minutes may be produced by the Secretariat or a Working Group member may be asked to serve as Rapporteur. Minutes are not publicly available and only publicly shared in the context of a SAGE session when included in the background documents.

With the Lead WHO Staff, the Chair of the Working Group develops a plan for routine operations of the group. Working Groups accomplish most of their work through teleconferences. A set day and time for routine monthly teleconferences may be established, in order to allow standing teleconferences to be arranged and Working Group members to anticipate and reserve time for these teleconferences. The frequency of Working Group teleconferences may be changed depending on the urgency of issues being considered by the group and the amount of preparatory work needed prior to a topic being brought up for plenary discussion and decision making at SAGE. Some Working Groups may more effectively achieve their purpose through exchange of e-mail communications with intermittent teleconferences. WHO will establish a telephone bridge for the teleconferences and ensure free access that telephone charges are not impacted to Working Group members.

In-person meetings of Working Groups may facilitate the proceedings of the group and Working Groups are expected to have at least one face-to-face meeting. If a Working Group is planning to conclude its proceedings at a given face-to-face meeting, this meeting should be held at least one month in advance of the SAGE meeting during which the Working Group is expected to report to SAGE. These face-to-face meetings are normally held in Geneva but they may also be held in different locations if this minimizes cost and facilitates participation of Working Group members and necessary experts.

Individuals other than Working Group members and the Secretariat may participate in Working Group meetings only if their contribution is required by the Working Group. These may include organization representatives, industry representatives/experts, public health officials, faculty of academic institutions or other experts. These experts are excluded from any discussions and deliberations within the Working Group and are solely invited to provide specific requested information on a predefined topic. Observers are not allowed to attend Working Group proceedings.

Working Groups are terminated after completion of the TOR and reporting to SAGE unless SAGE asks for additional work. Working Group focused on the development of recommendations on vaccine use may only be closed after the WHO position paper is published following the issuance of recommendations by SAGE. Working Group members will be asked to contribute to the peer-review of the document prior to publication and might be asked to help address reviewer's comments.

Working Groups are encouraged to submit publications of the reviews of the scientific evidence in peer-review journals. This could be done before or after the SAGE meetings. If published before the SAGE meeting, the publications should reflect the scientific evidence only and not pre-empt the view of SAGE with stating the proposed recommendations and if published after the SAGE meeting should reference the SAGE report.

Management of Conflict of Interest
The value and impact of SAGE recommendations and WHO policy recommendations are critically dependent upon public trust in

the integrity of the process. Reported interests are assessed and managed according to SAGE procedures. Summarized Declarations of Interest are publicly posted on the SAGE website in conjunction with the Working Group's TORs and composition (http://www.who.int/immunization/sage/working_mechanisms/en/). Members are expected to proactively inform WHO on any change in relevant interests. The posted summary will then be updated accordingly.

1. SAGE working group on polio (Established August 2008)

Terms of Reference

1. Prepare SAGE for the development of comprehensive policy guidance on the use of IPV in the post-eradication era in low and middle income settings, including by:

    - Reviewing long-term Polio Risks & Risk Management Strategies:
      reviewing the long-term risks associated with live polioviruses after wild polio transmission globally, and reviewing the range of strategies for mitigating those risks in low-income settings (e.g. coordinated OPV cessation, mOPV stockpiles and response mechanism).
    - Assessing Current & Future IPV Products:
    - Reviewing the existing range of IPV products, in terms of supply capacity, production cost, price, presentations, etc, and their appropriateness and suitability for low-income settings, particularly sub-Saharan Africa; and studying the IPV 'pipeline' and its implications for post-eradication IPV use in terms of potential new products (e.g. Sabin-IPV, adjuvanted-IPV, fractional dose IPV), production costs, and prices.
    - Establishing Potential IPV Policies & Implications:
      establishing the range of IPV vaccination schedule options that could be utilized in a post-eradication world, given the difference in polio immunization objectives and polio risks compared with a polio-endemic world; and identifying and characterizing the programmatic implications, economics and opportunity costs of those policy options, for both IPV stand-alone and combination formulations, in low-income settings and particularly sub-Saharan Africa;
    - Identifying and prioritizing knowledge gaps that should be addressed to facilitate SAGE decision-making on the role(s) and options for IPV use in the post-eradication era in low-income settings.

2. Propose key recommendations to SAGE for updating the 2003 position paper on IPV and consolidating it with other relevant documents (including the 2006 supplement to the IPV position paper) into one vaccine position paper on routine polio immunization covering both IPV and OPV and giving consideration to the ongoing polio eradication efforts.
3. Advise SAGE on technical guidance to WHO and the GPEI for the development and finalization of the overall polio eradication 'endgame strategy' to reduce long-term risks associated with OPV and to accelerate wild poliovirus eradication, including:

    - policy and programmatic options for the use of different OPV formulations and IPV delivery options, and
    - Strategy and priorities in the related areas of outbreak response, surveillance, containment, risk assessment (esp. Vaccine Derived Polio Viruses - VDPVs), research and product development, and vaccine supply.

Composition

SAGE Members

- Yagob Al-Mazrou, Secretary General - Health Services Council of the Kingdom of Saudi Arabia, Saudi Arabia (Joined the group in February 2015), (Chair of the Working Group and SAGE member since August 2015).
- Peter Figueroa, University of the West Indies, Jamaica, (Chair of Working Group and SAGE member until August 2015)
- Hyam Bashour, changed as of February 2013- retired from Damascus University, Syria (SAGE member until April 2011)
- Zulfiqar Bhutta, The Aga Khan University, Pakistan (Joined the Working Group in March 2012), (SAGE member until August 2015)
- Elizabeth Miller, Health Protection Agency, United Kingdom, (SAGE member and Chair of the Working Group until February 2014)

Experts

- Walter Dowdle, Task Force for Child Health, USA
- Nick Grassly, Imperial College, UK
- Jacob John, Christian Medical College, India
- Antoine Kabore, retired (formally of WHO/AFRO), Burkina Faso
- Francis Nkrumah, retired (formally of Noguchi Memorial Institute for Medical Research, University of Ghana Medical School, Ghana)
- Walter Orenstein, Emory University, USA
- Kimberley Thompson, Kids Risk Project, Harvard School of Public Health, USA

Updated: October 2015

2. Joint technical expert group (JTEG) on malaria vaccines entering pivotal phase 3 trials & beyond (established April 2009)

JTEG acts as a SAGE (Strategic Advisory Group of Experts on Immunization) Working Group and also as a MPAC (Malaria Policy Advisory Committee) Technical Expert Group. The constitution of JTEG took into account both SAGE and MPAC considerations. The Chair, Peter Smith, is neither a SAGE nor MPAC member. Peter Smith was chosen as an expert in both immunization and malaria policy, having also served as Chair of other immunization and malaria-related WHO advisory committees.

Terms of reference

JTEG provides advice to SAGE and MPAC on activities related to the development of malaria vaccines at or nearing the pivotal phase 3 trial stage. The specific responsibilities of the group are to provide recommendations on:

- The clinical trial data necessary and desirable for evaluation of the public health impact of a malaria vaccine in malaria endemic countries
- The design, conduct, analyses and interpretation of Phase 2, Phase 3 and Phase 4 trials of malaria vaccines.
- The duration and nature of follow-up of participants in planned Phase 3 trials of malaria vaccines.
- The minimum safety and efficacy data to be collected in clinical trials, and data on any impact of malaria vaccines on the immunogenicity of other vaccines, to enable evaluation by WHO for policy recommendations.
- The evaluation of immunogenicity of malaria vaccines in Phase 3 trials and beyond, in particular with regard to possible development of surrogate markers for efficacy.

Composition

SAGE Members

- Zulfiqar Bhutta, Aga Khan University, Pakistan, (SAGE member until August 2015)
- Claire-Anne Siegrist, University of Geneva, Switzerland
- Fred Were, Executive Director - Professor, Department of Paediatrics and Child Health, University of Nairobi, Kenya, (SAGE member and Group member since September 2014)

Experts

- Peter Smith, (Chair of the Group), London School of Hygiene and Tropical Medicine, UK
- Fred Binka, University of Ghana, Ghana
- Kalifa Bojang, MRC Laboratories, The Gambia
- Blaise Genton, University of Lausanne, Switzerland
- Robert Johnson,National Institutes of Allergy and Infectious Disease, USA
- Kamini Mendis, Independent Consultant, Colombo, Sri Lanka
- Paul Milligan, London School of Hygiene and Tropical Medicine, UK
- Malcolm Molyneux, University of Malawi, Malawi
- Mahamadou Thera, University of Bamako, Mali
- Janet Wittes, Statistics Collaborative Inc., USA

3. SAGE working group on measles and rubella vaccines (established November 2011)

Terms of Reference

- Review progress towards 2015 global measles control targets and regional measles and rubella elimination goals.
- Prepare for regular updates and review by SAGE on progress and challenges in achieving existing measles and rubella control targets and propose necessary updating of current WHO recommendations on vaccine use (including outbreak response immunization) and surveillance strategies.
- Identify gaps in essential evidence and programme barriers to achieving measles and rubella/CRS elimination targets and present SAGE with proposed areas for operational or basic science research. The working group will liaise with SAGE Sub-Committees (i.e., IVIR-AC and IPAC) to address relevant quantitative issues as well as those related to immunization practices.
- Advise SAGE on the appropriate timing for establishing target dates for global eradication of measles and global control or eradication targets for rubella and/or CRS.

Composition

SAGE Members

- Narendra Arora, International Clinical Epidemiology Network, India, (Chair of the Working Group since September 2015)
- El Tayeb Ahmed El Sayed, Federal Ministry of Health, Sudan (SAGE member until June 2012)
- David Durrheim, Hunter New England Area Health Service and Professor of Public Health, Australia (SAGE member until April 2012)
- Peter Figueroa, Chair of Working Group. University of the West Indies, Jamaica, (SAGE member until April 2015 and Chair of the Working Group until August 2015)
- Helen Rees, University of Witwatersrand, South Africa (SAGE member until August 2013)
- Ilesh Jani, Director General, Instituto Nacional de Saude (INS), Mozambique (Joined the Working Group in October 2015)
- Nikki Turner, Department of General Practice and Primary Health Care, The University of Auckland, New Zealand (Joined the Working Group in October 2015)

Experts

- Hyam Bashour, Department of Family and Community Medicine, Damascus University, Syria (SAGE member until April 2011)
- Natasha Crowcroft, Surveillance and Epidemiology, Public Health Ontario, Canada
- Heidi Larson, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, UK (resigned from the Working Group in February 2015)
- Pier Luigi Lopalco, European Centre for Disease Prevention and Control, Sweden (resigned from the Working Group in February 2015)
- William Moss, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
- Susan Reef, Global Immunization Division, Centers for Disease Control and Prevention, USA
- Makoto Takeda, Department of Virology, National Institute of Infectious Diseases, Japan

4. SAGE Working Group on the Decade of Vaccines (established March 2013)

Terms of Reference

The SAGE Working Group (WG) will facilitate a yearly SAGE independent review of the implementation of the Decade of Vaccines' Global Vaccine Action Plan (GVAP) and assessment of progress.

Specifically, the WG will:

- review the quality of the data on the GVAP indicators and make recommendations on changes to the formulation of the indicators, operational definitions and/or the processes for data collection;
- independently evaluate and document progress towards each of the 6 GVAP Strategic Objectives and towards the achievement of the Decade of Vaccines Goals (2011-2020), using the GVAP Monitoring & Evaluation / Accountability Framework;
- identify successes, challenges and areas where additional efforts or corrective actions by countries, regions, partners, donor agencies or other parties, are needed;
- identify and document best practices;
- prepare the GVAP implementation annual report to be presented to the SAGE, and thereafter, with SAGE inputs, be submitted for discussion to the WHO January EB meeting, to the WHA and the independent Expert Review Group (iERG) for the UN Secretary General's Global Strategy for Women's and Children's Health.

In its review the WG should take a broad perspective, encompassing the general environment, including the health system context.

Composition

SAGE Members

- Narendra Arora, Chair of the Working Group, Executive director, International Clinical Epidemiology Network, India
- Yagob Al-Mazrou, Secretary General - Health Services Council of the Kingdom of Saudi Arabia, Saudi Arabia
- Helen Rees, Executive Director - Reproductive Health Research Unit, University of Witwatersrand, South Africa (SAGE member until August 2013)

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- Alejandro Cravioto-Chief Scientific Officer, International Vaccine Institute, Seoul, Republic of Korea, (SAGE member since August 2015)

Experts

- Fuqiang Cui, Epidemiology Professor, Deputy Director National Immunization Program, China CDC, China
- Elizabeth Ferdinand, Senior Medical Officer of Health and Barbados EPI Manager, Barbados
- Shawn Gilchrist, President, S. Gilchrist Consulting Services Inc., Canada (resigned from the Working Group May 2014 for personal reasons and replaced by Yvette Madrid)
- Alan Hinman, Senior Public Health Scientist - Task Force for Global Health, USA
- Stephen Inglis, Director, National Institute Biological Standards & Control, Health Protection Agency, UK
- Yvette Madrid, PATH, Switzerland
- Amani Mahmoud Mustafa, EPI Ministry of Health, Sudan
- Rebecca Martin, Director Global Immunization Division, US CDC, USA
- Rozina Mistry, Lecturer and Course Director, Aga Kahn University, Pakistan
- David Salisbury, Director Immunization, Department of Health, UK

5. SAGE Working Group on Ebola Vaccines and Vaccination (established November 2014)

Terms of Reference

The Strategic Advisory Group of Experts (SAGE) on Immunization Working Group is exceptionally established with an urgent program of work to facilitate a SAGE review of available evidence and advice to WHO on the potential post-licensure use of the Ebola vaccines in order to mitigate the public health impact of the disease and possibly curtail the ongoing epidemic, as well as to prevent or reduce the risk of spread of disease in the future. The Working Group will consult with the Task Force for Immunization for the African region to get their inputs into the operationalization of immunization delivery and consolidate the feedback into a report to SAGE with recommendations on potential strategies for the deployment of vaccines.

In order to facilitate the review, the Working Group will provide technical advice and support to the WHO secretariat by:

- Reviewing the essential evidence required for making policy recommendations and on strategies for deployment of vaccines.
- Reviewing the available epidemiological data to define the risk of disease and mortality in different population groups in order to allow prioritization of vaccination.
- Reviewing the evidence, as it becomes available, on the safety, and efficacy of candidate vaccines, including the optimal vaccination schedules to be used for each vaccine.
- Reviewing the data on the projected impact of different vaccination strategies generated by mathematical models.
- Reviewing the synthesis of the above data for presentation to SAGE and in drafting recommendations for consideration by SAGE.
- Reviewing the projections of vaccine supply to inform recommendations on the deployment of vaccines.

Composition

SAGE Members

- Tomori, Oyewale (Co-Chair), Professor of Virology, Redeemer's University, Nigeria; (SAGE member until August 2015)
- O'Brien, Kate; Professor, Department of International Health & Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, USA
- Were, Fred; Executive Director - Professor, Department of Paediatrics and Child Health, University of Nairobi, Kenya
- Wiysonge, Charles (Member of TFI), Professor in Community Health Stellenbosch University; Deputy Director Centre for Evidence-based Heath Care Stellenbosch University, South Africa; (SAGE member since August 2015)

Experts

- Rees, Helen (Co-Chair, Chair of the African Task Force on Immunization (TFI) Executive Director - Reproductive Health Research Unit, University of Witwatersrand, South Africa (SAGE member until August 2013);

- Andrews, Nick; Deputy Head of Statistics Unit, Public Health England, UK
- Bonsu, George; Immunization program manager Ghana, Ghana
- Durrheim, David; Hunter New England Area Health Service and Professor of Public Health, Australia, (SAGE member until August 2012)
- Goodman, Jesse; Professor of Medicine, Georgetown University, USA
- Jemmy, Jean-Paul; Medical Coordinator of Operations, Médecins San Frontières, Belgium
- Kelly, Ann; Senior Lecturer in Anthropology, Department of Philosophy, Sociology, and Anthropology, University of Exeter, UK.
- Moodley, Keymanthri; Director, Centre for Medical Ethics and Law, Department of Medicine, Stellenbosch University, South Africa.
- Ndack, Diop: Lecturer in Socio-Anthropology & Methodology of research in social science. University Cheikh Anta Diop, Dakar, Senegal
- Ockenhouse, Chris; Director, Medical and Clinical Operations, Malaria Vaccine initiative, PATH, USA
- Velasco Muñoz, Cesar; Preventive Medicine and Epidemiology Unit, Hospital Clínic-Universitat de Barcelona-Barcelona Centre for International Health Research, Barcelona, Catalonia, Spain. / Public Health Capacity and Communication Unit, European Center for Disease Control, Sweden

Ex-Officio members

- Breiman, Robert; (Chair of WHO Immunization and vaccines related implementation research advisory committee (IVIR-AC))
- Griffiths, Elwyn; (Chair of WHO Expert Committee on Biological Standardization (ECBS))
- Morgan, Chris; (Chair of WHO Immunization Practices Advisory Committee (IPAC))
- Wharton, Melinda; (Chair of WHO Global Advisory Committee on Vaccine Safety (GACVS))

WHO Secretariat

Focal point: Cherian, Thomas

6. SAGE Working Group on Dengue (established March 2015)

Terms of reference

The Working Group will be asked to review the evidence, identify the information gaps, and formulate proposed recommendations on the use of licensed dengue vaccines for a SAGE review. This review is tentatively scheduled for April 2016. This will lead to the publication of a WHO position paper on the use of dengue vaccines.

- The Working Group will specifically be asked to review data relating to:
- the global prevalence and burden of disease caused by dengue
- the safety, efficacy, and immunogenicity profile of licensed dengue vaccines
- the schedule, age of administration, and potential vaccination strategies for dengue vaccines, including setting-specific attributes that may be important for designing immunization programs
- the disease impact and cost-effectiveness of dengue immunization programs
- identification of key data gaps that may be important for decisions about immunization programs, and recommendations for data collection related to key issues such as long-term safety, duration of protection, etc.
- additional critical issues that need to be considered in drafting proposed recommendations.

Composition

SAGE Members

- Terry Nolan, (Co-Chair of the Working Group), Melbourne School of Population and Global Health, Australia
- Piyanit Tharmaphornpilas, Ministry of Public Health, Thailand

Experts

- Jeremy Farrar, (Co-Chair of the Working Group), Wellcome Trust, UK
- Amanda Amarasinghe, Ministry of Health, Sri Lanka
- Alan Barrett, University of Texas Medical Branch, USA
- Anna Durbin, Johns Hopkins Bloomberg School of Public Health, USA
- Elizabeth Ferdinand, Ministry of Health, Barbados (Retired)
- Maria Guzman, Pedro Kouri Tropical Medicine Institute, Cuba

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- Maria Novaes, Universidade de São Paulo, Brazil
- Lee Ching Ng, National Environment Agency, Singapore
- Amadou Sall, Institut Pasteur de Dakar, Senegal
- Peter Smith, London School of Hygiene and Tropical Medicine, UK
- Wellington Sun, U.S. Food and Drug Administration, USA
- Steve Thomas, Walter Reed Army Institute of Research, USA

WHO Secretariat

- Joachim Hombach
- Kirsten Vannice

7. SAGE Working Group on Maternal and Neonatal Tetanus Elimination (MNTE) - Beyond

Terms of reference

- To critically look into the reasons why the previously set elimination target dates have been missed and how to address these.
- To propose a process for "resetting" the MNT elimination agenda in a sustainable manner, and including looking into the risk of tetanus in other age groups and genders, and the deadlines being targeted.
- To discuss the role of strengthening ANC as part of the "reset" strategy.
- To review experiences especially from the countries that attained MNT elimination with limited or no campaigns.
- To think out of the box including on how to capitalize on infant routine immunization and on the strategies that have to be adapted to the local context, like conflict affected areas, and linkages with other programmes targeting the poor and marginalised groups.
- To discuss the learning agenda from MNT as pathfinder for further maternal vaccines.

Composition

Call for nominations recently issued and composition of the Working Group under finalization

World Health Organization

Strategic Advisory Group of Experts on Immunization

20 - 22 October 2015
Geneva

Provisional list of participants as of 01 October 2015

SAGE members

Abramson, Jon (Chair) Professor Department of Pediatrics Wake Forest Baptist Health 27157 Winston-Salem United States of America
Al-Mazrou, Yagob Yousef Secretary General Saudi Health Council 3161-13315 Riyadh Saudi Arabia
Arora, Narendra Kumar (Vice-Chair) Executive Director The INCLEN Trust International 110020 New Delhi India
Cravioto, Alejandro Senior Epidemiologist Global Evaluative Sciences USA, Inc. 98109 Seattle United States of America
Eskola, Juhani Director General National Institute for Health and Welfare (THL) FI-00270 Helsinki Finland
Jani, Ilesh Director General Instituto Nacional de Saúde Maputo Mozambique
Jawad, Jaleela Head of immunization Public Health Directorate Ministry of Health Manama Bahrain
Johansen, Kari Expert VPD + IRV European Centre for Disease Prevention and Control (ECDC) 17183 Stockholm Sweden
Nolan, Terry Head Melbourne School of Population and Global Health The University of Melbourne 3010 Carlton Australia

O'Brien, Kate Professor International Health Johns Hopkins Bloomberg School of Public Health 21231 Baltimore United States of America
Siegrist, Claire-Anne Head WHO Collaborating Centre for Vaccine Immunology University Hospital of Geneva 1211 Geneva Switzerland
Tharmaphornpilas, Piyanit Senior Medical Advisor Disease Control Ministry of Public Health 11000 Nonthaburi Thailand
Turner, Nikki Associate Professor General Practice and Primary Care University of Auckland 6012 Wellington New Zealand
Were, Fredrick Dean School of Medicine University of Nairobi 00202 Nairobi Kenya
Wiysonge, Charles Shey Professor & Deputy Director Centre for Evidence-based Health Care Stellenbosch University 7460 Cape Town South Africa

Malaria Policy Advisory Committee (MPAC) Members

Binka, Fred Vice-Chancellor Central Administration University of Health and Allied Sciences 99999 Ho Ghana
Graves, Patricia James Cook University 4870 Cairns Australia
Greenwood, Brian Professor of Tropical Medicine Department of Infectious and Tropical Diseases London School of Hygiene and Tropical Medicine WC1E 7HT London United Kingdom of Great Britain and Northern Ireland
Leke, Rose MPAC member Emeritus Professor Department of Immunology and Infectious Diseases Biotechology Center, University of Yaounde 1 Yaoundé Cameroon

Marsh, Kevin chair of MPAC Senior Advisor African Academy of Sciences Nairobi Kenya
Meek, Sylvia MPAC member Technical Director Malaria Consortium EC2A 4LT London United Kingdom of Great Britain and Northern Ireland
Mendis, Kamini Consultant Independent 05 Colombo Sri Lanka
Schapira, Allan Independent consultant 4500 Legazpi City Philippines
Slutsker, Laurence Director Division of Parasitic Diseases and Malaria CDC 30329 Atlanta United States of America
White, Nicholas Faculty of Tropical Medicine Mahidol University 10400 Bangkok Thailand

Chairs of Regional Technical Advisory Groups

Figueroa, Peter (Chair, PAHO TAG) Department of Community Health & Psychiatry University of the West Indies Kingston 7 Jamaica
Finn, Adam Chair, ETAGE Professor of Paediatrics Schools of Clinical Sciences and Cellular and Molecular Medicine University of Bristol BS2 8AE Bristol United Kingdom of Great Britain and Northern Ireland
Hall, Robert (Chair, WPRO TAG) Senior Lecturer School of Public Health and Preventive Medicine Monash University 3004 Melbourne Australia
Kang, Gagandeep (Chair, SEARO TAG)) Professor and Head Division of Gastrointestinal Sciences Christian Medical College 632004 Vellore India

Rees, Helen (Chair, TAG/TFI AFRO)
Executive Director
Wits Reproductive Health and HIV Institute
2001 Johannesburg
South Africa

Chairs of other WHO Immunization Advisory Groups

Griffiths, Elwyn
Chair, WHO Expert Committee on Biological Standardization
Consultant
KT2 7PT Kingston upon Thames
United Kingdom of Great Britain and Northern Ireland

Kaslow, David
Chair, Global Advisory committee on Vaccine Safety (PDVAC)
Vice President
PATH - Product Development
98121 Seattle
United States of America

Morgan, Christopher
Chair, Immunization Practices Advisory Committee (IPAC)
Principal Fellow
Centre for International Health
Macfarlane Burnet Centre for Medical Research and Public Health
3004 Melbourne
Australia

Tanner, Marcel
Director
Swiss Tropical & Public Health Institute (Swiss TPH)
4002 Basel
Switzerland

Wharton, Melinda
Chair, Global Advisory Committee on Vaccine Safety (GACVS)
Director, Immunization Services Division
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention
30333 Atlanta
United States of America

Other registered participants

Aaby, Peter
Site Leader
Bandim Health Project
2300 Copenhagen S
Denmark

Adjagba, Alex
Director
SIVAC/Agence de Médicine Préventive
75015 Paris
France

Agocs, Mary
American Red Cross
22101 Washington DC
United States of America

Alsalhani, Alain
Vaccine Pharmacist
MSF access campaign
75011 paris
France

Ba-Nguz, Antoinette
Regional Coordinator
SIVAC Initiative
Agence de Medecine Preventive
75015 Paris
France

Bergsaker, Marianne A Riise
Deputy Director
Department of Vaccines
Norwegian Institute of Public Health
0403 Oslo
Norway

Bierbrier, Rachel
Student Intern
International Vaccine Access Center
21231 Baltimore
United States of America

Birkett, Ashley
Director
Malaria Vaccine Initiative (MVI)
PATH Malaria Vaccine Initiative
20001 Washington
United States of America

Botting, Carla
Managing Director, RTS,S Malaria Vaccine Project
Malaria Vaccine Initiative (MVI)
Program for Appropriate Technology in Health
20001 Washington
United States of America

Bristol, Nellie
Senior Fellow
Global Health Policy Center
Center for Strategic and International Studies
20036 Washington
United States of America

Chuang, Yin Ching
superintendent
Infectious Disease
Chi Mei Medical Center
710 Tainan
The People's Republic of China

Cochi, Stephen
Senior Advisor
Global Immunization Division
Centers for Disease Control and Prevention
30333 Atlanta
United States of America

Curry, David
Executive Director
Division of Medical Ethics/NYU Medical School
Center for Vaccine Ethics and Policy
10016 New York City
United States of America

Cutts, Felicity
Consultant
La Londe les Maures
France

Dellepiane, Nora
Senior Regulatory Advisor
Serum Institute of India
1260 Nyon
Switzerland

Delrieu, Isabelle
Scientist
Agence de Médecine Préventive (AMP)
75015 Paris
France

Denis, Martine
Consultant
06210 Mandelieu La Napoule
France

Dochez, Carine
Director NESI
Epidemiology and Social Medicine
Network for Education and Support in Immunisation (NESI)/University of Antwerp
2610 Antwerp
Belgium

Ebirim, Obinna
Research Associate
Research
Direct Consulting and Logistics (DCL)
900271 Abuja
Nigeria

Essoh, Téné-Alima
New Vaccines introduction / Pharmacovigilance /Vaccine safety programmme
Agence de Médecine Préventive
75015 Paris
France

Ethelston, Sally
Director, Communications & Advocacy
Malaria Vaccine Initiative
PATH
20001 Washington
United States of America

Fisker, Ane
Postdoc
Research Center for Vitamins and Vaccines (CVIVA) Bandim Health Project, Statens Serum Institut, Denmark and Bandim Health Project, Guinea-Bissau
2300 Kbh S
Denmark

Gessner, Brad
Scientific Director
Agence de Médecine Préventive
75724 Paris
France

Ghani, Azra
Imperial College London
London
United Kingdom of Great Britain and Northern Ireland

Giangiulio, Anne Marie
Global Health Officer
United Nations Foundation
20006 Washington
United States of America

Hahné, Susan
Senior epidemiologist
Centre for Epidemiology and Surveillance of Infectious Diseases
RIVM
3720 BA Bilthoven
Netherlands

Hinman, Alan
Director for Programs
Center for Vaccine Equity, Task Force for Global Health
Task Force for Global Health
30030 Decatur
United States of America

Juan Giner, Aitana
Médecins Sans Frontières
75011 Paris
France

Kallenberg, Judith
Head of Policy
Gavi, The Vaccine Alliance
Geneve
Switzerland

Kingshott, Elesha
Global Health Officer
Global Health
United Nations Foundation
20006 Washington
United States of America

Kirk, Karen
Associate Director - Policy, Advocacy and Communications
International Vaccine Access Center
Baltimore
United States of America

Knoll, Maria
IVAC, International Health
Johns Hopkins School of Public Health
21231 Baltimore
United States of America

Lamontagne, D. Scott
Director, HPV vaccines and country preparedness
Vaccine Access & Delivery
Program for Appropriate Technology in Health
1218 Geneva
United States of America

Lange, John
Co-Chair, GPEI Polio Partners Group
Ambassador (Ret.) & Senior Fellow
Global Health Diplomacy
United Nations Foundation
20006 Washington
United States of America

Levine, Orin
Director, Vaccine Delivery
Global Development
Bill & Melinda Gates Foundation
98102 Seattle
United States of America

Limwattanayingyong, Attaya
EPI manager
Department of Disease Control
Bureau of General Communicable Diseases
11000 Nonthaburi
Thailand

MacNeil, Adam
Centers for Disease Control and Prevention
30333 Atlanta
United States of America

Macete, Eusebio
Director
Centro de Investigaçao em Saude da Manhiça
CP 1929 Maputo
Mozambique

Martin, Rebecca
Director, acting
Center for Global Health
U.S. Centers for Disease Control Prevention
30329 Atlanta
United States of America

Masserey Spicher, Virginie
Head Vaccinations Section
Communicable Diseases
Federal Office of Public Health
3003 Bern
Switzerland

Mengel, Martin
Coordinator - African Cholera Surveillance Network
Enteric Diseases
Agence de Médecine Preventive
75015 Paris
France

Meyer, Heidi
Paul-Ehrlich-Institut
63303 Langen
Germany

Millard, Chris
Program Manager and Research Associate
Global Health Policy Center
Center for Strategic and International Studies
22036 Washington
United States of America

Miller, Daniel
VAD Associate Director
PATH
1218 Geneva
Switzerland

Modlin, John
Deputy Director
The Bill & Melinda Gates Foundation
98102 Seattle
United States of America

Moss, William
Professor
Epidemiology
Johns Hopkins Bloomberg School of Public Health
21205 Baltimore
United States of America

Musunga, John
Head, Supranationals
Global Vaccines Commercial
GSK
1300 Wavre
Belgium

Neels, Pieter
Vaccine Advice BVBA
2980 Zoersel
Belgium

Nguyen, Thuy Linh
Johns Hopkins Bloomberg School of Public Health
21231 Baltimore
United States of America

Nic Lochlainn, Laura
Epidemiologist
Centre for Infectious Disease Control
RIVM/National Institute for Public Health and the Environment
3721 MA Bilthoven
Netherlands

Nokleby, Hanne
Chief Scientific Adviser
Norwegian Institute of Public Health
0403 Oslo
Norway

Olivé, Jean-Marc
Consultant
75016 Paris
France

Ortega-Perez, Inmaculada
Senior Project Associate
AMP-Agence Medecine Preventive
75015 Paris
France

Pagvajav, Nyamdavaa
Co-Chair
NITAG, Mongolia
14210 Ulaanbaatar
Mongolia

Palmier, Catherine
Counsellor
Canada Permanent Mission to the UN in Geneva
1202 Geneva
Switzerland

Perronne, Christian
Président de la Commission Maladies Transmissibles Haut Conseil de la Santé Publique - France
Infectious Diseases
University Hospital Raymond Poincaré
92380 Garches
France

Peyraud, Nicolas
Médecins Sans Frontières (MSF)
1205 Geneva
Switzerland

Poulton, Lynette
U.S. Department of State
Washington
United States of America

Privor-Dumm, Lois
Johns Hopkins University/IVAC
21205 Baltimore
United States of America

Romeu, Belkis
Third Secretary
Permanent Mission of Cuba
1292 Geneva
Cuba

Salvati, Anna Laura
Evaluation and Registration Office
AIFA- Italian Medicines Agency
00187 Rome
Italy

Shen, Angela
Director Access and Innovation
National Vaccine Program Office
US Department of Health and Human Services
Washington DC
United States of America

Solomon, Roma
Director
GAVI CSO Steering Committee
CORE Group Polio Project
122002 Gurgaon
India

Steinglass, Robert
Director
Immunization Center
JSI
22209 Rosslyn
United States of America

Su, Wei-Ju
Centers for Disease Control
10050 Taipei
The People's Republic of China

Thompson, Kimberly
Professor of Preventive Medicine and Global Health
College of Medicine
University of Central Florida
32832 Orlando
United States of America

Uhnoo, Ingrid
Program Manager
Unit for vaccination programs
Public Health Agency of Sweden
SE-17182 Stockholm
Sweden

Vanden Bossche, Geert
Ebola Vaccine Programme Manager
Vaccine Implementation
GAVI
1202 Geneva
Switzerland

Wonodi, Chizoba
Nigeria Program Lead/ Epidemiologist
International Health
Johns Hopkins International Vaccine Access Center (IVAC)
21205 Baltimore
United States of America

da Silva, Alfred
Executive Director
Agence de Médicine Préventive (AMP)
75015 Paris
France

de Smet, Martin
malaria coordinator
MSF intenationa office
MSF
1050 Brussels
Belgium

le Tallec, Yann Director Vaccine Delivery Clinton Health Access Initiative 8003 Zurich Switzerland
van Damme, Pierre Vaccine & Infectious Disease Institute University of Antwerp 2610 Wilrijk Belgium

Industry

Benson, Joan Executive Director Program Partnerships Merck & Co. Inc. 19486 West Point United States of America
Biernaux, Sophie Lead DDW program R&D GlaxoSmithKline Vaccines 1300 Wavre Belgium
Bigger, Laetitia Vaccines Policy, Senior Manager International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) 1211 Geneva 20 Switzerland
Ella, Krishna Murthy Chairman & Managing Director Bharat Biotech International Limited 500078 Hyderabad India
Fletcher, Mark Andrew AfME & India Medical Lead Pfizer Vaccines PFIZER Inc 75014 Paris France
Guerra-Mendoza, Yolanda GlaxoSmithKline Vaccines 1300 Wavre Belgium
Jadhav, Suresh Executive Director Quality Assurance & Regulatory Affairs Serum Institute of India Ltd. 411028 Pune India
Lapierre, Didier Head Clinical Development Malaria R&D GlaxoSmithKline Vaccines 1300 Wavre Belgium
Leach, Amanda R&D GlaxoSmithKline Vaccines 1300 Wavre Belgium

Lobos, Fernando
Business Development Director
Business Development
Sinergium Biotech S.A
B1619IEA Garín
Argentina

Meurice, Francois
Industry Representative for GSK
Ambassador Vaccines
Global Medical Affairs
GlaxoSmithKline
1300 Wavre
Belgium

Millogo, Jules
Director
International Organizations
Merck & Co., Inc.
19486 West Point
United States of America

Musunga, John
Head, Supranationals
Global Vaccines Commercial
GSK
1300 Wavre
Belgium

Oriol Mathieu, Valerie
Janssen
2333 CP Leiden
Netherlands

Poonawalla, Adar
Member of Board of Governing Council, Trustee
Serum Institute of India Research Foundation
Pune, Maharastra 411028
India

Popova, Olga
VP Global Vaccines Policy & Partnerships
Global Vaccines Policy & Partnerships
Janssen
Leiden
Netherlands

Prasad, Rayasam S
President = Global Dev. (Vaccines & Biologics)
Development (Vaccines & Biologics)
Biological E Limited
500078 Hyderabad
India

Rae, Logan
Senior Director, Government Affiars
Medical Affairs
Takeda Pharmaceuticals International GmBH
8152 Glattpark- Opfikon
Switzerland

Reers, Martin
Executive Vice President
Technical Development
BE Vaccines
44800 Nantes
France

Romero, Monica Researcher Viral Vaccines R&D Birmex 11340 Distrito Federal Mexico
Soubeyrand, Benoît Medical Director Europe Medical Affairs Europe sanofi pasteur MSD 69007 Lyon France
Stegman, Jens-Ulrich R&D GlaxoSmithKline Vaccines 13 Wavre Belgium
Suhardono, Mahendra Marketing Director Bio Farma 40161 Bandung Indonesia
Tippoo, Patrick Head Product Development and Business Development Biovac Institute 7430 Cape Town South Africa
Tsai, Theodore Head Policy Scientific Affairs Takeda Vaccines 02139 Cambridge United States of America
Viviani, Simonetta Director Clinical Development BioNet-Asia Co., Ltd. 13160 Ayutthaya Thailand
Wu, Ke BravoVax Co., Ltd. Wuhan The People's Republic of China

WHO staff

Abeysinghe, Nihal Regional Office for South-East Asia (SEARO) Vaccine Preventable Diseases, Immunization & Vaccine Development
Banerjee, Kaushik World Health Organization Immunization, Vaccines and Biologicals/EPI
Bloem, Paulus Joannes Nicolaas World Health Organization Immunization, Vaccines and Biologicals
Butler, Robb Regional Office for Europe (EURO) Vaccine Preventable Diseases and Immunization (VPI)

Chang Blanc, Diana World Health Organization Immunization, Vaccines and Biologicals/EPI
Cherian, Thomas World Health Organization Immunization, Vaccines and Biologicals/EPI
Cohen, Olivia World Health Organization Immunization, Vaccines & Biologicals
Cox, Sarah World Health Organization
Davison, Laura WHO WPRO and AMP
Diorditsa, Sergey Regional Office for the Western Pacific (WPRO)
Duclos, Philippe World Health Organization Immunization, Vaccines and Biologicals
Hutubessy, Raymond Christian W. World Health Organization Immunization, Vaccines and Biologicals/IVR
Kahn, Anna-Lea World Health Organization IVB/EPI
Kirorei Corsini, Catherine World Health Organization Immunizations, Vaccines and Biologicals (IVB)
Marti, Melanie World Health Organization Immunization, Vaccines and Biologicals
Mihigo, Richard Regional Office for Africa (AFRO) Immunization and Vaccine-Preventable Diseases
Mir, Tahir World Health Organization Polio Eradication
Moorthy, Vasee World Health Organization Immunization, Vaccines and Biologicals/IVR
Okwo-Bele, Jean-Marie World Health Organization Immunization, Vaccines and Biologicals
Ruiz Matus, Cuauhtémoc WHO Regional Office for the Americas (AMRO) Immunization/Family, Gender and Life Course
Senouci, Kamel World Health Organization DoV Project Monitoring, Immunization, Vaccines and Biologicals
Teleb, Nadia Regional Office for the Eastern Mediterranean (EMRO) Vaccine Preventable Diseases and immunization
Vannice, Kirsten World Health Organization Immunization, Vaccines and Biologicals

Zuber, Patrick Louis F.
World Health Organization
Essential Medicines and Health Products/QSS

World Health Organization
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Meeting of the Strategic Advisory Group of Experts on immunization, April 2015: conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization[1] met on 14–16 April 2015 in Geneva, Switzerland. This report summarizes the discussions, conclusions and recommendations.[2]

Report from the WHO Department of Immunization, Vaccines and Biologicals

The report focused on: the implementation of the Global Vaccine Action Plan (GVAP) and the related discussions during meetings of the WHO Governing Bodies at global and regional levels; the programmatic priorities to close the immunization gap; an update on implementation of selected SAGE recommendations; and agenda items on the horizon for future meetings.

The report stressed that reaching the GVAP goals is resource intensive (human and financial) and emphasized the urgent need for adequate investments and focus in order to increase routine immunization coverage which has been almost static, at global level, since 2009 and below the expected 90% coverage.

The report noted the current global shortage of bacille Calmette–Guérin (BCG) vaccine and proposed interim solutions while stressing the need for the global community to pay more attention and take measures to avoid future shortages of other recommended vaccines.

[1] See http://www.who.int/immunization/sage/en

[2] The complete set of presentations and background materials used for the SAGE meeting of 14-16 April 2015 together with the list of SAGE members and the summarized declarations of interests provided by SAGE members are available at http://www.who.int/immunization/sage/meetings/2015/april/en; accessed in April 2015.

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, avril 2015: conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination[1] s'est réuni du 14 au 16 avril 2015 à Genève (Suisse). Le présent rapport résume les discussions, conclusions et recommandations auxquelles il est parvenu.[2]

Rapport du Département Vaccination, vaccins et produits biologiques de l'OMS

Le rapport s'est concentré sur: la mise en œuvre du Plan d'action mondial pour les vaccins (GVAP) et les débats s'y rapportant au cours des réunions des organes directeurs de l'OMS réunis aux niveaux mondial et régional; les priorités programmatiques visant à combler les lacunes de la couverture vaccinale; un point sur la mise en œuvre de certaines recommandations du SAGE; et un aperçu des points inscrits à l'ordre du jour des futures réunions.

Le rapport a souligné que la réalisation des objectifs du GVAP exige des ressources humaines et financières importantes et qu'il est urgent d'y consacrer les investissements et les efforts requis pour améliorer la couverture de la vaccination systématique, demeurée à un niveau quasi statique à l'échelle mondiale depuis 2009, en-deçà du taux escompté de 90%.

Constatant la pénurie actuelle de vaccins par le bacille Calmette-Guérin (BCG) à l'échelle mondiale, le rapport a proposé des solutions temporaires, tout en soulignant que la communauté mondiale doit prêter une plus grande attention à la question et prendre les mesures nécessaires pour éviter des pénuries d'autres vaccins recommandés à l'avenir.

[1] Voir http://www.who.int/immunization/sage/fr/

[2] La série complète des communications et des documents de travail de la réunion du SAGE tenue du 14 au 16 avril 2015, ainsi que la liste des membres du SAGE et les résumés des déclarations d'intérêts fournies par ces derniers sont disponibles à l'adresse: http://www.who.int/immunization/sage/meetings/2015/april/en/, consulté en avril 2015.

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SAGE took note of regional progress and commended the work carried out to advance regional vaccine action plans and promote activities to strengthen routine immunization.

SAGE stressed that additional disaggregation was needed in the analysis of the progress achieved on the ground, and in identifying bottlenecks for progress, and recommended that reports display disparities observed at subnational levels.

In view of weak infrastructure in some countries with a related inability to deliver vaccines, SAGE called for new politically supported initiatives to mobilize partners and resources to apply technological know-how in fragile countries and find ways to build infrastructure in fragile systems. SAGE reaffirmed the need for solutions that simplify operations on the ground, including delivery technologies such as compact pre-filled autodisable injection technology. In this context SAGE also acknowledged the importance of the polio infrastructure and noted how it had been critical in helping to deal with the Ebola situation, particularly in Nigeria.

SAGE stressed the importance of applying rigour and science in implementation programme design and evaluation of delivery of vaccines, in order to maximize the impact of current and future vaccines and delivery technologies.

SAGE also stressed the need to draw lessons from the Ebola epidemic regarding mobilization of communities as well as the encouragement of countries and partners to mobilize the private sector.

SAGE supported WHO's plan to expand guidance beyond the current framework on the use of vaccines in humanitarian emergencies to include guidance on how to re-establish routine vaccination in those settings.

At the January 2015 WHO Executive Board meeting, Member States endorsed a resolution for pre-emptive development of vaccines against emerging infectious diseases such as Ebola virus disease. WHO was asked to provide leadership in supporting a prioritized research agenda. A framework for action in relation to vaccine development was proposed, which would include public health criteria, technical feasibility, regulatory pathways, and economic considerations. The issues will be reviewed by SAGE, the Product Development for Vaccines Advisory Committee (PDVAC), the Expert Committee on Biological Standardization (ECBS) and other forums, with the aim of reaching an agreement within a year.

A SAGE Working Group on Dengue Vaccine was established in March 2015.

Subject to the completion and conclusions of the vaccine assessment by the European Medicines Agency, it is planned that SAGE and the Malaria Programme Advisory Committee will issue policy recommendations on the use of RTS,S malaria vaccine during a joint session in October 2015.

Le SAGE a pris note des progrès accomplis au niveau régional, saluant le travail réalisé pour promouvoir les plans d'action régionaux pour les vaccins et appuyer les activités de renforcement de la vaccination systématique.

Le SAGE a jugé que l'analyse des progrès accomplis sur le terrain et l'identification des obstacles devraient être présentées de manière plus détaillée et a recommandé que les rapports futurs fassent état des disparités observées aux niveaux infranationaux.

Compte tenu de la faiblesse des infrastructures dans certains pays et des difficultés de distribution des vaccins qui en découlent, le SAGE a appelé à de nouvelles initiatives, soutenues politiquement, pour mobiliser les partenaires et les ressources nécessaires à l'application du savoir-faire technologique dans les pays vulnérables et à la mise en place d'infrastructures dans les systèmes fragiles. Le SAGE a réaffirmé la nécessité de mettre en place des solutions qui simplifient les opérations sur le terrain, notamment par l'adoption de certaines techniques d'administration des vaccins comme l'utilisation de dispositifs d'injection compacts préremplis autobloquants. Dans ce cadre, le SAGE a également reconnu l'importance de l'infrastructure mise en place pour la poliomyélite, qui a été d'une aide précieuse dans la lutte contre Ebola, en particulier au Nigéria.

Le SAGE a affirmé que la conception des programmes de mise en œuvre et l'évaluation de la distribution des vaccins devaient relever d'une approche rigoureuse et scientifique pour maximiser l'impact des vaccins et des technologies d'administration actuels et futurs.

Le SAGE a également souligné la nécessité de tirer les enseignements de l'épidémie d'Ebola pour mieux mobiliser les communautés et encourager les pays et les partenaires à impliquer le secteur privé.

Le SAGE a soutenu le projet de l'OMS visant à étendre la portée de ses lignes directrices relatives à l'utilisation des vaccins dans les situations d'urgence humanitaire pour y inclure des recommandations sur le rétablissement de la vaccination systématique dans de telles situations.

Lors de la réunion du Conseil exécutif en janvier 2015, les États Membres ont approuvé une résolution portant sur le développement anticipé de vaccins contre les maladies infectieuses émergentes comme la maladie à virus Ebola. Il a été demandé à l'OMS d'assumer le rôle de chef de file pour appuyer un programme de recherche prioritaire. Un cadre d'action relatif à la mise au point des vaccins a été proposé, traitant notamment des critères de santé publique, de la faisabilité technique, des voies réglementaires et des considérations d'ordre économique. Ces différents points seront examinés par le SAGE, le Comité consultatif sur le développement de produits pour les vaccins (PDVAC), le Comité d'experts de la standardisation biologique (ECBS) et d'autres instances dans l'objectif de parvenir à un accord dans un délai d'un an.

Un groupe de travail du SAGE sur le vaccin contre la dengue a été établi en mars 2015.

Sous réserve des conclusions de l'évaluation du vaccin menée par l'Agence européenne des médicaments, il est prévu que le SAGE et le Comité consultatif du Programme mondial de lutte antipaludique émettent des recommandations politiques sur l'utilisation du vaccin antipaludique RTS,S lors d'une session conjointe en octobre 2015.

Report from Gavi, the Vaccine Alliance

The recent key decisions by the Gavi Board and updates on the 2016–2020 strategic framework were presented, as well as programmatic and policy issues.

In December 2014, the Board endorsed Gavi's engagement in future Ebola outbreak responses through funding for vaccine production and procurement, vaccine roll-out, future vaccine preparedness, and recovery of health and immunization systems in Ebola-affected countries.

At the Gavi pledging conference in January 2015, donors pledged over US$ 7.5 billion for the next 5 years. This will enable the immunization of an additional 300 million children with the vaccines recommended by WHO, which is expected to avert 5–6 million deaths.

The 2016–2020 strategic framework will require new ways of working, focusing on: vaccine coverage and equity; developing strategies in key areas including supply chain, data and vaccine demand promotion; improving sustainability beyond co-financing; extending market shaping beyond vaccines; targeted country support; and leadership management and coordination. The current focus on finalizing the global level indicators and establishing mechanisms for tracking progress will be presented to the Board for approval in June 2015.

Regarding policy updates, the eligibility, co-financing and graduation policies are under review, towards ensuring successful graduation and sustainability of Gavi support in the 24 countries projected to graduate by 2020. Key recommendations will be submitted to the Gavi Board for consideration in June 2015. In addition, 3 focus areas have been proposed in the area of investing in data and measurements: immunization delivery, coverage and equity; surveillance of vaccine-preventable diseases; and vaccine safety.

Report of the Global Advisory Committee on Vaccine Safety (GACVS)

At its December 2014 meeting, GACVS[3] discussed preparedness for safety monitoring of new vaccines against malaria, dengue and Ebola virus and is preparing related guidance. This includes addressing safety signals from clinical trials and defining other events of special interest to propose practical approaches adapted to the context of early adopter countries. GACVS also endorsed an initial performance indicator for assessing progress towards establishing functional safety monitoring systems. It discussed criteria for assessing websites with vaccine safety information with respect to credibility, content, accessibility and design. SAGE

[3] See No. 4, 2015, pp. 17–24.

Rapport de Gavi, l'Alliance du Vaccin

Ce rapport a porté sur les principales décisions prises récemment par le conseil d'administration de Gavi et a fait le point sur le cadre stratégique 2016-2020 et ses enjeux programmatiques et politiques.

En décembre 2014, le conseil d'administration a approuvé l'engagement du Gavi dans les futures ripostes aux flambées d'Ebola, par un financement consacré à la production et à l'achat des vaccins, à leur déploiement sur les marchés, aux activités de préparation à l'administration des futurs vaccins et au rétablissement des systèmes de santé et de vaccination dans les pays touchés par l'épidémie d'Ebola.

À la conférence d'annonce des contributions de Gavi en janvier 2015, les donateurs se sont engagés à verser des contributions totalisant plus de US$ 7,5 milliards au cours des 5 prochaines années. Cette somme permettra d'administrer les vaccins recommandés par l'OMS à plus de 300 millions d'enfants supplémentaires, ce qui devrait sauver 5 à 6 millions de vies.

Le cadre stratégique 2016-2020 exigera d'adopter de nouvelles méthodes de travail, axées sur: l'équité et la couverture vaccinales; l'élaboration de stratégies dans certains domaines clés, notamment la chaîne d'approvisionnement, les données et la promotion de la demande en vaccins; le renforcement de la pérennité de l'action de Gavi au-delà du cofinancement; l'extension de l'influence de Gavi sur le marché au-delà des vaccins; l'apport d'un appui ciblé aux pays; et la gestion de l'encadrement et la coordination. Les activités actuellement entreprises pour finaliser les indicateurs au niveau mondial et mettre en place des mécanismes de suivi des progrès seront présentées à l'approbation du Conseil en juin 2015.

Concernant l'actualisation des politiques, celles sur l'éligibilité, le cofinancement et l'affranchissement progressif des pays vis-à-vis de l'aide de Gavi (politique dite de «graduation») sont en cours d'examen, l'objectif étant d'assurer la pérennité des investissements de Gavi et la réussite de la phase de transition dans les 24 pays qui devraient s'affranchir de son aide d'ici à 2020. Les principales recommandations à ce sujet seront soumises à la considération du conseil d'administration de Gavi en juin 2015. En outre, 3 domaines clés relatifs à l'investissement dans les données et le suivi ont été proposés: administration, couverture et équité de la vaccination; surveillance des maladies à prévention vaccinale; et innocuité des vaccins.

Rapport du Comité consultatif mondial de la sécurité vaccinale (GACVS)

Lors de sa réunion de décembre 2014, le GACVS[3] a discuté de l'état de préparation des systèmes de suivi de l'innocuité pour les nouveaux vaccins contre le paludisme, la dengue et le virus Ebola. Le GACVS élabore actuellement des orientations à ce sujet, portant notamment sur la prise en compte des signaux sur la sécurité vaccinale issus des essais cliniques, et la définition d'autres événements présentant un intérêt particulier pour proposer des approches pratiques adaptées au contexte des premiers pays à adopter les nouveaux vaccins. Le GACVS a également approuvé un premier indicateur de performance pour évaluer les progrès accomplis dans l'établissement de systèmes fonctionnels de suivi de l'innocuité. Il a discuté des

[3] Voir N° 4, 2015, pp. 17–24.

was pleased with the emphasis on communication as it is essential that updated and reliable safety information be provided on the internet.

SAGE noted that safety monitoring is frequently the weakest component of immunization programmes. Implementation of the Global Vaccine Safety Blueprint has enabled strengthened capacity for vaccine pharmacovigilance in several Asian and Latin American countries. Since 2014 a priority effort has begun in African countries.

Report of the Product Development for Vaccines Advisory Committee (PDVAC)

An overview was provided of the process by which PDVAC assessed the large number of vaccines in the pipeline during its first meeting in September 2014. The Jordan Report produced by the National Institute of Allergy and Infectious Diseases estimated that 110 pathogens were the subject of ongoing vaccine research and development as of 2012. These were screened to derive a list of 20 pathogens by assessing stage of development, unmet public health need, and potential role of WHO. For each of the 20 potential vaccines, a partner organization was identified to produce a global pipeline analysis using a standardized template. PDVAC was then asked to prioritize vaccines for WHO engagement according to 3 criteria: unmet public health need, likelihood of a product emerging within 5–10 years, and whether there was a clear role for WHO in advancing product development for low and middle income country (LMIC) populations.

Respiratory syncytial virus (RSV) vaccine was highlighted as a pathogen with no available vaccines, substantial disease burden, advanced vaccine development activities and a clear role for WHO in advising on trial design in LMICs, developing preferred product characteristics to guide target product profiles for use, and develop a vaccine development roadmap focusing on LMIC indications. WHO held its first RSV Vaccine Consultation in March 2015. A RSV session is planned in April 2016 to inform SAGE.

Group A & B streptococcal (GAS, GBS) vaccine development was considered to be technically feasible using a conjugated polysaccharide approach; there is a substantial disease burden and a vaccine would fit within a maternal immunization agenda for GBS. So far, there is only modest industry engagement. Enterotoxigenic Escherichia coli, Shigella and norovirus were highlighted as enteric pathogens for which PDVAC should provide WHO enabling guidance if additional resources become available.

critères pouvant être utilisés pour évaluer la crédibilité, le contenu, l'accessibilité et la conception des sites Web présentant des informations sur l'innocuité des vaccins.

Le SAGE a apprécié cette attention portée à la communication, estimant qu'il est crucial que des informations fiables et actualisées sur la sécurité soient disponibles en ligne. Le SAGE a constaté que la surveillance de l'innocuité est souvent le maillon le plus faible des programmes de vaccination. La mise en œuvre du Plan pour la sécurité vaccinale dans le monde («Global Vaccine Safety Blueprint») a permis le renforcement des capacités de pharmacovigilance des vaccins dans plusieurs pays d'Asie et d'Amérique latine. Depuis 2014, les pays africains font l'objet d'un effort prioritaire.

Rapport du Comité consultatif sur le développement de produits pour les vaccins (PDVAC)

Le SAGE a pris connaissance de la procédure générale qu'a employée le PDVAC pour évaluer les nombreux vaccins en cours d'élaboration lors de sa première réunion de septembre 2014. Le rapport *Jordan*, publié par le National Institute of Allergy and Infectious Diseases, estimait que 110 agents pathogènes faisaient l'objet de travaux de recherche-développement à visée vaccinale en 2012. Parmi ces derniers, une liste restreinte de 20 pathogènes a été sélectionnée en tenant compte du stade de développement du vaccin, des besoins de santé publique non satisfaits et du rôle potentiel de l'OMS. Pour chacun de ces 20 vaccins potentiels, un organisme partenaire a été identifié afin de produire une analyse des vaccins en cours d'élaboration à l'échelle mondiale à partir d'un modèle standard. Le PDVAC a alors été chargé de définir les vaccins propices à un engagement prioritaire de l'OMS, selon 3 critères: la présence d'un besoin de santé publique non satisfait, la probabilité que le produit soit disponible à un horizon de 5 à 10 ans et la possibilité claire pour l'OMS de promouvoir le développement du produit pour les populations des pays à revenu faible ou intermédiaire.

L'accent a été mis sur le virus respiratoire syncytial (VRS) en raison de l'absence de vaccin disponible contre cet agent pathogène, de sa forte charge de morbidité, de l'avancement des activités d'élaboration du vaccin et du rôle clair que pourrait jouer l'OMS en fournissant des conseils sur la conception des essais cliniques dans les pays à revenu faible ou intermédiaire, en identifiant les caractéristiques à privilégier pour orienter les profils cibles d'utilisation du produit et en élaborant une feuille de route de développement du vaccin qui soit axée sur les besoins des pays à revenu faible ou intermédiaire. La première consultation de l'OMS sur le vaccin contre le VRS a eu lieu en mars 2014. Une séance consacrée au VRS sera organisée pour informer le SAGE en avril 2016.

L'élaboration de vaccins contre les streptocoques des groupes A et B est considérée comme techniquement réalisable, par une approche polyosidique conjuguée. La charge de morbidité est importante et le vaccin s'inscrirait naturellement dans le programme de vaccination maternelle contre les streptocoques du groupe B. À ce jour, l'industrie n'a consacré que peu de moyens au développement de ces vaccins. Les discussions ont également porté sur *Escherichia coli* entérotoxinogène, *Shigella* et *Norovirus*, des agents entéropathogènes pour lesquels il a été estimé que le PDVAC devrait fournir des orientations d'appui à l'OMS si des ressources supplémentaires devenaient disponibles.

WHO is sometimes asked to have a role in early stage vaccine development, as with Ebola virus vaccine and monovalent oral polio vaccine development. It is important to ensure close interaction between PDVAC and SAGE, with guidance on public health criteria for vaccine development being an area identified for SAGE input. A forward looking framework on emergency vaccine development, based on lessons learnt during the 2014-5 Ebola emergency, was considered an example where PDVAC and SAGE can have synergistic and complementary interactions to provide robust advice to WHO. The development of a framework is now at the inception stage.

Polio eradication

SAGE reviewed progress towards eradication of wild poliovirus (WPV) and elimination of persistent circulating vaccine-derived poliovirus type 2 (cVDPV2) as well as the plans, preparedness and timeline for withdrawal of type 2 oral polio vaccine (OPV2).

SAGE noted that the programme had made substantial progress since the previous SAGE meeting. No WPV case has been reported in the Middle East or Africa since April 2014 and August 2014, respectively. In polio-endemic countries there were definite improvements in the quality of supplementary immunization activities (SIAs), increasing access to children in conflict-affected areas of Pakistan, improvements in AFP surveillance and expansion of environmental surveillance.

Persistent cVDPV2 transmission has been detected only in Nigeria and Pakistan since the beginning of 2014. The number of poliomyelitis cases due to cVDPV2 declined in both countries after mid-2014 following increased use of trivalent OPV (tOPV) and targeted use of inactivated polio vaccine (IPV) in SIAs. In Nigeria, the last case of persistent cVDPV2 was detected in November 2014 and the last detection in environmental surveillance was in March 2015. Circulation of the 2 persistent cVDPV2 lineages in Pakistan has been stopped, with the last case detected in June 2014. However, a new persistent cVDVP2 strain was detected in an environmental sample in Gadaap, Karachi, in July 2014, with the only case due to this strain reported in December 2014. The last detection of this strain was in an environmental sample in March 2015.

Between March 2015 and March 2016, Nigeria and Pakistan will conduct 7 and 8 large-scale tOPV campaigns, respectively, especially targeting areas affected by persistent cVDPV2. IPV will be included in tOPV campaigns in selected highest-risk areas, and intensive mopping-up will be implemented in response to detection of any cVDPV2. Both countries will focus on strengthening routine immunization to further reduce the risk of emergence of new cVDPV2. IPV was introduced in routine immunization in North and Northeast Nigeria in February 2015, in a phased nationwide introduction. IPV will be introduced in Pakistan's routine immunization programme in July 2015. SAGE noted the increased scope of planned tOPV SIAs that

On attend parfois de l'OMS qu'elle intervienne à un stade précoce du processus de mise au point des vaccins, comme cela a été le cas pour le vaccin contre le virus Ebola et le vaccin antipoliomyélitique oral monovalent. Il importe que le PDVAC et le SAGE maintiennent des contacts étroits, le SAGE pouvant fournir des orientations quant aux critères de santé publique applicables à la mise au point des vaccins. Sur la base des enseignements tirés de l'épidémie d'Ebola de 2014-2015, le PDVAC et le SAGE pourraient notamment établir une collaboration synergique et complémentaire pour élaborer un cadre prospectif de développement d'urgence des vaccins et fournir en la matière des conseils solides à l'OMS. L'élaboration de ce cadre en est à ses débuts.

Éradication de la poliomyélite

Le SAGE a examiné les progrès accomplis en vue d'éradiquer le poliovirus sauvage (PVS) et d'éliminer les poliovirus circulants dérivés d'une souche vaccinale de type 2 (PVDVc2) persistants, ainsi que la planification, l'état de préparation et le calendrier des activités de retrait du vaccin antipoliomyélitique oral de type 2 (VPO2).

Le SAGE a constaté que le programme avait considérablement progressé depuis sa dernière réunion. Aucun cas de PVS n'a été signalé au Moyen-Orient ou en Afrique depuis avril 2014 et août 2014 respectivement. Dans les pays d'endémie, des améliorations notables ont été enregistrées en termes de qualité des activités de vaccination supplémentaire (AVS), d'accès aux enfants situés dans des zones de conflit au Pakistan, de la surveillance de la PFA et d'extension de la surveillance environnementale.

Seuls le Nigéria et le Pakistan ont enregistré une transmission persistante du PVDVc2 depuis le début 2014. Dans ces 2 pays, le nombre de cas de poliomyélite dus au PVDVc2 a reculé à partir de mi-2014 suite à une utilisation accrue du vaccin antipoliomyélitique oral trivalent (VPOt) et une administration ciblée du vaccin antipoliomyélitique inactivé (VPI) lors des AVS. Au Nigéria, le dernier cas de PVDVc2 persistant a été détecté en novembre 2014 et la dernière fois que le virus a été décelé dans le cadre de la surveillance environnementale date de mars 2015. Au Pakistan, la circulation des 2 lignées persistantes de PVDVc2 a été stoppée et le dernier cas a été détecté en juin 2014. Cependant, une nouvelle souche persistante de PVDVc2 a été identifiée dans un échantillon prélevé dans l'environnement à Gadaap, à Karachi, en juillet 2014. Le seul cas imputable à cette souche a été signalé en décembre 2014. La dernière détection de cette souche, dans un échantillon environnemental, date de mars 2015.

De mars 2015 à mars 2016, le Nigéria et le Pakistan mèneront respectivement 7 et 8 campagnes à grande échelle d'administration du VPOt, ciblant en particulier les zones concernées par les PVDVc2 persistants. Le VPI sera intégré aux campagnes d'administration du VPOt dans certaines zones à très haut risque et des opérations intensives de ratissage seront mises en œuvre en cas de détection de PVDVc2. Les 2 pays s'attacheront à renforcer la vaccination systématique pour réduire encore le risque d'émergence d'un nouveau PVDVc2. En février 2015, le VPI a été intégré à la vaccination systématique dans les régions du nord et du nord-est du Nigéria, dans le cadre d'une introduction échelonnée à l'échelle nationale. Au Pakistan, le VPI sera inscrit dans le programme de vaccination systématique en juillet 2015. Le SAGE a noté que les AVS d'administration du

will be implemented to reduce the risk of emergence of new cVDPV2, building on the risk-based approach endorsed by SAGE in October 2014.

SAGE endorsed the proposed cVDPV2 elimination strategies in Nigeria and Pakistan and the programme's risk-based approach to prevent and respond to new cVDPV2 emergence in any location. Detection of VDPV2 from any source will result in a detailed epidemiologic investigation and risk assessment. The findings of the investigation and risk assessment, including any evidence of circulation of the VDPV, likelihood of spread, and proximity of date of detection to the date of OPV2 withdrawal, will inform the nature of the response. In addition to the full implementation of planned tOPV campaigns, the range of responses will include intensified surveillance, mopping-up and targeted use of IPV.

SAGE concluded that progress towards elimination of persistent cVDPV2 is on track. SAGE recommended that all countries and GPEI should plan firmly for April 2016 as the designated date for withdrawal of OPV2. SAGE will consider delaying OPV2 withdrawal only if the WG reports in October 2015 that the assessed risk of continued cVDPV2 transmission is high. SAGE requested the polio WG to continue monitoring progress towards cVDPV2 elimination and ensuring that remaining challenges are addressed including contingencies for vaccine supplies (IPV, bOPV and tOPV), registration of bOPV for routine use, surveillance sensitivity, and reaching inaccessible children. The Working Group will make a full report to SAGE in October 2015, when SAGE may reconfirm April 2016 as the definite date for OPV2 withdrawal.

SAGE endorsed the proposed approach to verification of compliance of poliovirus containment in essential facilities. Under the WHO Global Action Plan (GAP III), facilities planning to handle or store type 2 poliovirus are requested to implement containment measures and appropriately manage associated biorisks. National Regulatory Authorities for containment (NRAcs) are expected to certify facilities according to GAP III. Certification reports are submitted to Regional Certification Commissions (RCCs) for evaluation. In support of this process, RCCs, NRAcs or concerned facilities may request that WHO verify compliance of certified facilities in keeping with GAP III. SAGE requested that the programme consider mechanisms to address the risks associated with research and therapeutic uses of live polioviruses.

Finally, SAGE noted the importance of the work on the polio legacy and asked for a full report on this at its October 2015 meeting.

VPOt devant être menées pour réduire le risque d'émergence de nouveaux PVDVc2 seront d'une portée accrue, reposant sur l'approche fondée sur le risque adoptée par le SAGE en octobre 2014.

Le SAGE a approuvé les stratégies proposées pour éliminer les PVDVc2 au Nigéria et au Pakistan, ainsi que l'approche fondée sur le risque adoptée par le programme pour prévenir et combattre l'émergence de nouveaux PVDVc2 en tout point de la planète. La détection de PVDV2, quelle qu'en soit la source, donnera lieu à une enquête épidémiologique et une évaluation des risques complètes. La nature de la riposte sera décidée au regard des résultats de ces enquêtes, en tenant compte notamment des signes éventuels de circulation de PVDV, de la probabilité de propagation et de la proximité entre la date de la détection et la date de retrait du VPO2. Outre la pleine mise en œuvre des campagnes prévues d'administration du VPOt, la riposte s'appuiera aussi bien sur une intensification de la surveillance que sur des opérations de ratissage, en passant par l'administration ciblée du VPI.

Le SAGE a conclu à la bonne progression des activités visant à éliminer les PVDVc2 persistants. Il a recommandé que tous les pays, ainsi que l'Initiative mondiale pour l'éradication de la poliomyélite, se fixent l'échéance d'avril 2016 pour le retrait du VPO2. Le SAGE n'envisagera de reporter le retrait du VPO2 à une date ultérieure que si le rapport d'octobre 2015 du Groupe de travail fait état d'un risque élevé de poursuite de la transmission du PVDVc2. Le SAGE a demandé au groupe de travail sur la poliomyélite de continuer à suivre les progrès accomplis en vue d'éliminer le PVDVc2 et de veiller à ce que des solutions soient apportées aux problèmes qui subsistent, comme la prévision de stocks de vaccins suffisants en cas d'urgence (VPI, VPOb et VPOt), l'homologation du VPOb aux fins d'une administration systématique, la sensibilité de la surveillance et la couverture des enfants dans les zones inaccessibles. Le groupe de travail présentera un rapport complet au SAGE en octobre 2015, sur la base duquel le SAGE décidera si l'échéance d'avril 2016 peut être confirmée pour le retrait du VPO2.

Le SAGE a approuvé l'approche proposée pour vérifier la conformité des principales installations de confinement du poliovirus. Au titre du Plan d'action mondial de l'OMS (GAP III), il est demandé aux centres dans lesquels des poliovirus de type 2 doivent être manipulés ou stockés d'appliquer les mesures de confinement et de gérer convenablement les risques biologiques associés. La certification de ces centres par les autorités nationales de réglementation chargées du confinement devrait se faire conformément au GAP III. Les rapports de certification sont soumis aux commissions régionales de certification pour évaluation. Pour appuyer ce processus, les commissions régionales de certification, les autorités nationales de réglementation du confinement ou les centres concernés peuvent demander à l'OMS de vérifier la conformité des installations certifiées au regard du GAP III. Le SAGE a demandé que le programme envisage de définir des mécanismes pour aborder les risques associés à l'utilisation de poliovirus vivants pour la recherche ou à des fins thérapeutiques.

Enfin, le SAGE a relevé l'importance des travaux engagés sur la transmission des acquis de la lutte contre la poliomyélite et demandé qu'un rapport complet à ce sujet lui soit présenté lors de sa réunion d'octobre 2015.

Administration of multiple injectable vaccines in a single visit

Many countries administer multiple vaccine injections (including ≥3 injections) to infants in a single visit and achieve high vaccine coverage and acceptability. Other countries, particularly LMICs, are in the process of introducing additional injectable vaccines into their routine immunization schedule including pneumococcal conjugate vaccine (PCV) and IPV, which will make receiving 3 injections during a single visit a common occurrence. In this context, some countries have raised concern about the administration of multiple injectable vaccines in a single infant vaccination visit, both for the primary schedule when DTP-HepB-Hib (i.e. pentavalent vaccine) is given and in older infant and toddlers visits. Consequently, SAGE had requested a systematic review of the evidence on the safety of administering multiple injectable vaccines during a single visit (specifically for IPV, PCV and pentavalent vaccines – other combinations were not reviewed at this time), techniques for administering multiple injectable vaccines, and evidence on health-care provider and infant caregiver attitudes and practices regarding multiple injections.

The review showed that multiple injections of the studied vaccines are generally well tolerated by infants and found no increase in reactogenicity compared with vaccines injected in separate visits. The thigh (vastus lateralis) is the generally recommended site for intramuscular (IM) injections, with the hip muscles (ventrogluteal area) also acceptable; the deltoid muscle is not preferred in infants due to inadequate muscle mass. IM administration for IPV appears to provide equal immunogenicity and fewer local reactions than subcutaneous (SC) administration. The review provided no clear evidence for a specific distance between injection sites or for a preferred vaccine preparation process for a multiple injections visit.

Studies on provider and caregiver attitudes and practices indicated that both have concerns about infant pain, potential vaccine side effects and uncertainty about vaccine effectiveness when multiple vaccines are given during the same visit. Parental acceptance of all injections was associated with a positive provider recommendation to the caregiver and high concern about the severity of the disease against which the child is being vaccinated. Providers often overestimated caregiver concerns about multiple injections. Nearly all studies were conducted in high income countries, although two recent studies in Tanzania and South Africa reported similar results, with very high rates of acceptance of multiple injections (97%) despite approximately half of caregivers expressing some level of concern (52%), demonstrating that concerns can be addressed with effective communication and immunization practices.

SAGE reviewed the evidence on the administration of IPV, pentavalent and PCV vaccines during the same visit

Administration en une seule visite de plusieurs vaccins injectables

De nombreux pays administrent aux nourrissons plusieurs vaccins injectables en une seule visite (parfois ≥3 injections) et parviennent à des taux élevés de couverture et d'acceptation de la vaccination. D'autres pays, en particulier parmi les pays à revenu faible ou intermédiaire, sont en train d'introduire de nouveaux vaccins injectables dans leurs calendriers de vaccination systématique, notamment le vaccin antipneumococcique conjugué (VPC) et le VPI, l'administration concomitante de 3 injections en une seule visite étant ainsi appelée à devenir courante. Dans ce cadre, certains pays ont fait part de leurs inquiétudes quant à l'injection concomitante de plusieurs vaccins aux nourrissons, tant pour la primovaccination DTC-hépatite B-Hib (vaccin pentavalent), que lorsqu'il s'agit de nourrissons plus âgés et de très jeunes enfants. De ce fait, le SAGE avait demandé un examen systématique des données sur la sécurité de l'administration concomitante de plusieurs vaccins injectables (axé spécifiquement sur le VPI, le VPC et le vaccin pentavalent, cet examen ne portant pas encore sur les autres associations), ainsi qu'une étude des techniques employées pour l'administration de plusieurs vaccins injectables et des données relatives aux attitudes et aux pratiques des prestataires de santé et des parents ou des autres personnes responsables à l'égard des injections multiples.

Cet examen a conclu que l'injection concomitante des vaccins étudiés est généralement bien tolérée par les nourrissons, sans augmentation de la réactogénicité par rapport à l'injection de ces vaccins lors de visites distinctes. La cuisse (muscle vaste externe) est le site généralement recommandé pour les injections intramusculaires, mais les muscles de la hanche (zone ventrogluétale) sont également acceptables; l'injection dans le muscle deltoïde n'est pas recommandée chez le nourrisson en raison de sa masse musculaire insuffisante. L'injection intramusculaire du VPI semble fournir le même niveau d'immunogénicité avec moins de réactions locales que l'administration sous-cutanée. Cet examen n'a pas mis en évidence de distance spécifique entre les sites d'injection, ni de processus de préparation des vaccins à privilégier pour l'administration de plusieurs injections en une seule visite.

Les études sur les attitudes et les pratiques des prestataires de soins et des parents ou des autres personnes responsables indiquent qu'ils ont tous 2 des inquiétudes quant à la douleur ressentie par le nourrisson, les effets secondaires potentiels et l'efficacité des vaccins lorsqu'ils sont administrés lors de la même visite. Les parents acceptaient d'autant mieux ces injections concomitantes que le prestataire de soins leur avait recommandé et que la maladie contre laquelle ils vaccinaient leur enfant les inquiétait de par sa gravité. Les prestataires surestimaient souvent les inquiétudes des parents à l'égard des injections multiples. Presque toutes ces études ont été menées dans des pays à revenu élevé, mais 2 études récentes réalisées en République-Unie de Tanzanie et en Afrique du Sud ont donné des résultats analogues, avec un taux très élevé d'acceptation des injections multiples (97%) malgré les inquiétudes exprimées par environ la moitié des parents ou des autres personnes responsables (52%), ce qui démontre qu'il est possible de répondre à ces inquiétudes par des pratiques de vaccination et une communication efficaces.

Le SAGE a examiné les données relatives à l'administration du VPI, du vaccin pentavalent et du VPC lors d'une même visite

and found that evidence supports co-administration of these vaccines. SAGE noted that combinations of other vaccines can be considered at the country level, provided that countries have reviewed evidence on immunogenicity and safety in multiple injection visits.

For IPV, pentavalent and PCV vaccines the recommendation is to administer vaccines IM due to evidence of equal immunogenicity but better tolerability than by the SC route. The SC route is a viable alternative for vaccines where this is indicated on the label. When 3 injections are given, 1 injection should be administered in 1 limb and 2 injections in the other limb, separated sufficiently to differentiate local reactions. A common acceptable practice is to separate same limb injections by 2.5 cm (approximately 1 inch).

SAGE recommended that countries provide training to health-care workers on vaccine co-administration practices, including techniques to mitigate pain at the time of vaccination, information about safety and effectiveness of vaccines when co-administered, information about the likely overestimation of parental concerns, as well as training on improved communication strategies with parents to assure them of the safety, effectiveness and value of multiple vaccine injections.

SAGE supported the following Good Practice Statement on multiple vaccine injections in a single visit, recognizing that the country context is an important determinant of success and acceptability among caregivers and providers: *National vaccination schedules recommending administration of multiple injections in the same visit are widely used and provide benefits insofar as they support timely and efficient vaccination of children. Where studies have evaluated the immunogenicity and safety of co-administered vaccines, these practices are encouraged based on the benefits they confer.*

SAGE concluded that countries should not make modifications to recommended immunization schedules with the aim of preventing multiple injections during the same visit when such modifications are not evidence-based.

SAGE noted the need for further research on multiple injections during the same visit and recommended the following research topics and activities: (i) impact of multiple injections in the same visit on vaccine coverage, disease reduction, vaccine programme success and caregiver and provider experience; (ii) development of a standardized monitoring protocol for acceptance and acceptability by caregivers and providers and for prevalence of adverse events; (iii) development of optimal provider and infant caregiver communication approaches; (iv) optimal multiple injection administration techniques, and (v) development of new technologies, such as intradermal patches and new combination vaccines, which would decrease the number of vaccine injections in a single visit.

et conclu qu'elles sont favorables à la coadministration de ces vaccins. Le SAGE a indiqué que d'autres associations de vaccins peuvent être envisagées au niveau national, tant que leur immunogénicité et leur innocuité ont été étudiées lors des injections concommitantes.

Pour les vaccins VPI, pentavalent et VPC, il est recommandé de privilégier l'administration intramusculaire, qui présente le même niveau d'immunogénicité que l'administration sous cutanée, avec une meilleure tolérance. La voie sous-cutanée est une solution de remplacement viable lorsque ce mode d'administration est indiqué sur l'étiquette. Lorsque 3 injections sont administrées, il convient de procéder à l'une d'entre elles dans une jambe, et aux 2 autres dans l'autre jambe, à une distance suffisante pour pouvoir distinguer les réactions locales. La pratique courante consiste à espacer les injections pratiquées sur la même jambe de 2,5 cm (environ 1 pouce).

Le SAGE recommande aux pays de former les agents de santé aux pratiques de coadministration des vaccins, y compris aux techniques d'atténuation de la douleur lors de la vaccination, de les informer sur l'innocuité et l'efficacité des vaccins coadministrés et sur la tendance à surestimer l'inquiétude des parents, et de leur fournir des stratégies pour mieux communiquer avec les parents et les assurer de la sécurité, de l'efficacité et de l'utilité des injections concomitantes de vaccins.

Le SAGE a appuyé la déclaration de bonnes pratiques suivante concernant l'injection de plusieurs vaccins en une seule visite, tout en reconnaissant que le contexte spécifique du pays est un facteur déterminant de réussite et d'acceptation de la part des prestataires de soins et des parents ou des autres personnes responsables: *les calendriers de vaccination nationaux recommandant l'administration de plusieurs injections lors d'une même visite sont largement utilisés et offrent des avantages car ils permettent une vaccination en temps utile et efficace des enfants. Dans la mesure où l'immunogénicité et l'innocuité des vaccins coadministrés ont été évaluées, ces pratiques de vaccination sont recommandés en raison des bénéfices qu'ils procurent.*

Le SAGE a conclu que les pays ne doivent pas modifier les calendriers de vaccination recommandés dans le seul objectif d'éviter les injections multiples au cours d'une même visite lorsqu'une telle démarche ne repose pas sur des bases factuelles.

Le SAGE a constaté un besoin de recherches supplémentaires sur le sujet des injections concomitantes lors d'une même visite et a recommandé les activités et thèmes de recherche suivants: i) l'incidence des injections concomitantes sur la couverture vaccinale, le recul de la morbidité, le succès des programmes de vaccination et l'expérience des parents et des prestataires de soins de santé; ii) l'élaboration d'un protocole normalisé de suivi de l'acceptation et de l'acceptabilité de la part des parents et des prestataires de santé et de la prévalence des manifestations indésirables; iii) la définition d'approches de communication optimales entre le personnel de santé et les parents ou les autres personnes responsables; iv) les techniques optimales d'administration concomitante de plusieurs injections; et v) la mise au point de nouvelles techniques, comme les timbres intradermiques et de nouveaux vaccins conjugués, qui permettraient de réduire le nombre d'injections réalisées lors d'une même visite.

Reducing pain and distress at the time of vaccination

Vaccine injections are a common source of iatrogenic pain and distress including among newborns. Concerns about pain by parents, children, adolescents, adults and health-care providers are common (30%–70%) in all settings where it has been asked about. Not addressing pain may have a negative impact on health behaviours and may lead to avoidance of future injections, including vaccination. While many immunization programmes have sustained high coverage without addressing it, mitigating pain at time of vaccination should be considered part of good immunization and clinical practice.

A Technical Consultation Group (TCG) on reducing pain and distress at the time of vaccination reviewed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Cochrane based HELPinKids&Adults 2.0 2015 Canadian Clinical Practice Guidelines (CPG) that systematically reviewed 55 possible interventions to mitigate pain at the time of vaccination. Of 136 articles reviewed, 34 (25%) came from low and middle income countries (LMICs). The GRADE-DECIDE process (benefits and harms, resource utilization and value for money, impact on equity, acceptability, feasibility and other considerations) was used to adapt the recommendations to global settings and propose recommendations to SAGE.

Based on the report of the TCG, SAGE concluded that there are effective, feasible, culturally acceptable and age-relevant evidence based interventions that can help mitigate pain and distress at the time of vaccination and that are recommended for national programmes.

Recommended interventions include:

1. For all ages: no aspiration for IM injection; administration of vaccines in order of increasing painfulness; proper positioning, i.e. holding infants and children less than 3 years, and sitting for those over 3 years of age; use of neutral words, avoidance of language that increases anxiety and/or promotes distrust.
2. For infants and children: breastfeeding (if feasible and culturally acceptable) during or just before injection; when part of the schedule, administration of rotavirus vaccine immediately prior to vaccine injection (the formulation of the currently licensed liquid rotavirus vaccines has been shown to have a pain mitigating effect through their sucrose content). For children under 6 years of age, caregiver presence and distraction such as music are recommended.
3. For adults: distraction with coughing or breath-holding.

For adolescents: no additional evidence-based age-specific recommendations are available.

Atténuation de la douleur et de la souffrance lors de la vaccination

L'injection de vaccins est souvent une source de douleur et de souffrance iatrogènes, y compris chez le nouveau-né. L'inquiétude face à la douleur est fréquente (30-70%) chez les parents, les enfants, les adolescents, les adultes et les professionnels de la santé, quel que soit le milieu où la question leur est posée. Si la question de la douleur n'est pas abordée, cela peut avoir des effets négatifs sur les comportements en matière de santé, risquant d'inciter les patients à éviter les injections futures, et notamment à ne pas se faire vacciner. Bien que de nombreux programmes de vaccination parviennent à maintenir un fort taux de couverture sans traiter de la question, l'atténuation de la douleur lors de la vaccination devrait être une composante importante des bonnes pratiques cliniques et vaccinales.

Un groupe consultatif technique sur la réduction de la douleur et de la souffrance lors de la vaccination a étudié les directives de pratiques cliniques canadiennes HELPinKids&Adults 2.0 2015 basées sur les approches GRADE et Cochrane, qui dressent un bilan systématique de 55 interventions possibles pour atténuer la douleur lors de la vaccination. Sur les 136 articles examinés, 34 (25%) provenaient de pays à revenu faible ou intermédiaire. Le processus GRADE-DECIDE (avantages et inconvénients, utilisation des ressources et rentabilité, incidence sur l'équité, l'acceptabilité, la faisabilité et d'autres aspects) a été utilisé pour adapter les recommandations au niveau mondial et proposer des recommandations au SAGE.

Sur la base du rapport du groupe consultatif technique, le SAGE a conclu que certaines interventions efficaces, réalisables, culturellement acceptables, adaptées à l'âge des patients et fondées sur des données probantes peuvent contribuer à atténuer la douleur et la souffrance lors de la vaccination et sont recommandées pour les programmes nationaux.

Parmi les interventions recommandées figurent:

1. Pour tous les âges: pas d'aspiration lors des injections intramusculaires; administration des vaccins par ordre de douleur croissante; positionnement correct du patient, qui doit être tenu s'il s'agit d'un nourrisson ou d'un enfant de moins de 3 ans et être assis s'il a plus de 3 ans; utilisation de mots neutres, en évitant les termes qui risquent de susciter l'angoisse ou la méfiance.
2. Pour les nourrissons et les enfants: allaiter au sein durant l'injection ou juste avant (si cela est possible et culturellement acceptable); si un vaccin antirotavirus est prévu dans le calendrier de vaccination, l'administrer juste avant l'injection des vaccins (la formulation des vaccins antirotavirus liquides actuellement homologués atténue la douleur du fait de sa teneur en sucrose). Pour les enfants de moins de 6 ans, la présence d'un parent est conseillée, ainsi que des distractions, comme de la musique.
3. Pour les adultes: distraire le patient en lui demandant de tousser ou de retenir sa respiration.

Pour les adolescents: les études n'ont mis en évidence aucune autre recommandation spécifique pour cette tranche d'âge.

There is little evidence on the impact of the setting where vaccination is carried out. However, based upon observations and principles, immunization-associated anxiety and related events (e.g. fainting, mass psychogenic illness), such as those that can arise in large open immunization clinics, in school based programmes and in mass campaigns, might be mitigated in part by ensuring more privacy.

Topical anaesthetics, while effective, are not recommended for global use because of cost, lack of general availability and additional time required to use them. Interventions not recommended due to lack of evidence of effectiveness and potential for altering vaccine effectiveness include warming the vaccine, and proactive systematic administration of oral analgesics (e.g. acetaminophen and ibuprofen) at the time of vaccination (these can be given some time after vaccination to mitigate pain and fever linked to delayed reactogenicity if any).

To support implementation, SAGE recommends that WHO: 1) includes pain mitigation recommendations with WHO immunization practice guidance materials; 2) disseminates pain/distress mitigation recommendations through the usual dissemination channels, immunization managers, National Immunization Technical Advisory Group (NITAG) and partner organizations; 3) monitors and evaluates the implementation success of pain mitigation measures; 4) works with industry, ECBS and regulatory agencies to advocate that grading of pain experienced during the vaccine injection be included in data for licensing and in the product monograph.

For countries, the following recommendations at the health system level include: (i) mitigation of pain and distress at the time of injection as part of good vaccination clinical practice; (ii) recommending preferred order of injection for country-specific vaccination schedules where possible; and (iii) inclusion of vaccine pain mitigation in health-care workers' training curricula.

It is recommended that pre-service education of health-care workers: (i) ensures understanding and appreciation of pain with vaccination by injection; and (ii) includes content on recognition of pain and distress during vaccination and mitigation strategies. Education about vaccination pain mitigation is recommended for caregivers, and those receiving vaccines who are old enough to be educated (older children, adolescents, adults). This could occur during pre-natal visits, with breastfeeding education, and at the time of vaccination. Methods might include giving pamphlets, individual or group verbal instructions, posters, and other techniques.

Il existe très peu d'informations sur l'effet éventuel du cadre dans lequel la vaccination a lieu. Cependant, certaines observations pratiques et théoriques laissent penser que l'angoisse liée à la vaccination et d'autres effets associés (par exemple, évanouissement, phénomène psychogénique de masse) observés dans de grands centres de vaccination, dans le cadre de la vaccination en milieu scolaire ou lors de campagnes de masse pourraient en partie être atténués si les vaccins étaient administrés dans un cadre plus respectueux de l'intimité des patients.

Les anesthésiques topiques sont certes efficaces, mais leur utilisation n'est pas recommandée à l'échelle mondiale en raison de leur coût, de leur manque de disponibilité et du temps supplémentaire requis pour les utiliser. Les interventions suivantes ne sont pas recommandées, d'une part parce que leur utilité n'a pas été démontrée, et d'autre part parce qu'elles risquent de compromettre l'efficacité du vaccin: chauffage du vaccin et administration proactive systématique d'analgésiques oraux (par exemple, paracétamol et ibuprofène) au moment de la vaccination (ces derniers peuvent parfois être administrés quelque temps après la vaccination pour atténuer la douleur et la fièvre associées à une réactogénicité retardée éventuelle).

Pour permettre la bonne mise en œuvre de ces recommandations, le SAGE conseille à l'OMS: i) d'inclure les recommandations relatives à l'atténuation de la douleur dans les documents d'orientation de l'OMS sur les pratiques vaccinales; ii) de divulguer les recommandations relatives à l'atténuation de la douleur et de la souffrance par le biais des canaux de diffusion habituels, des gestionnaires des programmes de vaccination, des groupes consultatifs techniques nationaux sur la vaccination et des organismes partenaires; iii) de suivre et évaluer les résultats de l'application des mesures d'atténuation de la douleur; iv) de collaborer avec l'industrie, le Comité d'experts de la standardisation biologique et les organismes de réglementation pour préconiser l'inclusion du niveau de la douleur ressentie lors de l'injection dans les données fournies aux fins de l'homologation et dans la monographie du produit.

Au niveau national, les recommandations suivantes s'appliquent aux systèmes de santé: i) intégrer l'atténuation de la douleur et de la souffrance lors de l'injection dans les bonnes pratiques cliniques vaccinales; ii) recommander un ordre spécifique d'administration des injections prévues dans le calendrier de vaccination de chaque pays, dans la mesure du possible; et iii) inclure l'atténuation de la douleur dans les programmes de formation des agents de santé.

Il est recommandé de veiller à ce que la formation préalable à l'entrée en service des agents de santé leur permette de: i) mieux comprendre et apprécier la douleur associée à la vaccination par injection; et ii) reconnaître la douleur et la souffrance lors de la vaccination et adopter des stratégies d'atténuation. Il est par ailleurs recommandé de fournir des informations sur l'atténuation de la douleur lors de la vaccination aux parents ou autres personnes responsables des enfants devant se faire vacciner, ainsi qu'aux patients eux-mêmes s'ils sont suffisamment âgés (grands enfants, adolescents, adultes). Cela pourrait être fait à l'occasion de visites prénatales, de séances d'information sur l'allaitement maternel, ou au moment de la vaccination. Les méthodes employées peuvent aller de la distribution de brochures à une instruction orale, individuelle ou en groupe, en passant par l'affichage de posters ou d'autres moyens.

Priority research areas include studies on: (i) the extent of concerns about pain at vaccination and its impact on vaccine hesitancy and acceptance in LMICs; (ii) other effective interventions, particularly for adolescents; (iii) interventions that are effective in mass campaigns and school-based programme settings; and (iv) assessing which vaccines are more and less painful on injection.

Les domaines de recherche prioritaires sont les suivants: i) degré d'inquiétude à l'égard de la douleur lors de la vaccination dans les pays à revenu faible et intermédiaire, et conséquences en termes de réticence ou d'acceptation de la vaccination; ii) autres interventions pouvant être efficaces, en particulier pour les adolescents; iii) interventions efficaces dans le cadre des campagnes de masse ou de la vaccination en milieu scolaire; et iv) détermination du degré de douleur ressenti selon le vaccin injecté.

Sustainable access to vaccines in middle-income countries (MICs): report of the WHO-convened MIC Task Force

The MIC Task Force, a group of 9 immunization partners, presented a proposed strategy for coordinated action to enhance sustainable access to vaccines in MICs. Over the past decade, access to vaccines in MICs has been much debated, fuelled by the fact that the majority of poor people are now in MICs and concern that this group of countries may be missing out on opportunities to introduce new vaccines, as donors focus on low-income countries. In view of this situation and at the request of SAGE, in June 2014 WHO convened the MIC Task Force to develop a coordinated strategy and plan of action.

A comprehensive review of MICs' performance shows that they are far from attaining the GVAP targets. While 40 MICs are well supported by Gavi, 63 do not benefit from a unified international strategy for action. In these countries, vaccine-preventable disease burden and numbers of unvaccinated children are relatively low compared to the Gavi-supported MICs, but nonetheless substantial and unacceptable. Many of these countries have strong health systems and potential for rapid gains if key barriers are removed. The MIC strategy, aligned with the GVAP time frame (2016–2020), proposes a way forward for non-Gavi countries. Importantly, solutions and platforms set up as part of the strategy would also benefit countries that graduate from Gavi support over time, ensuring sustainability of current investments.

The Task Force has undertaken a detailed survey of the needs of non-Gavi MICs and the types of support currently provided to these countries by immunization partners. The Task Force confirmed that that the issues of access to affordable prices and timely supply are main challenges for MICs, yet agreed that they should not be tackled in isolation and that activities to consolidate demand are key to success. Four main areas of action have been identified as the pillars of the MIC strategy: (i) strengthening evidence-based decision-making; (ii) enhancing political commitment in specific countries and ensuring financial sustainability of immunization programmes; (iii) enhancing demand for and equitable delivery of immunization services; and (iv) improving access to timely and affordable vaccine supplies. Within each area, the Task Force identified a set of focus activities and lead agencies, making this

Accès durable aux vaccins dans les pays à revenu intermédiaire (PRI): rapport du Groupe spécial sur les PRI convoqué par l'OMS

Le Groupe spécial sur les pays à revenu intermédiaire (PRI), constitué de 9 partenaires de la vaccination, a présenté la stratégie qu'il propose pour assurer une action coordonnée visant à renforcer l'accès durable aux vaccins dans les pays à revenu intermédiaire. Au cours des dix dernières années, l'accès aux vaccins dans les PRI a fait l'objet de nombreux débats, alimentés par le fait que la population pauvre mondiale se trouve aujourd'hui en majeure partie dans les PRI et par l'inquiétude de voir ce groupe de pays laissé pour compte en termes d'introduction des nouveaux vaccins, les bailleurs de fonds accordant l'essentiel de leur aide aux pays à revenu faible. Pour cette raison, et à la demande du SAGE, l'OMS a convoqué un Groupe spécial sur les PRI en juin 2014, le chargeant d'élaborer une stratégie et un plan d'action coordonnés.

Un examen approfondi de la performance des PRI révèle qu'ils sont loin d'atteindre les cibles du GVAP. Parmi ces pays, 40 bénéficient d'un appui soutenu de Gavi, mais 63 autres ne font l'objet d'aucune stratégie internationale harmonisée. Dans ces derniers, la charge des maladies à prévention vaccinale et le nombre d'enfants non vaccinés sont relativement faibles par rapport aux PRI soutenus par Gavi, mais demeurent toutefois à un niveau conséquent et inacceptable. Nombre de ces pays disposent de systèmes de santé solides et ont la capacité de progresser rapidement si certains obstacles clés sont éliminés. La stratégie pour les PRI, dont le calendrier est aligné sur celui du GVAP (2016-2020), propose une marche à suivre pour les pays ne bénéficiant pas du soutien de Gavi. Il importe de noter que les solutions et les plateformes mises en place dans le cadre de cette stratégie bénéficieraient également aux pays qui s'affranchiront peu à peu de l'aide de Gavi, garantissant la pérennité des investissements consentis.

Le Groupe spécial a entrepris une enquête détaillée sur les besoins des PRI ne bénéficiant pas de l'aide de l'Alliance et sur le type de soutien qui leur est actuellement offert par les partenaires de la vaccination. Il a confirmé que les problèmes principaux auxquels les PRI sont confrontés ont trait à l'accès à prix abordable et en temps utile aux vaccins, mais a convenu que ces aspects ne peuvent être traités de manière isolée et que la clé de la réussite réside également dans l'organisation d'activités visant à renforcer la demande. Quatre principaux domaines d'action ont été définis, constituant les piliers de la stratégie pour les PRI: i) renforcer le processus décisionnel fondé sur des données probantes; ii) renforcer l'engagement politique dans certains pays et assurer la viabilité financière des programmes de vaccination; iii) accroître la demande à l'égard des services de vaccination et veiller à leur équité; iv) améliorer l'accès aux vaccins à prix abordable et en temps utile. Dans chaque domaine d'action, le Groupe spécial a identifié un ensemble d'activités

the first comprehensive and coordinated strategy targeting MICs.

Critical to the MIC strategy is country-level political and financial commitment to immunization. To foster country ownership and account for considerable heterogeneity, the Task Force designed the strategy as a menu of options, from which countries can select the types of assistance they identify as priorities.

The Task Force evaluated the financial cost to provide technical support to MICs at approximately US$ 20 million per year for 5 years. Without predictable financial resources, only limited and fragmented efforts will be possible.

SAGE acknowledged that the strategy represents a strong proposal for a coordinated and comprehensive approach to the MIC situation. SAGE concurred with the general direction of the strategy and valued the menu of options as an approach to tailoring activities to the individual needs of a heterogeneous group of countries. SAGE appreciated that the strategy builds upon lessons learnt and existing activities as the most efficient way to use resources and achieve impact.

SAGE called on partners to support implementation of the strategy and on countries to take advantage of the proposed solutions.

SAGE noted that prompt implementation of the MIC strategy is particularly important given the impending graduation of several large Gavi countries, which will require long-term solutions to be put in place.

SAGE pointed to the need for innovation and creativity to bring the strategy forward to its implementation phase. The intention to expand access to revolving funds through the Vaccine Independence Initiative received particularly positive support as well as the potential involvement of development banks to attract longer-term national financial commitments. SAGE recognised that a critical next step will be to engage with high level country leaders to assess the level of country commitment.

SAGE recognized the importance of access to affordable and timely vaccine supplies but stressed that other areas should not be minimized. On access to affordable prices, the lack of proposals to engage MIC manufacturers was noted. SAGE recommended that the strategy be aligned with the Global Investment Framework for Women's and Children's Health and the Global health 2035 analysis, and noted that some of the approaches proposed may be useful in addressing challenges that MICs face in accessing other health commodities.

SAGE called upon WHO Secretariat to report back on progress in implementation of the strategy.

Ebola vaccines and vaccination

An update was presented on the status of: 1) the ongoing epidemic, 2) vaccine development, and 3) prepara-

ciblées et d'organismes pouvant jouer le rôle de chef de file, faisant de cette initiative la première stratégie globale et coordonnée axée sur les PRI.

L'engagement des pays, sur le plan politique et financier, en faveur de la vaccination est un élément déterminant de la stratégie pour les PRI. Pour favoriser l'appropriation par les pays et tenir compte des disparités considérables existant d'un pays à l'autre, le Groupe spécial a conçu cette stratégie comme un menu d'options, chaque pays pouvant choisir les types d'aide qu'il juge prioritaires.

Le Groupe spécial a estimé le coût financier de l'appui technique apporté aux PRI à environ US $20 millions par an pendant 5 ans. En l'absence de ressources financières prévisibles, seule une part limitée et fragmentée de ces efforts pourrait être menée à bien.

Le SAGE a estimé que la stratégie proposée apporte une solution globale et coordonnée convaincante à la situation des PRI. Le SAGE a approuvé l'orientation générale de cette stratégie et apprécié l'approche reposant sur un menu d'options, qui permet d'adapter les activités aux besoins individuels d'un groupe hétérogène de pays. Il a constaté avec satisfaction que la stratégie s'appuie sur les enseignements tirés des expériences passées et sur les activités existantes, considérant que c'est le moyen le plus efficace de mettre à profit les ressources disponibles et de parvenir au résultat souhaité.

Le SAGE a appelé les partenaires à soutenir la mise en œuvre de cette stratégie et invité les pays à tirer parti des solutions proposées.

Le SAGE a jugé important que la stratégie pour les PRI soit mise en œuvre rapidement car plusieurs grands pays sont sur le point de s'affranchir de l'aide de l'Alliance GAVI, ce qui exigera la mise en place de solutions à long terme.

Le SAGE a souligné qu'il faudra faire preuve d'innovation et de créativité pour permettre l'entrée en phase de mise en œuvre de cette stratégie. La possibilité d'étendre l'accès à des fonds renouvelables au travers de l'Initiative d'indépendance vaccinale a été particulièrement bien accueillie, ainsi que la participation potentielle des banques de développement pour attirer des engagements financiers à plus long terme au niveau national. Le SAGE a indiqué que la prochaine étape clé consistera à consulter les hauts responsables nationaux pour évaluer le niveau d'engagement de chaque pays.

Conscient de l'importance que revêt l'accès abordable et en temps utile aux vaccins, le SAGE a toutefois souligné que d'autres domaines ne doivent pas être négligés. Concernant l'accessibilité économique, il a relevé qu'aucune proposition n'avait été faite pour promouvoir la participation des fabricants de vaccins dans les PRI. Il a recommandé que la stratégie soit alignée sur le Cadre mondial d'investissement pour la santé de la femme et de l'enfant et l'analyse Santé mondiale 2035 et souligné que certaines des approches proposées pourraient s'avérer utiles pour aider les PRI à relever les défis relatifs à l'accès à d'autres produits de santé.

Le SAGE a demandé au Secrétariat de l'OMS de le tenir informé de l'avancement de la mise en œuvre de cette stratégie.

Vaccins et vaccination contre le virus Ebola

Un bilan a été présenté, faisant le point sur: i) l'épidémie en cours; ii) le développement des vaccins; et iii) les préparatifs

tion for supporting countries with vaccine deployment. SAGE was asked for feedback on a proposed framework for drafting recommendations on the possible deployment of vaccines.

The epidemic in the 3 most affected countries (Guinea, Liberia and Sierra Leone), appears to be on the decline. The epidemic curves and size of the epidemics differ between the 3 countries, with Guinea having the largest number of new cases distributed across multiple districts. Data suggested that earlier detection and isolation of cases may have contributed to the differences in the epidemic curves and led to the decline in cases. The incidence of disease was highest in adults and transmission was mainly adult-to-adult, followed by adult-to-child, with much less transmission from child-to-child or child-to-adult.

Four vaccine candidates that have shown efficacy in non-human primate models have been or are being evaluated in phase 1 trials. Preliminary results from some of these trials have been published and results from the others are expected soon. Available data show that the vaccines are immunogenic and the results have facilitated the selection of vaccine doses for the phase 2 and 3 trials. No serious adverse events have been noted so far, although about 20% of participants experienced self-limiting arthritis in a phase 1 study of the rVSV vaccine.

Three phase 2/3 trials, one each in Guinea, Liberia and Sierra Leone, have started. Enrolment for a fourth trial in Sierra Leone is scheduled to begin in May 2015. The trials vary with regard to the vaccines being used and the study design. Two of the trials (Liberia and Sierra Leone) are individually randomized controlled trials; the second trial in Sierra Leone uses a cluster randomized design, while the trial in Guinea uses a ring-vaccination design with each ring being randomized to immediate or delayed vaccination. Laboratory confirmed Ebola virus disease (EVD) is the primary end point for all the phase 3 trials.

In parallel with the vaccine trials, WHO and partners, including the 3 most affected countries, have established a framework to develop guidelines to support planning, implementing and monitoring vaccination once a vaccine becomes available for use, according to SAGE recommendations.

A proposed framework for making recommendations was presented, which aims to adopt a scenario-based approach, while also taking account of a number of programmatic, socio-cultural and other factors. Considerations guiding the use of the framework are: specific scenario relating to the epidemiology and the type of authorization for vaccine use; objectives for vaccination (primary – stopping transmission, secondary – individual protection); prioritization of target populations; and additional considerations which would inform SAGE's recommendations. The framework would be adjusted based on evolution of the current epidemic, the type of regulatory or emergency use authorization given for a vaccine, and on the data that become available from the clinical trials.

pour soutenir le déploiement des vaccins dans les pays. Le SAGE a été invité à donner son avis sur un cadre proposé pour l'élaboration de recommandations relatives au déploiement éventuel de vaccins.

L'épidémie semble être désormais en recul dans les 3 pays les plus gravement touchés (Guinée, Libéria et Sierra Leone). La courbe et l'ampleur de l'épidémie diffèrent entre ces 3 pays, la Guinée enregistrant le plus grand nombre de nouveaux cas, répartis dans plusieurs districts. Les données semblent indiquer que la rapidité de détection et d'isolement des cas pourrait en partie expliquer les différences observées dans les courbes épidémiques et le recul du nombre de cas. L'incidence de la maladie est plus élevée chez les adultes et la transmission se fait principalement d'adulte à adulte, puis d'adulte à enfant, avec très peu de cas de transmission d'enfant à enfant ou d'enfant à adulte.

Quatre vaccins candidats, efficaces dans des modèles primates non humains, ont été évalués ou sont en cours d'évaluation dans le cadre d'essais de phase 1. Les résultats préliminaires de certains de ces essais ont été publiés, les autres devant l'être prochainement. Les données obtenues démontrent l'immunogénicité des vaccins et ont permis la sélection des doses vaccinales pour les essais de phases 2 et 3. Aucune manifestation indésirable grave n'a été signalée à ce jour, bien qu'une arthrite à guérison spontanée ait été observée chez environ 20% des participants d'une étude de phase 1 du vaccin rVSV.

La Guinée, le Libéria et la Sierra Leone ont chacun entamé un essai de phase 2/3. Le recrutement pour un quatrième essai, en Sierra Leone, devrait commencer en mai 2015. Ces essais diffèrent de par les vaccins utilisés et la conception de l'étude. Deux d'entre eux (au Libéria et en Sierra Leone) sont des essais contrôlés randomisés individuellement; l'essai en Sierra Leone est un essai randomisé par grappes, tandis que l'essai en Guinée repose sur une vaccination en anneau, chaque anneau étant assigné de manière aléatoire à une vaccination immédiate ou une vaccination retardée. La maladie à virus Ebola, confirmée en laboratoire, est le critère d'évaluation principal de tous les essais de phase 3.

Parallèlement aux essais sur les vaccins, l'OMS et ses partenaires, y compris les 3 pays les plus touchés, ont établi un cadre d'élaboration de lignes directrices conformes aux recommandations du SAGE pour appuyer la planification, la mise en œuvre et le suivi de la vaccination une fois qu'un vaccin deviendra disponible.

Un cadre de formulation des recommandations a été proposé, reposant sur une approche fondée sur des scénarios qui tient également compte de plusieurs aspects programmatiques, socioculturels et autres. Ce cadre s'appuie sur la prise en compte des éléments suivants: un scénario spécifique quant à l'épidémiologie et le type d'autorisation obtenu pour l'utilisation du vaccin; les objectifs de la vaccination (objectif primaire de mettre un terme à la transmission, objectif secondaire de protection individuelle); les populations cibles prioritaires; et tout autre aspect susceptible de peser sur les recommandations du SAGE. Ce cadre serait ajusté en fonction de l'évolution de l'épidémie actuelle, du type d'autorisation réglementaire ou d'autorisation pour une utilisation d'urgence accordée pour le vaccin et des données issues des essais cliniques.

In the discussion that followed, it was noted that the quality of the reported disease data had limitations and that the data on cultural and other factors that may have contributed to differences in the epidemic patterns were not fully captured in the national databases. However, there was confidence that the available data correctly reflected the epidemic patterns and the relative incidence of disease in different age groups.

SAGE members expressed concern about the likelihood that efficacy estimates may not be generated from the phase 3 trials, given the declining number of cases in all 3 countries and felt that the trials must also contribute additional data (including those related to programmatic aspects) that could inform recommendations. Noting WHO's unique position to coordinate the development of Ebola vaccines, SAGE stressed the importance of transparent and prompt sharing of information on the trial protocols and data from the phase 3 clinical trials, and the need for a greater role for WHO in facilitating the sharing of information so that results between studies will generate the greatest benefit for policy decision-making.

SAGE supported the proposed framework for making recommendations, but asked that it be made explicit that the identification and prioritization of target populations for vaccination will be based on a thorough assessment of risks (from disease as well as from vaccination) and benefits. It was recognized that the final recommendations would be driven by the evolution of the current epidemic, the conditions laid down in the regulatory authorization for use of vaccines and social and cultural considerations.

SAGE recommended that the further development of the Emergency Use Assessment and Listing procedure being developed by WHO, which would allow use of a vaccine in the context of a Public Health Emergency of International Concern, be done in close consultation with relevant regulatory authorities, including those of the affected countries.

SAGE again noted the probability that efficacy data for any of the Ebola vaccines may not be available by the end of the current outbreak, and therefore recommended that future use of unproven Ebola vaccines should be in the context of studies that would generate safety and effectiveness data.

Maternal vaccination during pregnancy

SAGE reviewed progress towards building a platform to provide influenza vaccine during pregnancy. An interim report was provided from the WHO Working Group on evaluation of influenza data to inform vaccine impact and economic modelling. This group is evaluating disease burden data in pregnant women, infants aged <6 months, and the fetus. Preliminary findings from meta-analyses of existing evidence, mostly collected in high income countries during the 2009 H1N1 pandemic indicate that: (i) influenza during pregnancy is associated with an increased risk of hospitalization; (ii) the

Lors des discussions qui ont suivi, il a été observé que les données notifiées sur la maladie était d'une qualité limitée et que les données relatives aux aspects culturels et à d'autres facteurs, qui auraient pu en partie expliquer les différences entre les profils épidémiques, n'étaient pas intégralement consignées dans les bases de données nationales. Il a toutefois été estimé que les données disponibles reflètent correctement les profils épidémiques et l'incidence relative de la maladie dans différentes tranches d'âge.

Les membres du SAGE se sont inquiétés du fait que les essais de phase 3 risquent de ne pas générer d'estimations de l'efficacité, compte tenu de la diminution du nombre de cas dans les 3 pays concernés, et ont fait valoir que les essais devraient également être sources de données supplémentaires (y compris sur les aspects programmatiques), contribuant à la formulation des recommandations. Constatant que l'OMS est dans une position privilégiée pour coordonner le développement des vaccins contre Ebola, le SAGE a souligné l'importance cruciale que revêt le partage rapide et transparent des informations sur les protocoles d'essai et des données issues des essais cliniques de phase 3. Il a ajouté que l'OMS a un rôle crucial à jouer pour favoriser ce partage de l'information et veiller ainsi à ce que les résultats des essais profitent au mieux au processus de prise de décision politique.

Le SAGE a soutenu le cadre proposé pour la formulation des recommandations, mais a demandé l'ajout d'une mention explicite indiquant que l'identification et le classement prioritaire des groupes cibles seront réalisés sur la base d'une évaluation complète des avantages et des risques (liés aussi bien à la maladie qu'à la vaccination). Il s'est dit conscient que les recommandations finales dépendront de l'évolution de l'épidémie actuelle, des conditions stipulées dans l'autorisation réglementaire d'utilisation des vaccins, ainsi que de facteurs sociaux et culturels.

Le SAGE a conseillé à l'OMS que la poursuite de son travail de formulation de la procédure d'évaluation et d'homologation pour les situations d'urgence, qui permettrait l'utilisation d'un vaccin dans le cadre d'une urgence de santé publique de portée internationale, se fasse en consultation étroite avec les autorités réglementaires compétentes, y compris celles des pays touchés par l'épidémie.

Le SAGE a constaté une nouvelle fois que les données sur l'efficacité des différents vaccins contre Ebola risquent de ne pas être disponibles avant la fin de la flambée actuelle et a donc recommandé que l'utilisation des vaccins contre Ebola dont l'efficacité n'a pas été prouvée se fasse à l'avenir dans le contexte d'études visant à générer des données sur l'innocuité et l'efficacité.

Vaccination maternelle durant la grossesse

Le SAGE a examiné les progrès accomplis en vue d'établir une plateforme d'administration des vaccins antigrippaux durant la grossesse. Un rapport intérimaire a été présenté par le groupe de travail de l'OMS chargé d'évaluer les données sur la grippe pour étudier l'impact de la vaccination et établir des modèles économiques. Ce groupe évalue actuellement les données sur la charge de morbidité chez la femme enceinte, le nourrisson de <6 mois et le fœtus. Les conclusions préliminaires des méta-analyses réalisées sur les données existantes, recueillies essentiellement dans les pays à revenu élevé lors de la pandémie de grippe H1N1 de 2009, indiquent que: i) la grippe en cours

evidence to date shows no or little impact of maternal influenza virus infection on birth outcomes; (iii) there are limited data to estimate incidence rates of severe influenza disease in these groups; and (iv) given the limited amount of disease burden data, the potential vaccine impact on mortality or severe disease is unclear. It was emphasized that influenza hospitalization is an outcome of public health importance, and immunization programmes may choose to vaccinate pregnant women in order to prevent it.

SAGE then heard a summary from a technical consultation on maternal influenza immunization evidence and implementation. This included preliminary data from 3 randomized clinical trials of maternal influenza immunization. The vaccine was found to be effective in preventing laboratory-confirmed influenza illness in mothers and their infants <6 months of age. The trials were not designed to evaluate vaccine efficacy against severe laboratory-confirmed influenza. There were mixed results regarding the effect of vaccine exposure on birth outcomes (including low birth weight). There were no safety signals. A pooled analysis of the 3 trials is planned to evaluate any association of vaccine with rare safety and efficacy outcomes.

SAGE reiterated that its 2012 recommendation for prioritization of influenza vaccine for pregnant women was made in the context of what was known about disease burden, vaccine effectiveness and programmatic opportunities. This was not a universal recommendation for all countries to immunize pregnant women but a recommendation to maximize the benefits of influenza vaccines in countries with existing or initiating new influenza vaccination programmes. Given major gaps in the evidence base, a recommendation to broaden influenza vaccination for all pregnant women everywhere cannot be made at this time.

SAGE encouraged WHO to promote more implementation research to generate generalizable data on the best ways to integrate maternal immunization into routine antenatal care in low resource settings. SAGE also encouraged the Regional Office for the Americas to document the successful regional experience of delivering influenza vaccine to pregnant women.

It was considered unnecessary to establish a SAGE working group to review maternal influenza immunization at present, given that substantial data still being generated will not be available until late 2015–2016. SAGE emphasized the importance of the maternal immunization platform, in general, and called upon WHO to affirm its commitment to building the evidence base to strengthen vaccine delivery during pregnancy, as it has great potential for infection prevention in high-risk groups worldwide.

de grossesse est associée à un risque accru d'hospitalisation; ii) selon les données disponibles à ce jour, l'infection de la mère par le virus de la grippe semble avoir un effet nul ou minime sur l'issue de la naissance; iii) on ne dispose que de données limitées pour estimer le taux d'incidence des formes graves de la grippe dans ces groupes; et iv) compte tenu de l'insuffisance des données sur la charge de morbidité, l'effet potentiel du vaccin sur la mortalité ou l'apparition des formes graves de la maladie n'est pas clair. Le rapport a souligné que l'hospitalisation due à la grippe est un événement significatif en termes de santé publique et qu'il peut être décidé, dans le cadre des programmes de vaccination, de vacciner les femmes enceintes pour éviter de telles hospitalisations.

Le SAGE s'est ensuite vu présenté un résumé des résultats d'une consultation technique sur les données et la mise en œuvre de la vaccination maternelle contre la grippe. Parmi les informations présentées figuraient les données préliminaires de 3 essais cliniques randomisés portant sur la vaccination maternelle contre la grippe, qui ont conclu à l'efficacité du vaccin pour prévenir l'infection par le virus de la grippe, telle que confirmée en laboratoire, chez la mère et le nourrisson de <6 mois. Ces essais n'ont pas été conçus pour évaluer l'efficacité du vaccin contre les formes graves de la grippe, telles que confirmées en laboratoire. Les résultats relatifs à l'effet d'une exposition au vaccin sur l'issue de la naissance (y compris le faible poids de naissance) étaient mitigés. Aucun signal de sécurité n'a été identifié dans ces essais. Une méta-analyse des 3 essais est prévue pour évaluer tout lien entre la vaccination et la survenue d'événements rares en termes de sécurité et d'efficacité.

Le SAGE a rappelé que sa recommandation de 2012, selon laquelle le vaccin antigrippal devrait être administré en priorité aux femmes enceintes, s'inscrivait dans le contexte des informations alors disponibles sur la charge de morbidité, l'efficacité du vaccin et les possibilités programmatiques. Il ne s'agissait pas d'une recommandation universelle appelant tous les pays à vacciner les femmes enceintes, mais plutôt d'une recommandation visant à maximiser les bénéfices de la vaccination dans les pays où des programmes de vaccination contre la grippe existent déjà ou sont en train d'être lancés. En raison d'importantes lacunes de la base de connaissances, il n'est pas possible, à l'heure actuelle, de recommander une extension de la vaccination contre la grippe à toutes les femmes enceintes partout dans le monde.

Le SAGE a encouragé l'OMS à promouvoir une intensification de la recherche pour générer des données généralisables sur l'intégration de la vaccination maternelle dans les soins prénatals de routine en situation de ressources limitées. Le SAGE a également encouragé le Bureau régional des Amériques à consigner et partager l'expérience concluante menée dans la Région pour vacciner les femmes enceintes contre la grippe.

Le SAGE a estimé qu'il n'était pas nécessaire pour l'instant d'établir un groupe de travail pour étudier la vaccination maternelle contre la grippe étant donné que de nombreuses données générées actuellement ne seront disponibles que fin 2015 ou en 2016. Le SAGE a souligné l'importance de la plateforme générale de vaccination maternelle et appelé l'OMS à affirmer sa volonté de constituer la base de connaissances nécessaire au renforcement des services de vaccination pendant la grossesse, une initiative qui pourrait être d'une contribution précieuse pour la prévention des infections chez les groupes à haut risque à l'échelle mondiale.

Other items discussed during this session concerned: i) progress made during the past 3 years particularly the plan to include immunization in the WHO Antenatal Care Guidelines 2016 and the ongoing development of clinical guidelines for the evaluation of new vaccines in pregnant women; and (ii) the potential of RSV and Group B Streptococcus vaccines under development for use in pregnant women to prevent disease in young infants, as well as hepatitis E vaccine to protect pregnant women themselves.

SAGE commended WHO for its comprehensive set of activities to support maternal immunization.

Pertussis vaccination schedules

In August 2014, the SAGE Working Group on pertussis met to review the implications of different vaccination schedules for diphtheria, tetanus and pertussis (DTP). Discussions focused on DTP – with some discussions of tetanus toxoid (TT) and DT (diphtheria, tetanus) boosters. Reviews were presented of (i) current DTP schedules and vaccines in use (based on the 2014 UNICEF/WHO Joint Reporting Form), (ii) actual age of vaccination and age-specific coverage, and (iii) age distribution of pertussis, diphtheria, and neonatal and non-neonatal tetanus in pre- and post-vaccine eras. A systematic review of RCTs and observational (cohort and case-control) studies yielded data on the comparative efficacy/effectiveness, immunogenicity and reactogenicity of different whole cell pertussis (wP) and acellular pertussis (aP) vaccines in primary vaccination schedules in children aged <18 months, and different booster vaccination schedules with wP or aP vaccines among children aged <5 years. Comparative efficacy/effectiveness data from the systematic review were used to model the direct impact of 2p+1 and 3p wP schedules on pertussis deaths among children aged <5 years. The impact was modelled in settings with different age distributions of pertussis deaths and different age-specific vaccination coverage rates for DTP1, DTP3 and measles (the latter as a proxy for a 9 month DTP3 coverage). Data presented were insufficient for a full discussion of booster schedules necessary to ensure continuous protection as compared to current recommendations/practices. Work will continue to retrieve and interpret additional data, acknowledging the major limitations of the currently available data.

SAGE focused on reviewing evidence supporting/against different schedules for DTP-containing vaccines and the impact of different vaccination strategies, bearing in mind that DTP schedules affect other antigens (in particular Hib, HepB, IPV, and PCV) particularly if combined vaccines such as pentavalent (DTP-Hib-HepB) vaccine are used. Key questions addressed by SAGE were the

Les discussions ont également porté sur: i) les progrès accomplis au cours des 3 dernières années, notamment le projet d'intégrer la vaccination dans les lignes directrices 2016 de l'OMS sur les soins prénatals et l'élaboration en cours des lignes directrices cliniques sur l'évaluation des nouveaux vaccins chez les femmes enceintes; et ii) l'administration potentielle des vaccins actuellement en développement contre le VRS et les streptocoques du groupe B aux femmes enceintes pour prévenir ces maladies chez le jeune nourrisson, ainsi que l'utilisation du vaccin contre l'hépatite E pour protéger la femme enceinte elle-même.

Le SAGE a félicité l'OMS pour ses nombreuses initiatives soutenant la vaccination maternelle.

Calendriers de vaccination contre la coqueluche

En août 2014, le groupe de travail du SAGE sur la coqueluche s'est réuni pour étudier les ramifications des différents calendriers de vaccination contre la diphtérie, le tétanos et la coqueluche (DTC). Les débats ont essentiellement porté sur le DTC, et dans une moindre mesure, sur les doses de rappel d'anatoxine tétanique (TT) et de DT (diphtérie et tétanos). Des études ont été présentées, portant sur: i) les calendriers et les vaccins actuellement utilisés dans le cadre de la vaccination DTC (informations extraites du formulaire conjoint de notification 2014 de l'OMS/UNICEF); ii) l'âge effectif lors de la vaccination et la couverture vaccinale en fonction de l'âge; et iii) la répartition, selon l'âge, de la coqueluche, de la diphtérie et du tétanos néonatal et non néonatal aux ères prévaccinale et postvaccinale. Un examen systématique des essais contrôlés randomisés et des études d'observation (de cohortes et cas-témoins) a produit des données comparatives sur l'efficacité potentielle/réelle, l'immunogénicité et la réactogénicité de différents calendriers de primovaccination par les vaccins anticoquelucheux à germes entiers et acellulaires chez les enfants de <18 mois et de différents calendriers d'administration d'une dose de rappel des vaccins à germes entiers et acellulaires chez les enfants de <5 ans. Les données comparatives sur l'efficacité potentielle/réelle dérivées de cet examen systématique ont été utilisées pour modéliser l'impact réel des calendriers prévoyant 2 doses de primovaccination et un rappel (2p+1) ou 3 doses de primovaccination (3p) par le vaccin à germes entiers sur la mortalité due à la coqueluche chez les enfants de <5 ans. Cet impact a été modélisé dans des situations présentant des répartitions différentes de la mortalité due à la coqueluche en fonction de l'âge et des taux différents de couverture vaccinale selon l'âge par le DTC1, le DTC3 et le vaccin antirougeoleux (comme indicateur de substitution de la couverture à 9 mois par le DTC3). Les données présentées étaient insuffisantes pour déterminer précisément les calendriers des rappels requis pour garantir une protection durable par rapport aux recommandations/pratiques actuelles. Des efforts continueront d'être déployés pour extraire et interpréter des données supplémentaires, compte tenu de l'insuffisance manifeste des informations actuellement disponibles.

L'examen du SAGE a principalement porté sur les données qui plaident soit en faveur, soit contre divers calendriers d'administration des vaccins DTC, ainsi que sur les conséquences de différentes stratégies de vaccination, sachant que les calendriers DTC ont une incidence sur d'autres antigènes (notamment Hib, HepB, VPI et VPC), en particulier si des vaccins conjugués, comme le vaccin pentavalent, (DTC-Hib-HepB) sont utilisés. Le

number and timing of primary pertussis vaccine doses and the intervals between doses.

The Working Group had concluded that the pertussis vaccine should be the main driver behind considering different schedules to protect infants against pertussis-related mortality which is highest in the first year of life. Emphasis was therefore placed on an early start for pertussis immunization (≥6 weeks) and achieving high coverage with the primary course.

Results from the systematic review of wP vaccination schedules showed increased post-dose 3 immunogenicity with 2p+1 compared to 3p schedules, but no evidence was found for increased clinical protection.

Modelling studies done in selected LMICs (India, Kenya and Senegal) showed that current evidence on pertussis is not strong enough to preclude a move to a 6-week, 10-week, 9-month (6w,10w,9m) schedule, should it be advantageous for other antigens administered as part of the same combined vaccine. SAGE cautioned that a move to a 6w,10w,9m schedule could be detrimental if coverage and timeliness of the 10w dose is adversely affected given the substantial increase in effectiveness of dose 2 over dose 1. Thus, it would be prudent to carefully assess its operational implications. Additional findings were that a 6w,14w,9m schedule, which would allow simultaneous administration of 2 doses of PCV, 8 weeks apart, is likely to be inferior to 6w,10w,9m in many settings unless major improvements can be achieved in coverage and timing of the current 14w dose visit.

SAGE concluded that current schedules with 3 primary infant doses remain the preferred option for countries where it is currently used. Any changes to primary pertussis vaccination schedules would be complex, potentially costly, and programmatic changes may have repercussions beyond pertussis for co-administered antigens.

There is no compelling evidence to change to a 2p+1 schedule (6w,10w,9m or 6w,14w,9m). There seems to be sustained efficacy during first year of life with a 3p course and no evidence of early waning which might favour a late dose at 9 months. Although the systematic review confirmed the protection afforded by 1 or 2 doses of vaccine there was additional benefit from the third dose; delaying its administration until 9 months may negatively impact on completion of the full course of vaccination and, without rapid waning, could reduce overall protection against severe disease in the first year of life.

Any proposed change in schedule and strategy, including a possible move from a 3p to a 2p+1 schedule for

SAGE s'est essentiellement intéressé au nombre de doses de vaccins à inclure dans la primovaccination contre la coqueluche, à leur calendrier d'administration et à l'intervalle les séparant.

Le Groupe de travail avait conclu que le vaccin anticoquelucheux devait être le déterminant principal du choix d'un calendrier vaccinal visant à protéger les nourrissons contre la mortalité liée à la coqueluche, qui est à son niveau le plus élevé lors de la première année de vie. L'accent a donc été mis sur la nécessité de démarrer la vaccination anticoquelucheuse rapidement (≥6 semaines) et de parvenir à une forte couverture par la primovaccination.

Les résultats de l'examen systématique des calendriers d'administration du vaccin à germes entiers indiquent une immunogénicité accrue après la dose 3 pour le calendrier 2p+1 par rapport au calendrier 3p, mais aucune évidence n'a été trouvée pour indiquer une protection clinique accrue.

Les études de modélisation réalisées dans certains pays à revenu faible ou intermédiaire (Inde, Kenya et Sénégal) montrent que les données actuelles sur la coqueluche ne sont pas suffisamment concluantes pour écarter la transition vers un calendrier à 6 semaines, 10 semaines et 9 mois si ce dernier s'avère avantageux pour les autres antigènes administrés dans le même vaccin conjugué. Le SAGE a mis en garde contre le fait que la transition vers un calendrier à 6 semaines, 10 semaines et 9 mois pourrait être préjudiciable si la couverture et le délai d'administration de la dose à 10 semaines étaient compromis, compte tenu que la dose 2 est notablement plus efficace que la dose 1. Il serait donc prudent d'évaluer avec soin les conséquences opérationnelles d'une telle transition. Il est également ressorti de cet examen qu'un calendrier à 6 semaines, 14 semaines et 9 mois, qui permettrait l'administration simultanée de 2 doses de VPC à 8 semaines d'écart, serait vraisemblablement moins favorable que le calendrier à 6 semaines, 10 semaines et 9 mois dans la plupart des situations, à moins d'une amélioration marquée de la couverture et du respect des délais de la visite à 14 semaines actuelle.

Le SAGE a conclu que les calendriers prévoyant 3 doses de primovaccination chez le nourrisson demeurent la solution à privilégier dans les pays où ils sont actuellement en vigueur. Toute modification apportée au calendrier de primovaccination contre la coqueluche pourrait s'avérer complexe et coûteuse et les changements programmatiques pourraient avoir des répercussions sur les antigènes coadministrés, au-delà de la coqueluche.

Rien ne plaide clairement en faveur de l'adoption d'un calendrier 2p+1 (6 semaines, 10 semaines, 9 mois ou 6 semaines, 14 semaines, 9 mois). L'efficacité semble persistante au cours de la première année de vie dans le cadre d'une administration 3p et rien n'indique un déclin de l'immunité qui pourrait arguer en faveur d'une dose plus tardive, à 9 mois. Bien que cet examen systématique ait confirmé la protection conférée par 1 ou 2 doses du vaccin, la troisième dose offre des bénéfices supplémentaires; si elle était retardée pour n'être administrée qu'à 9 mois, cela pourrait compromettre l'achèvement de la série complète de vaccination et, en l'absence d'un déclin rapide de l'immunité, risquerait de réduire la protection globale contre une forme grave de la maladie durant la première année de vie.

Toute proposition de modification du calendrier et de la stratégie de primovaccination contre la coqueluche, y compris le

the pertussis primary immunization series, should be informed by data, taking account of the current epidemiological context and potential impact on pertussis and Hib in relation to the vaccination coverage achieved at different ages and timeliness of these vaccinations.

Countries successfully using alternate primary vaccination schedules with adequate surveillance should continue using these schedules.

All countries should try to reach the highest coverage and timeliness of delivery possible with the current vaccination strategy, and implement disease surveillance. Continued efforts should be made to improve surveillance and assessment of pertussis burden, particularly in LMICs. Primary immunization schedules should ensure flexibility to enable countries to tailor their schedules based on their local epidemiology, the objective(s) of their immunization programmes, and any particular programmatic issues.

Concerning the timing of the pertussis booster dose, SAGE concluded that no revisiting of the current statement was needed or possible, as there was no new information regarding this schedule. The pertussis booster dose should be administered at 1–6 years of age, preferably in the second year of life (≥6 months after last primary dose). This contact could further be used to catch up any missed doses of other vaccines. This schedule should provide protection for at least 6 years in countries using wP vaccine. In countries using aP vaccine, protection may not last as long, as evidenced in the United States of America and Australia.

SAGE is not currently recommending any change from the current diphtheria and tetanus vaccination recommendations. Further efforts to review the evidence to determine the optimal timing and necessary number of diphtheria and tetanus boosters to achieve long-term or lifelong protection would be helpful.

The SAGE recommendations will be used in the preparation of a revised WHO pertussis vaccine position paper, with publication planned for the third quarter of 2015. ■

passage potentiel d'un calendrier 3p à un calendrier 2p+1, doit se fonder sur des données probantes et tenir compte du contexte épidémiologique actuel, ainsi que de l'impact potentiel sur la coqueluche et le Hib, en termes de couverture vaccinale obtenue à des âges différents et de l'administration en temps utile de ces vaccins.

Les pays qui utilisent déjà avec succès d'autres calendriers de primovaccination, avec une surveillance adéquate, devraient conserver leur approche actuelle.

Quelle que soit la stratégie utilisée, tous les pays doivent s'efforcer d'atteindre le meilleur taux possible de couverture et d'administration en temps utile des vaccins et veiller à la mise en œuvre d'un système de surveillance de la maladie. Les efforts devront se poursuivre pour améliorer la surveillance et l'évaluation de la charge de morbidité de la coqueluche, en particulier dans les pays à revenu faible ou intermédiaire. Les calendriers de primovaccination doivent être souples pour permettre aux pays de les adapter à l'épidémiologie locale, aux objectifs de leurs programmes de vaccination et aux enjeux programmatiques qui leur sont spécifiques.

Pour ce qui est de la date d'administration de la dose de rappel contre la coqueluche, le SAGE a conclu qu'il n'était ni nécessaire ni possible de revoir la recommandation actuelle car aucune nouvelle information n'est disponible à ce sujet. La dose de rappel contre la coqueluche doit être administrée entre 1 an et 6 ans, de préférence dans la seconde année de vie (≥6 mois après la dernière dose de primovaccination). Cette visite peut également être utilisée pour rattraper les doses éventuellement omises d'autres vaccins. Ce calendrier devrait conférer une protection d'au moins 6 ans dans les pays utilisant un vaccin anticoquelucheux à germes entiers. Dans les pays qui utilisent un vaccin acellulaire, la protection peut être de plus courte durée, comme cela a été observé aux États-Unis d'Amérique et en Australie.

Le SAGE ne propose actuellement aucune modification des recommandations existantes sur la vaccination antidiphtérique et antitétanique. Un examen plus approfondi des données serait utile pour déterminer le calendrier optimal et le nombre de doses de rappel antidiphtériques et antitétaniques requises pour parvenir à une protection à long terme, voire à vie.

Une note de synthèse révisée sur le vaccin anticoquelucheux, s'appuyant sur les recommandations du SAGE, devrait être publiée au troisième trimestre 2015. ■

Monthly report on dracunculiasis cases, January-April 2015

In order to monitor the progress accomplished towards dracunculiasis eradication, district-wise surveillance indicators, a line list of cases and a line list of villages with cases are sent to WHO by the national dracunculiasis eradication programmes. Information below is summarized from these reports. ■

Rapport mensuel des cas de dracunculose, janvier-avril 2015

Afin de suivre les progrès réalisés vers l'éradication de la dracunculose, les programmes nationaux d'éradication de la dracunculose envoient à l'OMS des indicateurs de surveillance des districts sanitaires, une liste exhaustive des cas ainsi qu'une liste des villages ayant signalé des cas. Les renseignements ci-dessous sont résumés à partir de ces rapports. ■

SAGE TRACKING RECORD OF RECOMMENDATIONS AND ACTION POINTS

SAGE recommendations are reflected in the SAGE tracking sheet. The “Recommendations/Action item” column reflects the specific recommendation made by SAGE. The “Meeting Date” column displays the date of the SAGE meeting during which the recommendation was originally made. The “Status” column indicates whether the work is currently ongoing, pending or completed.

Each recommendation has an appointed WHO focal point (not displayed in SAGE Yellow Book). The focal points are requested to update their recommendation in advance of each SAGE meeting and report on progress towards the recommendation in the “Comments and Follow Up” column.

When the recommendation is finalized, it is displayed as “Completed” in the SAGE yellow book. This item is then included in the SAGE Yellow Book for one additional SAGE meeting. After, the completed item is archived. Archived recommendations are no longer displayed in the SAGE Yellow Book but may still be accessed upon request to the SAGE secretariat. Therefore, the online tracking sheet provides a historical record of all SAGE recommendations and the Yellow Book displays the current recommendations.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
General	A recommendation was made for consideration of a platform for immunization coverage in the 2nd year of life, in view of potential necessary booster doses and opportunities to catch up with incomplete vaccination, and removing the artificial barrier often experienced after the 1st birthday.	Apr 2014	Ongoing	The proposal to the Bill and Melinda Gates Foundation (BMGF) was successful, and the Working Group (WG) is being put together at this time. Two pilot countries are being identified to review their experience with the establishment of a vaccination visit in the second year of life, and to propose strategies to improve on these visits. This will be used in the next two years to develop generic guidance to countries wishing to establish such a visit.
General	SAGE called for the identification of novel communication strategies for the work of GACVS to have a greater impact and help maintain confidence in vaccines.	Apr 2014	Ongoing	A review paper on the Global Advisory Committe on Vaccine Safety (GACVS) future is currently under preparation and will address this issue in particular. The final draft should be submitted by end 2015 to a peer-reviewed journal.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
General	SAGE encouraged the European region to document and share its experiences in country profiling, tailoring responses and using novel communication strategies to effect behaviour change.	Nov 2010	Ongoing	WHO European Regional Office (EURO) is working to support countries in addressing vaccine hesitancy at the individual and community levels, in building risk and crisis communication capacity, in strengthening resource mobilization and advocacy capacity, and in using behavioural insights methodologies to tailor programme delivery and to drive demand for vaccines. This includes activities in the following areas: 1. Application of the Tailoring Immunization Programs "TIP" toolkit, which allows a country or sub-national level authorities to segment/profile a population based on behaviors rather than background characteristics. The resulting group profile can help inform programmatic responses that could be communication-oriented or inform improved service delivery. Best practices from other disease programs are included that can be adapted for country-specific issues. Pilot testing of the framework has been conducted in several European countries: TIP was implemented in Bulgaria and on three projects in Sweden (Somali immigrants, migrants, and anthroposophic communities) in 2014, and in the UK, Kazakhstan and Germany in 2015. In partnership with Wits University in South Africa, TIP is being adapted for use on a global level and a second edition (LIC, low income country, field guide) to be published in 2016. 2. Strengthening the ability of Member States to handle crises in vaccine confidence and trust through a guidelines document on vaccine safety communication, which was published in 2013. In 2014, 13 countries received exercise/simulation-based training on managing the communications response to vaccine safety events with an additional 11 countries having received training in 2015 (as of August 2015). 3. A resource mobilization and immunization advocacy workbook has been developed and was launched during European Immunization Week 2015. A subregional training has already been delivered with a further group of countries due to receive training later in 2015. 4. A vaccine communications review methodology has been developed by EURO and has been applied in 2 Member States in 2014 and in Montenegro, Georgia, and Moldova in 2015. An additional review is planned to take place in the Russian Federation later in 2015. 5. A vaccines social media strategy has been launched. A vaccination reminder 'app' for smart phones has been developed and country versions have been launched in 4 Member States launching the app during European Immunization Week 2015. 6. An online vaccines resource centre was launched in 2012 and has been strengthened and improved through 2014, with a number of member states using or translating the caregiver and health-care worker tools presented. 7. In 2015 work continues on developing the school-based learning module on vaccines and immunization – drawing on a 'flipped learning' methodology – with children aged 8-10 learning with parents at home and reinforcing understanding in the classroom setting.
General	SAGE recommended that ways to improve curricula for medical personnel should be explored.	Nov 2008	Ongoing	A workshop organized by WHO/AFRO (African Regional Office) was held in Grand Bassam (Cote d'Ivoire) from 13-17 May 2013, in collaboration with the Ministry of Health MOH and other immunization partners (GAVI, UNICEF, United States Agency for International Development USAID/Maternal and Child Health Integrated Program MCHIP and Network for Education and Support in Immunisation NESI) to revise the 2006 EPI (Expanded Program on Immunization) prototype curricula for medical & nursing/midwifery schools in the African Region of WHO (AFR). During the workshop, 4 drafts of EPI prototype curricula were produced and were to be harmonized, finalized and edited. That is 2 curricula for medical schools in French and 2 curricula French & English for nursing/midwifery schools. AFR staff steering this work has retired, there are no immediate plans communicated by AFRO to HQ to replace this position or to continue with the project.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
General	SAGE encouraged the Regional Office in EMRO to pay special attention to countries affected by political turmoil and requested specific monitoring for any adverse impacts on immunization programmes in GAVI graduating countries.	Apr 2011	Ongoing	EMRO is working closely with and is paying special attention to the countries affected by political turmoil. The following support was provided since the last SAGE meeting in April 2015: •Egypt: Provision of technical support to Ministry of Health (MOH), Egypt, for controlling measles outbreak and planning outbreak response supplemental immunization activities (SIAs). The SIAs are planned for November 2015. Conducting desk review for routine immunization system to identify the factors behind the lower coverage. •Iraq: conducting national workshop for provincial EPI managers to discuss the strengthening routine immunization services, measles outbreak and outbreak response, introduction of IPV and PCV •Syria: conducting national training workshops on effective vaccine management, on development of cMYP as well as development of cMYP for the period 2015-2017 •Northern Syria: provision of all technical support for planning of MR SIAs, and resuming routine immunization. WHO EMRO is providing back-up to 2 dedicated consultants recruited to provide the day to day technical support •Yemen: conducting outreach strategy and periodic intensification of routine immunization (PIRI) in the low coverage governorates. Provision of financial and technical support for procurement of cold chain equipment to replace the destruction. Mobilizing financial resources for procurement of fuel for the cold chain. Supporting reprogramming of GAVI HSS funds to be utilized to support the crises. WHO remained functional under the difficult war situation and EPI WHO medical officer was one of the 3 priority staff allowed to remain in country
General	SAGE recommended strengthening national vaccination programs, integrating health services and strengthening health systems to promote universal health coverage.	Apr 2013	Ongoing	A teleconference was held May 13 2013 with J. Abramson, P. Figueroa, and N. Arora and EPI (M. Zaffran and T. Goodman) to discuss the issue and provide briefing on the integration activities that historically and presently Expanded Program on Immunization (EPI) is working on. Subsequently, in early June a draft typology was produced and shared that summarizes this area of work. The topic was discussed at the April 2014 SAGE meeting. SAGE concluded that addressing integration, by its very nature, requires a broader discussion beyond SAGE. In this regard, it was proposed that the SAGE working group on the Decade of Vaccines (DoV) consider options for moving forward, as integration is reflected as both a guiding principle and a strategic objective of the Global Vaccine Action Plan (GVAP). The Department secured funding at the end of 2014 to establish a position dedicated to the issue of integration. Recruitment has been completed and the recruited staff will start in October 2015.
General	SAGE requested that a paper be developed, highlighting the circumstances under which off-label use of any vaccine can be recommended, while clarifying the differences between regulatory decisions and public health recommendations. Legal and programmatic implications of off-label recommendations and the need for clear communication should be considered.	Apr 2012	Ongoing	Advice being sought through the Expert Committee on Biological Standardization (ECBS) - added to agenda of next meeting, 15-19 October 2012. SAGE had previously requested that a paper be developed, highlighting the circumstances in which off-label use of any vaccine could be recommended, while clarifying the differences between regulatory decisions and public health recommendations. During the November 2012 SAGE meeting, SAGE further requested that ECBS prepare guidance for national regulatory authorities on studies needed to support evidence-based, off-label use of vaccines which would benefit public health. It was noted that for regulators, product specific data are paramount. SAGE requested that an additional document be prepared to advise the national immunization technical advisory committees about the type of data that might support a policy recommendation to use a vaccine outside its licensed schedule in order to achieve public health benefits such as operational simplicity or cost savings. The ECBS guidance document has been delayed and preparation only started to be prepared after the October 2014 meeting. A paper clarifying the differences between regulatory decisions and public health recommendations has been commissioned. Unfortunately there have been sustained protracted delays in finalization of the publication. It is now hoped that submission will occur prior to end of year 2015.
General	SAGE stressed that additional disaggregation was needed in the analysis of the progress achieved on the ground, and in identifying bottlenecks for progress, and recommended that reports display disparities observed at sub-national levels.	Apr 2015	Pending	WHO HQ is working closely with regional offices to obtain subnational level data. Surveillance data for measles and rubella as well as for new vaccines is collected on district level on regular basic and there are efforts to collect sub-national level coverage data. Currently it has been done in AFR on monthly as well as annual basis and in SEAR and EUR on annual basis.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Accessibility of affordable vaccines: gaps and WHO's role in supporting emerging manufacturers	SAGE suggested to monitor gaps and opportunities and consecutively develop a systematic process to responds to these needs in collaboration with key partners. A perspective is to be presented at a future SAGE meeting on accessibility of affordable vaccines.	Nov 2010	Ongoing	WHO is actively contributing to increasing global access to vaccines through the following activities: 1) close collaboration (participation in annual meetings and bilateral meetings) with International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and Developing Country Vaccine Manufacturer Network (DCVMN) as federations of manufacturers from developing and industrialized countries to ensure that they all have clarity on the needs of developing countries both in terms of types of vaccines but also in terms of their programmatic suitability; 2) Active participation in the annual DCVMN meeting to update them on new developments, concerns, and issues related to vaccine presentations, prequalification, regulation financing and priority country need. 3) WHO has resurrected and chaired the VPPAG (Vaccines Presentations and Packaging Advisory Group) a forum for discussion between the public and private sectors on the characteristics of vaccines required for developing countries. The full participation of industry enables them to have more visibility of the needs and constraints of countries; 4) The Decade of Vaccines (DoV) work stream on global access and vaccine price indicator which gets reported every year to the SAGE working group on the DoV. 5) General discussions on the process of technology transfers are taking place under the leadership of the Evidence Information and Research Cluster. 6) A new committee known as the Product Development for Vaccines Advisory Committee was established and met for the first time 8-10 Sep 2014. The group reviewed 19 pathogen specific global pipeline analyses (all available from the meeting website) and advised WHO on strategic prioritization for WHO activities related to early stage vaccine R&D (pre-licensure to Phase 2). The group will oversee the development of Vaccine Preferred Product Characteristics. 7) The Vaccine Product, Price and Procurement project (V3P) to support GAVI graduating and middle income countries through the provision of improved vaccine product and price information for decision-making. More information on V3P is provided under the topic of financing in the tracking sheet. 8) A Task Force on Middle Income Countries (MIC) has been established. More information on this is also provided elsewhere in the tracking sheet.
Administrative matter	Members asked that a clarification of what members were asked to report (i.e. what directly concerns their department or the departments under their line of authority) be included in the web posting of the Declarations of Interests summary in the future.	Apr 2015	Pending	This was followed up with WHO Ethics and Compliance Department. It was specified that SAGE members would need to report only interests directly linked with their respective research unit as sub-unit of the department, not the entire institution. A brief on the process for declaring and assessing interests of SAGE members was posted on the WHO SAGE website.
Agenda item	SAGE requested a global shortage of vaccines discussion at the next meeting .	Apr 2015	Pending	The topic is tentatively scheduled for the April 2016 SAGE meeting.
Childhood mortality	SAGE noted the recommendation by IVIR-AC that WHO would encourage countries to collect local data at country level and not only estimated age specific mortality rates by epidemiological modeling or expert elicitation.	Nov 2010	Ongoing	All models reviewed by the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) are hampered by the lack of primary data, and more efforts should be made to make such data readily available. Specifically, for pertussis disease burden estimation, IVIR-AC suggests validating the parameter estimates against data from Senegal and Europe as a first step, although primary data from developing countries that is currently not publicly available would provide a more compelling comparator for validation. For polio more primary data should be made available for all models. IVIR-AC recommends that polio related data should be made available for multiple modeling groups to encourage comparison of results using different approaches.Ongoing/standing issue for many other diseases.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Decade of vaccines/GVAP	SAGE also recognized the urgency for having approximate cost and impact estimates and recommended that the technical group provide preliminary estimates for SAGE review in November 2013.	Nov 2012	Completed	IVIR-AC (Immunization and Vaccines related Implementation Research Advisory Committee) concluded that the Decades of Vaccine (DoV) study presented on the approximate cost and impact may be adequate for high level use such as tracking of the Global Vaccine Action Plan (GVAP) and justifying its funding to donors on return of investment but had observations with the regard to the state of the art of the individual modeling components. Furthermore, IVIR-AC identified the need for increased transparency and clarity in all methods used including refined sensitivity and uncertainty analysis. In June 2015 IVIR-AC reviewed the DOVE project. More information can be found in the IVIR-AC recommendations 2015.
Decade of vaccines/GVAP	The SAGE working group should continuously review the need for reformulation of the indicators or mechanisms for collection and reporting of data.	Nov 2012	Ongoing	The SAGE report of progress with the Global Vaccine Action Plan (GVAP) was presented to the WHO 68th World Health Assembly in May 2015. Fifty-two speakers, including 46 representatives from Member States, one observer (Chinese Taipei), four civil society organizations and GAVI, the Vaccine Alliance took the floor during the discussion on the Global Vaccine Action Plan. Delegates welcomed the GVAP assessment report and commended the Strategic Advisory Group of Experts (SAGE) and WHO on the report. The recommendations in the report were welcomed by most of the delegations who took the floor. Countries took note and expressed concern that the progress with the implementation of GVAP was patchy and slow and “far off-track” for achieving five out of six targets for 2014 and 2015. While Member States acknowledged WHO’s fundamental role in facilitating the implementation of the GVAP, they also stressed the important and leading role that WHO could play to: - Improve vaccine price transparency and build mechanisms that promote healthy and competent vaccine markets, tackle the problems faced by middle income countries to secure sustainable supplies of vaccines at affordable prices, particularly for the newer vaccines. - Work to enhance awareness of the value of vaccines to increase acceptance of immunization and to mitigate the risks posed by misinformation leading to vaccine hesitancy and refusal. - Analyse the causes of vaccine stock out and develop tools to respond immediately to any supply shortfalls. - Regularly convene countries that remain off-track to assist with diagnosing the problems and finding solutions. - Support countries to improve the quality of data and to use data for informing decisions and for improving programme performance. - Expand the existing guidance for vaccination in humanitarian emergencies to also include guidance on sustaining routine immunization during periods of conflict and crisis, including outbreaks of disease, such as the current Ebola epidemic in west Africa. Delegates acknowledged that countries and particularly national governments play a leading role in making the needed investments in immunization. Governments are accountable for the progress as well as the monitoring of their own programme performance. The Health Assembly adopted a resolution tabled by Libya that specifically addressed the issue of access to sustainable supplies of affordable vaccines for low and middle income countries, including the promotion of vaccine price transparency, support for pooled procurement mechanisms and for increased capacity for the manufacture of vaccines of assured quality to foster competition for a healthy vaccine market. http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R6-en.pdf

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Decade of vaccines/GVAP	The Director-General of WHO should convene a special session at the 2015 World Health Assembly for countries with routine vaccination (DTP3) coverage of less than 80%, to which each Minister of Health will be asked to report on their challenges, plans and timelines to improve coverage to meet the GVAP goals. In addition the SAGE's GVAP assessment reports should remain as standing items at the WHA until 2020.	Oct 2014	Ongoing	As recommended by SAGE, the Director-General of WHO convened a side session at the 2015 World Health Assembly for countries with routine vaccination (DTP3) coverage of less than 80%. The aim was to have a discussion with the Member States to understand the reasons for low coverage and find ways to collectively work together to overcome obstacles. Ministers of Health and high-level senior officials from several targeted countries attended and participated. The meeting was chaired by Dr Flavia Bustreo, Assistant Director General, Family, Women's and Children's Health (FWC), WHO. Dr Margaret Chan, Director General of WHO was in attendance. The sponsors of the meeting were the National Governments of Thailand, the Democratic Republic of Congo (DRC), and the United States of America (USA), respectively. Representatives of agencies comprising the Global Vaccine Action Plan (GVAP) secretariat, namely Gavi, the Vaccine Alliance (Seth Berkley), UNICEF (Nina Schwalbe), and the Bill & Melinda Gates Foundation (Chris Elias), were in attendance. The Civil Society Organizations were represented by the International Federation of the Red Cross and Red Crescent Societies (Amy Dietterich). Countries (e.g. Iraq, Haiti, Pakistan, Uganda, Benin, Niger...) presented their own issues and challenges and shared solutions and activities in place or to be implemented. Partners expressed their views and reiterated their willingness to support countries to address low coverage. WHA confirmed GVAP assessment report to stay a standing item for future meeting until 2020.
Dengue	A SAGE dengue working group should be convened to revise the data and prepare recommendations to SAGE as clinical trial data is expected to be submitted to the regulatory authorities in early 2015.	Oct 2014	Ongoing	The SAGE Working Group on Dengue Vaccines has been constituted and is holding monthly teleconferences. A face-to-face meeting of the Working Group was held 23-25 September 2015. The SAGE session for decision is still planned for April 2016.
Dengue Vaccine	SAGE requested that future recommendations on dengue vaccine safety be linked to the dengue vaccine development strategy.	Apr 2012	Ongoing	The dengue vaccine safety profile will be updated once an application for licensure has been filed. The Global Advisory Committee for Vaccine Safety (GACVS) has reviewed the company's risk management plan at its June 2015 meeting.
Ebola vaccines	SAGE was asked to immediately establish a SAGE working group on Ebola vaccines and vaccination.	Oct 2014	Ongoing	The working group (WG) was established and has met three times via teleconference. A face-to-face meeting of the WG took place on March 9 and 10, 2015. The WG reviewed the current epemiological data on Ebola Virus Disease (EVD), the preliminary results of the phase 1 trials, the status of the phase 2 and 3 trials, and the preparations for the large scale deployment of vaccines. They also identified the scope of the recommendations and the key questions and data for formulating recommendations. The framework was presented to SAGE at the April 2015 meeting. The SAGE working group met on August 19-20 in Geneva to review the available information and begin to start framing recommendations, based on the framework approved by SAGE in April 2015. The working group input will be presented to SAGE at the October 2015 meeting.
Ebola vaccines	Noting WHO's unique position to coordinate the development of Ebola vaccines, SAGE stressed the importance of transparent and prompt sharing of information on the trial protocols and data from the phase 3 clinical trials, and the need for a greater role for WHO in facilitating the sharing of information so that results between studies will generate the greatest benefit for policy decision-making.	Apr 2015	Ongoing	The paper published in the Lancet " Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomized trial." was shared with SAGE members. The positive results of the trial prompted SAGE to schedule an extraordinary teleconference mid- August after the SAGE Ebola Working Group meeting to discuss the further steps and the possible need for a preliminary statement/recommendation from SAGE.

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Hepatitis A	Long-term protection from single or 2-dose schedules should be regularly monitored by countries and reviewed by SAGE.	Apr 2012	Ongoing	Post-market surveillance continues in Argentina and a detailed report on the recent epidemiological situation was provided to WHO in January 2015. In 2014 in the context of a localized outbreak in a border area, 8 potential breakthrough cases were identified. For 5 of them there is uncertainty about the vaccination status and/or conditions (cold chain) in which vaccination was administered. Seven of these cases are in the 5-9 age group (distributed throughout the period) and one in the 1-4 age group. This has resulted in an enhanced vigilance in the country. Currently, however, there is still no evidence of waning immunity and the situation is still compatible with very high vaccine effectiveness. The situation continues to be investigated. Hepatitis A cases have reached an all time low in 2013 and have remained low in 2014. As exemplified by the outbreak in San Martin the risk persists in the population. As also requested by SAGE, an economic analysis of the impact of the single dose immunization strategy against hepatitis A in Argentina was done. Estimated total vaccination cost for the 2006-2010 post vaccination period was ~US$ 45 million. The total of medical and societal costs plus immunization cost decreased from ~US$ 105 million for 2000-2004(prevaccination) down to ~US$ 56 million for the 2006-2010 post vaccination period i.e. a reduction rate of 46.5%. Both Colombia and Paraguay also introduced a single dose national immunization schedule for 1 year old children. Yearly review of the Argentina surveillance data will continue.
Hepatitis B	All regions and associated countries should develop goals for hepatitis B control appropriate to their epidemiologic situations. Serologic surveys of hepatitis B surface antigen (HBsAg) prevalence, representative of the target population, will serve as the primary tool to measure the impact of immunization and achievement of the control goals.	Nov 2008	Ongoing	The Eastern Mediterranean Region (EMR) has a Regional Committee (RC) goal of reducing childhood hepatitis B prevalence to <1% among children <5 years by 2015. Its regional office, EMRO is working with Member States to ensure achievement of this goal. The Western Pacific Region (WPR) established a Regional Committee goal to reduce hepatitis B infection to <1% among children at least 5 years of age by 2017. The South East Asian Regional Office (SEARO) has a drafted regional strategy. An HQ mission to discuss HepB control targets is scheduled for Aug 2015. The African Regional Office (AFRO) has convened a regional hepatitis Technical Advisory Group (TAG) and presented a plan for comprehensive viral hepatitis control during the 2014 RC Meeting. In 2014, the AFRO Regional Committee meeting adopted resolution to reduce Hep B infection to <2% among children under 5 years of age by 2020. The European Regional Office (EURO) will consider a regional hepatitis B control goal. The Pan American Health Organization (PAHO) has resolved to eliminate hepatitis B virus transmission and is formulating a regional strategy. Documenting the Impact of Hepatitis B Immunization: best practices for conducting a serosurvey (WHO/IVB/11.08) was published in 2011 by the department of Immunization, Vaccines and Biologicals. In 2012, WHO HQ has published a framework for global action to control viral hepatitis (http://www.who.int/csr/disease/hepatitis/Framework/en/index.html).

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Hepatitis B	SAGE recommended that the timely delivery of a birth dose of hepatitis B vaccine (that is, within 24 hours of birth) should be used as a performance measure for all immunization programmes. Reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose.	Apr 2009	Ongoing	A consultation on implementation of new universal birth dose recommendation was conducted in December 2010 with special focus on countries with a high percentage of home births. Outputs include a monograph documenting the systematic review and best practices from the consultation. Immunization Practices Advisory Committee (IPAC) reviewed this work in early 2011 and again in April 2012, and endorsed the 2013 publication of 'Practices to Improve Coverage of the Hepatitis B birth dose vaccine'. From this, work is ongoing to develop field guidelines for scaling up Hepatitis B birth dose. The JRF (Joint Reporting Form) and associated materials have been revised to improve reporting of birth dose with a particular focus in Western Pacific Regional Office (WPRO). The WHO/UNICEF estimate process was piloted in 2012 in WPRO and was applied globally for the first time to the 2013 JRF birth dose data. Analysis of timely birth dose data for 2008 shows no significant changes from 2006 analysis and major issue is lack of data quality. A study of the cost of scaling up the birth dose by country has been completed, based upon previously published methodology estimating the cost of implementing the Global Immunization Vision and Strategy (GIVS) goals. In 2012, WPRO convened Expanded Program on Immunization (EPI) and Maternal and Child Health (MCH) managers from the five priority countries to jointly propose actions towards improving birth dose uptake. In Jan 2015 the African Regional Office AFRO, and in March 2015 the WPRO, held Hep B birth dose consultations to improve birth dose coverage. An assessment of Sao Tome Principe's birth dose vaccination strategy took place in July 2015 and an assessment took place in Nigeria in September 2015.
HIV	SAGE requested regular updates on the progress of HIV-vaccine research.	Apr 2010	Ongoing	There are now 3 major streams of HIV vaccine related research and development. Firstly follow-on to the RV144 Phase 3 trial in Thailand reported in 2009. Two follow-on Phase 3 trials of similar protein-poxvirus prime-boost approaches are planned in Thailand and South Africa. It was initially stated that the South African trial would start in 2015, although the start dates may now be in 2016. Secondly there are several ongoing Phase 1-2 clinical trials of recombinant viral vectored approaches focusing on non Ad5 adenoviruses such as Ad26, Ad3, Ad35 and recombinant poxviruses such as MVA (Modified Vaccinia virus Ankara). Replicating vectored approaches (eg sendai virus) are also witnessing a renaissance in the global portfolio. Finally there are major, and promising, vaccine science initiatives underway to attempt to induce broadly neutralising antibodies through re-engineered antigens. These have a longer timeframe, but raise the prospect of cross-clade protection.
Immunization schedules	SAGE encouraged WHO to complete the project promptly. SAGE requested a critical appraisal of alternative schedules for pneumococcal conjugate vaccine, rotavirus vaccine and Hib vaccine in 2011.	Nov 2010	Ongoing	Pneumococcal Conjugate Vaccine (PCV): evidence was reviewed by SAGE on November 2011. New recommendation on schedules was issued and data was used to update the position paper. Rotavirus: evidence was reviewed by an ad-hoc group of experts in February 2012 and presented to SAGE in April 2012. An updated vaccine position paper on the use of rotavirus vaccines was published in February 2013. Haemophilus influenzae type b (Hib): The issue was revised during the April SAGE 2013 meeting. For all: review of number of contacts during first years of life (ongoing); cost of contacts (planned); update on actual age at vaccination data (completed and used in conjunction with rotavirus epidemiology). Completed for PCV, Rotavirus and Hib vaccines. Evidence on diphtheria-tetanus-pertussis (DTP) was presented to SAGE in April 2015, with a focus on Pertussis leading to the update of the Pertussis Position Paper, published in August 2015. Evidence on Hep B vaccines will be presented at the April 2016 meeting - delays due to impact of Ebola outbreak.

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Immunization Supply Chains	SAGE recommended that the EVM assessment include the measurement of human resource capacity and encouraged WHO to use EVM assessments in alignment with new vaccine introduction impact assessments, to strengthen the links between supply chain issues and programme outcomes. To further improve the EVM assessment, it was suggested that the tool be used for supervisory purposes and that a composite score be developed to complement the across-the-board benchmark of 80%.	Apr 2014	Ongoing	Under the umbrella of the WHO-UNICEF Immunization Supply Chain and Logistics Hub, a process has started to develop a revised version of the Effective Vaccine Management (EVM) assessment tool for it to become an assessment that covers broader immunization supply chain and logistics aspects beyond vaccine management policies and practise. Since this is a significant undertaking and a time consuming one, the approach in 2015 is to include additional data collection and/or assessment modules for Human Resources alongside the existing approach to EVM assessments. This Human Resource module is being developed by UNICEF Supply Division under the auspices of the People that Deliver (PtD) initiative and the Global Alliance for Vaccines and Immunizations (GAVI)People and Practise working group of the immunization supply chain taskforce. In addition, the revisions of the EVM assessment tool will include more supply chain performance measures and indicators that are more outcome oriented but aligned with the global key performance indicators being developed to track performance in countries with regards to the GAVI Supply Chain strategy.
Implementation	SAGE recommended the formation of an implementation group that had a broad array of expertise in this area.	Apr 2015	Pending	A document on applying rigour and science in implementation programme design and evaluation of delivery of vaccines was drafted by SAGE members. This document was then discussed by WHO/IVB. It was agree that as a first step, instead of forming a SAGE working group, the Director of the Department of Immunization, Vaccines and Biologicals will work with the WHO health systems strengthening (HSS) group and have them come to the feedback presented at the April 2016 SAGE meeting in order to look at what is being done in the context of universal health care. Then, it will be decided if a SAGE or extended working group is needed.
Implementation research	The implementation research agenda should define equity beyond traditional economic money metrics such as social economic status gradients, to include other measures of inequity such as the multidimensional poverty index or impacts on marginalized populations. SAGE suggested that studies to examine the integration of immunization with other health interventions should be included in the implementation research agenda.	Nov 2013	Ongoing	This recommendation is now part of the new Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) agenda under research to minimize barriers and improve coverage of vaccines currently in use. During the September 2014 meeting IVIR-AC identified the need for standardization of research tools and protocols to examine the integration of immunization with other health interventions and non-vaccination to be applied locally, by antigen including on how to translate the evidence to community messaging. IVIR-AC recommended to establish a sub-group to propose elements of the menu of solutions on the integration of care with immunization programs and another sub-group on non-vaccination. A two year time line selective approach on integration was proposed at two levels i.e. service delivery and management. IVIR-AC recommended to use the project proposal on “Evaluation of the Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) interventions: example for Mazabuka District in Zambia” as a case study. As part of the Broader Social and Economic Value of Vaccines work portfolio in WHO several research proposals on this topic were suggested by a network of international researchers from academia, NGOs and decision makers during a ad-hoc WHO consultation in November 2014. Proposals were submitted for funding at Centres for Disease Control and Prevention (CDC)/Global Immunization Division (GID), the Global Alliance for Vaccines and Immunizations (GAVI), and Bill and Melinda Gates Foundation (BMGF). In March 2015, the "Impact of reaching hard to reach populations through routine immunization" proposal was awarded funding and has been started. Currently the work is still ongoing as there have been some delays with the implementation of the projects.

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Implementation Research	SAGE identified the conditions necessary for pertussis resurgence and the effective strategies for prevention of resurgence as important topics for modelling research.	Apr 2014	Ongoing	The June 2015 meeting of the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) meeting agreed on the plan for phase 1 of the comparison of pertussis models from Australia, England & Wales and the United States of America, which is meant to be a rapid assessment on the relative contributions of vaccine formulations, waning immunity, vaccine coverage and schedule to observed pertussis resurgence in these countries. If successful, phase 2 offers further opportunities to test whether existing models are sufficiently robust to changes in factors such as demographics, spatial heterogeneity, immunity and contact matrices across multiple settings. In many countries using aP vaccine in the national immunization programme, aP vaccine is used in the private sector which represents a variable proportion of infant immunizations, so these complexities will need to be reflected when the models are extended to low and middle income settings. Pertussis surveillance and laboratory capacity are still extremely poor in LIMCs particularly in Africa), and beyond the scope of the model comparison exercise to address. The committee noted that data are expected to be forthcoming through ongoing studies and follow-on analysis of maternal influenza trials, and strongly endorses the identification or further opportunities to add pertussis markers (primarily PCR on respiratory specimens) to studies such as GAVI– or the BMGF– supported vaccine impact studies. There were concerns that the opportunistic process by which the 3 models were identified may not have included all relevant parameters or modelling approaches. The feasibility of taking into account other models and parameters identified through a literature review and/or open call should be assessed, focusing on the main results of the different models for phase 1, and if they are interested to include them in phase 2.
Implementation Research	SAGE outlined some considerations for IVIR-AC to include in their deliberations – assessment of the use of high quality randomized controlled trials where feasible (noting the substantial ethical and methodological challenges involved), with sufficient power to explore sex differences, and a priori defined and standardized immunological endpoints designed to answer the specific question of non-specific effects– and emphasized that future research should draw on a broad investigator pool and from a wide range of geographic locations using a standardized protocol.	Apr 2014	Ongoing	During the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) September 2014 meeting, it was suggested to develop standardized protocols and start implementing high quality Randomized Controlled Trials (RCTs) where feasible. At least studies should mimic RCT situations with sufficient power to explore sex differences, and a priori defined and standardized immunological endpoints. With Bill and Melinda Gates Foundation (BMGF) support a multi-disciplinary team with IVIR-AC participation will start reviewing the evidence and identify research questions.
Integration	WHO should discuss and develop guidelines on how to fully integrate vaccination (GVAP) into the operation of all aspects of the health-care system and to reduce missed opportunities to vaccinate.	Oct 2014	Ongoing	Guide on Missed Opportunities for Vaccination (MOV) Assessment Methodology has been finalized and is being used to conduct MOV assessments in Chad (July 2015) and Malawi (August 2015) in collaboration with AFRO. The plan to include an MOV Assessment module as part of larger revision on the Expanded Program on Immunization (EPI) Coverage Survey methodology is progressing.
IVIR-AC	SAGE noted that a sub-group of IVIR-AC members and external subject experts should make recommendations on the types of prospective studies to assess the non-specific effects of vaccines.	Oct 2014	Ongoing	Subject experts on non-specific immunological effects of vaccination came together 1-2 February 2015 in Oxford to discuss and review the available evidence, identify key questions regarding non-specific effects (NSE), discuss pilot studies and its designs. A meeting on NSE epidemiological effects is expected end of 2015.

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IVIR-AC	IVIR-AC should seek linkages with the WHO Alliance for Health Policy and Health Systems Research as they might be useful in priority setting and discussions.	Oct 2014	Ongoing	The Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) secretariat have had initial discussions with WHO staff of the Alliance for Health Policy and Health Systems Research (HPSHR) to update on the IVIR-AC deliberations in September 2014. Discussions for concrete steps for their involvement in vaccine implementation research are ongoing. The WHO Alliance for HPHSR will have a seat in the WHO Secretariat of the IVIR-AC. In addition, Initiative for Vaccine Research (IVR) was involved in a call for proposals issued by the WHO Alliance with financial support from the Global Alliance for Vaccines and Immunizations (GAVI) and UNICEF on implementation research studies in low and middle income countries (LMICs) in 2015. Seven proposals have been selected for funding and being implemented with a one year timeline until 2016
Japanese encephalitis	Commercial kits for detection of JE-specific IgM should be compared and validated.	Apr 2006	Ongoing	Assessment using serum was carried out by PATH and published in the American Journal of Tropical Medicine and Hygiene (Am J Trop Med Hyg) July 2007. Field validation of serum and cerebrospinal fluid (CSF) in India and Bangladesh was assessed in a joint WHO/CDC (Centre for Disease Control and Prevention) meeting, at the South East Asian Regional Office (SEARO), February 2008. Nepal and Cambodia field evaluations of Japanese encephalitis (JE) assays were completed and a paper was submitted to the Journal of Infectious Diseases (JID). Assessment of kits using CSF were accepted for publication in Am J Trop Med Hyg. CDC Fort Collins distributed the 3rd serum and CSF proficiency test panel to evaluate in-house and commercial JE ELISA assays, to Western Pacific Regional Office (WPRO) JE labs in the 4th quarter of 2012. The three Western Pacific region WPR JE regional reference labs (Japan, China and Republic of Korea) held their annual coordination meeting in Chengdu, China in the 2nd quarter 2012. China Centre for Disease Control CDC JE regional reference Lab was fully accredited by WPR and HQ Lab Coordinators, in August 2012. A WPR JE LabNet meeting took place on 15 March 2013 and a Regional JE workshop for WPR was held the week of 17 June in Seoul. Submission for publication of a paper summarizing the development of the JE LabNet is pending. The Regional Reference Laboratory for JE in the WPR at the Victorian Infectious Diseases Reference Laboratory, Melbourne, was fully accredited in Oct 2013. The Global Specialized Reference Laboratory for JE at the National Institute of Infectious Diseases, Tokyo, was also fully accredited in Oct 2013. The diagnostic assay produced by PanBio ceased production at the end of 2013. An alternative assay produced by InBios with similar performance will be used in the WHO laboratory network. The training workshop at the Korean CDC in June was intended to introduce the network to this kit. A bi-regional laboratory training workshop and laboratory network meeting was conducted 17-21 August 2015, at the National Institute of Health in Bangkok, bringing together JE lab staff from both WPR and SEAR South East Asian Region. The two-day meeting provided a forum of laboratory experts to update on progress and challenges for the program, the JE laboratory network, the renewal of the roles and responsibilities of the JE network laboratories in the WPR and SEAR, update on new technologies for the diagnosis of JE, and panel discussions on surveillance of JE and possible integration wirh other non JE causes of Acute Encephalitis Syndrome. The following 3-day laboratory workshop provided hands-on training using the newly introduced InBios diagnostic kits, and compare its performance with other kits used in the two WHO Regions. All laboratories represented used the opportunity to provide updates on the current JE situation with particular focus on laboratory-based surveillance.
Japanese encephalitis	Guidance is needed on how to approach Japanese encephalitis (JE) vaccine impact assessments. This guidance should address surveillance data sources and analysis to measure JE vaccine impact, design of surveillance and special studies for impact measurement, JE laboratory diagnostics, and data collection and analysis for observational studies to measure vaccine effectiveness	Apr 2015	Ongoing	WHO held a meeting May 26-27, 2015, on methods for JE vaccine effectiveness and impact studies. We are now working on the meeting report and guidance document (analogous to the one prepared for Haemophilus influenzae type b (Hib)/pneumococcus titled "Measuring impact of Streptococcus pneumoniae and Haemophilus influenzae type b conjugate vaccination" published in 2012).

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Lower middle-income countries: sustainable adoption and financing for new vaccines	SAGE requested that WHO facilitate the establishment of a partnership among all relevant stakeholders to consider: pooled procurement; tiered pricing; greater transparency of pricing; and exploring the role that UNICEF, the Pan American Health Organization and foundations can have in assisting these countries with procuring and financing vaccines.	Nov 2010	Ongoing	WHO has set up a MICs Task Force in June 2014. The Task Force includes main immunization stakeholders (WHO, UNICEF, World Bank, GAVI Secretariat, BMGF, AMP, Sabin, Task Force for Global Health) and is working to establish a shared strategy for sustainable access to vaccines in MICs in consultation with countries, CSOs and industry. The Task Force has first focused its work on redefining the problem statement. Following these analyses it was decided that the Task Force would concentrate its efforts on non-GAVI MICs only; that the Task Force would move away from the perceived issue of a lag between MICs and GAVI-supported countries, and would focus instead on the fact that MICs are far from reaching their Decade of Vaccines (DoV) targets. The strategy was finalised in April 2015 and presented at SAGE. It was approved to move into implementation phase. Four main areas of action have been identified as the pillars of the MIC strategy: i) Strengthening evidence-based decision-making; ii) Enhancing political commitment and ensuring financial sustainability of immunization programmes; iii) Enhancing demand for and equitable delivery of immunization services; and iv) Improving access to timely and affordable supply. Improving access to timely and affordable supply is seen as the main area where further efforts are needed, especially related to vaccine procurement. This area includes the following activities: increasing procurement skills and knowledge ; increasing access to revolving funds ; harmonizing product choice & registration processes ; increasing availability of price and contract information ; strengthening pooled procurement options and influencing market dynamics (supply). The timeline for the strategy is up to 2020 to align with the GVAP timeframe and up to 2025 for a longer term horizon. In the longer term, the MIC strategy could provide a platform to ensure sustainability of GAVI investments in graduated countries. In the implementation phase, the Task Force, with WHO as Secretariat, would continue its role of coordination and information sharing.
Malaria	SAGE noted the utility of PPCs to developers and funders, and proposed that the opportunity for input into future PPCs at an early stage for any vaccine of public health importance could be included as part of SAGE's global public health mandate.	Apr 2013	Ongoing	Malaria Vaccine Preferred Product Characteristics are finalized and available on WHO's website. RSV Preferred Product Characteristics are now under development. In addition, two Ebola vaccine Target Product Profiles are under development for reactive and prophylactic use.
Malaria	SAGE requested that it be kept informed of developments in the ongoing multi-country Phase 3 trial and indicated that further discussion on the optimal schedule for a malaria vaccine will need to occur.	Oct 2009	Ongoing	The European Medicines Agency (EMA) announced a positive article 58 scientific opinion on RTS,S/AS01 in July 2015. This is the first ever positive regulatory assessment of a submission of a malaria vaccine. It is not licensure, but may be helpful to African regulatory authorities that will consider licensing the vaccine during 2016-2017. For the first time a SAGE/Malaria Policy Advisory Committee (MPAC) joint decision session on malaria vaccines will occur in Oct 2015. The Joint Technical Expert Group (JTEG) is both the SAGE WG on malaria vaccines, and the MPAC's expert group on malaria vacines (reporting to two departments). JTEG met on June 29-30, and agreed by consensus candidate policy recommendations for decision by SAGE and MPAC. These will be submitted to SAGE/MPAC as part of the background paper on malaria vaccines in mid September. A separate process has coordinated harmonization and comparison of the malaria models available for RTS,S/AS01 impact and cost-effectiveness predictions. The report from this process will also be submitted to SAGE and MPAC in mid September.
Maternal Immunization	SAGE encouraged the Regional Office for the Americas to document the successful regional experience of delivering influenza vaccine to pregnant women.	Apr 2015	Pending	

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Maternal Immunization	SAGE encouraged WHO to promote more implementation research to generate generalizable data on the best ways to integrate maternal immunization into routine antenatal care in low resource settings	Apr 2015	Ongoing	IVR is in conversations with partners to develop a proposal to conduct maternal immunization implementation research in low-resource settings. IVR is in the process of producing many implementation research tools and guidance regarding: 1) assessment of vaccine confidence/hesitancy in pregnant women; 2) maternal influenza immunization program costing tool; 3) guidance document to estimate the influenza economic burden of a country; 4) guidance document to estimate the cost effectiveness of influenza vaccines in a country; 5) field guide for the evaluation of influenza vaccine effectiveness; 6) maternal immunization AEFI surveillance guidance; and 7) implementation guidance document. IVR is planning to develop 1) maternal influenza immunization implementation evaluation research tool and post-introduction evaluation guidance; 2) guidance for the estimation of vaccine coverage among pregnant women; and 3) principles document for influenza vaccine program implementation.
Maternal Immunization	SAGE concluded that the recommending bodies, including WHO, need to engage in a dialogue with regulators and manufacturers to review current regulatory practices against the evidence on risks and benefits and biological plausibility on product safety. SAGE requested WHO to develop a process and a plan to move this agenda forward in support of an increased alignment of data safety evidence, public health needs and regulatory processes.	Nov 2013	Ongoing	WHO has reviewed various regulatory approaches to labelling of the pregnancy and lactation sections of product inserts, and it has convened two meetings on the subject: a consultation at WHO in July 2014 and a session at a meeting of the Developing Country Vaccine Regulators' Network (DCVRN) in China in November 2014. No regulatory consensus was achieved in these meetings regarding data requirements for product labelling, and further consultations are planned to discuss this issue further in 2015. The meetings did identify potential alternative methods by which WHO could promote more permissive language in package inserts regarding vaccine use in pregnancy, including use of WHO Prequalification (PQ) Model Package Inserts for influenza vaccines. WHO is currently planning to convene a working group of regulators to draft guidance for the completion of pregnancy/lactation sections of influenza vaccine package inserts, and it is exploring other mechanisms that would promote evidence-based, permissive language in package inserts and that would improve understanding of precautionary language in package inserts.
Meeting preparation	SAGE members asked that in the executive summaries inserted in the Yellow Book for each section, an orientation be included describing the entire package of documents inserted.	Apr 2015	Ongoing	This has been specifically flagged and requested from each WHO session focal point in preparation for the October 2015 SAGE meeting.
Meningococcal A conjugate vaccine	SAGE recommended that countries completing mass vaccination campaigns introduce meningococcal A conjugate vaccine into the routine childhood immunization programme within 1–5 years following campaign completion, along with a one-time catch-up campaign for birth cohorts born since the initial mass vaccination and which would not be within the age range targeted by the routine immunization programme. SAGE recommended a 1-dose schedule, with vaccine administration by deep intramuscular injection, preferably in the anterolateral aspect of the thigh, at 9–18 months of age based on local programmatic and epidemiologic considerations. This recommendation for routine immunization programmes is based on the high level of herd immunity following mass campaigns, epidemiologic evidence on the age distribution of disease, and programmatic and economic considerations. Any children who miss vaccination at the recommended age should be vaccinated as soon as possible thereafter.	Oct 2014	Ongoing	The recommendations from SAGE are reflected in an update to the WHO meningococcal vaccine position paper. The updated guidance has been published in the Weekly Epidemiological Record WER on 20 February 2015: http://www.who.int/wer/2015/wer9008/en/. One of the meningitis belt countries (Ghana) has already submitted an application to Gavi, the Vaccine Alliance in January 2015 for introduction of the meningococcal A conjugate vaccine into their routine immunization programme, with a single dose at 18 months of age concomitantly with the administration of the second dose of Measles/Rubella vaccine. Another 6 meningitis belt countries intend to apply for the introduction of the vaccine into their routine programme at the next Gavi application window closing on 8 September 2015 (Burkina Faso, Chad, Mali, Niger, Nigeria and Sudan).
Middle Income Countries Strategy	SAGE called upon WHO Secretariat to report back on progress in implementation of the Middle Income Strategy.	Apr 2015	Pending	WHO will work on the implementation of the MIC strategy and will report back to SAGE in 2016.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Middle Income Countries Strategy	SAGE recommended that the MICs strategy be aligned with the Global Investment Framework for Women's and Children's Health and the Global health 2035 analysis, and noted that some of the approaches proposed may be useful in addressing challenges that MICs face in accessing other health commodities.	Apr 2015	Completed	This has been done, the MIC Task Force looked into these initiatives and aligned analyses as relevant.
Multiple injections	SAGE noted the need for further research on multiple injections during the same visit and recommended the following research topics and activities: (i) impact of multiple injections in the same visit on vaccine coverage, disease reduction, vaccine programme success and caregiver and provider experience; (ii) development of a standardized monitoring protocol for acceptance and acceptability by caregivers and providers and for prevalence of adverse events; (iii) development of optimal provider and infant caregiver communication approaches; (iv) optimal multiple injection administration techniques, and (v) development of new technologies, such as intradermal patches and new combination vaccines, which would decrease the number of vaccine injections in a single visit.	Apr 2015	Ongoing	A multiple injection study is soon to be conducted in Nepal in collaboration with US CDC (delayed due to the recent earthquake). A protocol was submitted for WHO ERC clearance to evaluate healthcare provider and infant caregiver attitudes and practices regarding administration of multiple injectable vaccines in the same visit following introduction of IPV and PCV. A separate work stream in WHO IVB - in conjunction with WHO EMP - is investigating the development of intradermal patch technologies with IPV and MR including the relevant regulatory pathways.
Pain mitigation	SAGE recommends that WHO: 1) includes pain mitigation recommendations with WHO immunization practice guidance materials; 2) disseminates pain/distress mitigation recommendations through the usual dissemination channels, immunization managers, National Immunization Technical Advisory Group (NITAG) and partner organizations; 3) monitors and evaluates the implementation success of pain mitigation measures; 4) works with industry, ECBS and regulatory agencies to advocate that grading of pain experienced during the vaccine injection be included in data for licensing and in the product monograph.	Apr 2015	Ongoing	Internal discussions have taken place on how to move forward across relevant WHO departments. A brief position paper was drafted based on the SAGE recommendations and published in the Weekly Epidemiological Record on 25 September 2015. This will form the basis for more proactive communication activities. Work is also ongoing to ensure appropriate incorporation of pain mitigation in WHO guidance documents when they get updated and to ensure that any recommendation posted on the web that would be at odd with SAGE's guidance would be adjusted/removed.
PDVAC	SAGE requested to be updated by Product Development for Vaccines Advisory Committee (PDVAC) on the criteria used for prioritizing vaccines for IVR's work.	Oct 2014	Ongoing	SAGE was updated at the April 2015, and updates will be provided each year at the October meeting. A major area of activity in pipeline vaccines relates to RSV vaccines, where a pivotal Phase 3 trial is due to start soon. There will be a For Information session on RSV vaccines at the April 2016 SAGE meeting.
Pertussis control	The SAGE recommendations will be used in the preparation of a revised WHO pertussis vaccine position paper, with publication planned for the third quarter of 2015.	Apr 2015	Completed	An updated position paper has been finalized and was published in the Weekly Epidemiological Record on 28 August 2015.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Polio	The documentation for 'legacy planning' should include contributions from communities and front-line health workers on their experiences with the polio programme, what it has meant for them and how lessons learnt could further improve the routine vaccine and health programme.	Apr 2013	Ongoing	The Global Polio Eradication Initiative (GPEI) has constituted a Legacy Working Group (LWG), currently comprised of representatives from the spearheading partners (Rotary, WHO, CDC and UNICEF) and the Bill and Melinda Gates Foundation to take forward the legacy planning work. The LWG has finalized and is implementing its workplan. One of the major activities within the workplan is to hold broad consultations with relevant stakeholders to document the lessons learnt and knowledge of the programme, to guide the direction of the legacy work, and to establish what benefit the lessons and resources of the GPEI could be to other initiatives. These consultations began in early 2014 and were continuing through the rest of the year. The consultation included plans for soliciting contributions from communities and front-line health workers' on their experiences of polio eradication. In addition, the GPEI has contracted a consultant group that will conduct in-country interviews that will include learning lessons of polio eradication. As well as having produced a paper for the Journal of Infectious Diseases (JID) on the lessons of polio eradication (Cochi, Freeman, Guirguis, Jafari, Aylward, Global Polio Eradication Initiative: Lessons Learned and Legacy), the GPEI Legacy Management Group is seeking input on lessons at the country level. This work will be led by Regional and Country-based colleagues and will involve the input of front-line workers. In addition, a team from the Boston Consulting Group supporting the legacy planning work in 2014 and early 2015 have sought input from 10 countries on contributions of polio-funded staff to other health priorities including immunization. The first segment of this work was reported to the Polio Partners Group and the Polio Oversight Board in December 2014. The Legacy Planning guidelines were revised in June 2015, including key steps in its planning and development (including engagement of donor and civil society, coordination and oversight, communication strategy). As part of the 2015-16 transition plan 10 priority countries for GPEI transition planning were identified. A survey of the focus countries (Afghanistan, Pakistan, Nigeria, South Sudan, India, Nigeria, DRC, Chad, Ethiopia, Angola), indicated that polio country personnel currently devote 46% of their working schedule to RI and EPI related activities, of which 22% is dedicated to RI. The guidelines outline how assets and capabilities of the GPEI (staff, infrastructure and know-how) can be transferred and used to benefit other global health and development programs, as exemplified by the recent Nigerian response to the Ebola outbreak.
Polio	Sufficient capacity should be established at the global level to provide technical and programmatic support to countries to plan and implement all activities associated with type 2 oral polio vaccine (OPV2) withdrawal and introduction of inactivated polio vaccine (IPV).	Apr 2013	Ongoing	The Immunization Systems management group, co-chaired by WHO and UNICEF, has been established to coordinate efforts towards the activities relating of OPV2 (type 2 component of oral polio vaccine) withdrawal and IPV (inactivated polio vaccine)introduction. The multi partner group has been operating since mid-April 2013 in five areas of work : Regulatory, vaccine implementation, communication, financing and routine immunization strengthening. The time investment dedicated by the staff of the six agencies engaged in the Immunization Systems Management Group, IMG (Centre for Disease Control and Prevention CDC, WHO, UNICEF, Bill and Melinda Gates Foundation BMGF, Rotary and Global Alliance for Vaccines and Immunization GAVI) since April 2013 has been impressive. WHO/EPI (Expanded Programme on Immunization) has filled an additional 3 professional staff positions at HQ to contribute to this effort. UNICEF HQ has filled two additional HQ positions. Significant numbers of staff and consultants have also been deployed at Regional levels of both organizations, and funding has been sent to all regional offices. All of the expected GAVI eligible countries (71) have applied and been approved for IPV introduction support. For non GAVI countries, a financing mechanism has been rolled out to support 16 countries in Tier 2 and Tier 3 or LMIC (low and middle income countries) which are not GAVI eligible. This mechanism will enable partners to support some countries that need it with vaccine introduction grants and/or time limited procurement of IPV. In December 2014 the above financing mechanism was extended to another 9 countries from the American (AM) and Western Pacific (WP) regions to help them, in a catalytic manner, initiate the procurement of IPV.Of the 25 countries offered this opportunity, 18 have requested and been approved for funding. As of June 30, 2015, all 126 OPV-only using countries have committed to IPV introduction, and 22 countries have introduced to date. The effort is now focusing on managing the IPV supply and providing countries with the necessary information and technical assistance to develop a plan to carry out a switch from trivalent OPV (tOPV) to bivalent OPV (bOPV) in April 2016.

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Polio	SAGE recommended working closely with countries on activities towards type 2 oral polio vaccine (OPV2) withdrawal.	Apr 2013	Ongoing	In January 2014 a joint letter to all oral polio vaccine (OPV)-only using countries was sent by the WHO Director General and UNICEF Executive Director, and the Global Alliance for Vaccines and Immunizations (GAVI) CEO where applicable, highlighting the importance of inactivated polio vaccine(IPV) introduction and outlining the SAGE recommendation on IPV introduction schedules and planning timelines. This was followed up in May 2015 with a joint letter from the DG and UNICEF ED to all tOPV using countries on the importance of planning for the switch. All regions have held, at least one meeting that included a substantive focus on IPV introduction in 2014/5 and have held or will hold the same on the tOPV to bOPV switch in 2015. Joint WHO/UNICEF regional coordination mechanisms are established to ensure countries are suitably supported in the decision making process and in the development and implementation of introduction plans for IPV and the switch. Work is now ongoing to i) ensure that declared intent materializes into commitment and ii) countries with no plan developed for the switch have one ready before the end of the year. In alignment with the SAGE April meeting discussions and the WHO resolution on the Switch, technical materials and standard operating procedures (SOPs) have been developed to accelerate switch planning at country level and have been shared with countries through regional consultations.
Polio eradication	SAGE requested the polio Working Group to continue monitoring progress towards cVDPV2 elimination and ensuring that remaining challenges are addressed including contingencies for vaccine supplies (IPV, bOPV and tOPV), registration of bOPV for routine use, surveillance sensitivity, and reaching inaccessible children. The Working Group will make a full report to SAGE in October 2015, when SAGE may reconfirm April 2016 as the definite date for OPV2 withdrawal.	Apr 2015	Ongoing	This is being closely monitored by the Polio WG. In June, there was a conference call of WG where WG reviewed the progress towards eliminating persistent cVDPVs. This was again reviewed by the WG during its September meeting and the WG will report back to SAGE in October 2015.
Polio eradication	SAGE noted the importance of the work on the polio legacy and asked for a full report on this at its October 2015 meeting.	Apr 2015	Pending	It will be discussed during the September WG meeting and presented to SAGE during the October 2015 meeting.
Polio eradication	"To facilitate prioritization, planning and implementation of IPV introduction at country level, SAGE recommended that consideration be given to developing a resolution on accelerated IPV introduction for submission to the World Health Assembly (WHA) in 2014."	Nov 2013	Ongoing	The World Health Assembly (WHA) noted the progress of inactivated polio vaccine (IPV) introductions in 2014, based on the report from Immunization systems Management Group (IMG). During the WHA 2014, the 5 criteria for withdrawal were discussed. These criteria include a) status of introduction of IPV in oral polio vaccine OPV-only using countries, b) registered bivalent OPV for routine immunization, c) establishment of stockpile and outbreak response protocol for type 2 virus, d) completion of phase 1 containment activities under the Global Action Plan (GAP) and e) affirmation of wild poliovirus type 2 eradication by the Global Commission for the Certification of the Eradication of Poliomyelitis (GCC). In 2015, WHA adapted the resolution that calls on member states to prepare for the OPV2 withdrawal in April 2016.
Regulatory	SAGE recommended that the further development of the Emergency Use Assessment and Listing procedure being developed by WHO, which would allow use of a vaccine in the context of a Public Health Emergency of International Concern, be done in close consultation with relevant regulatory authorities, including those of the affected countries.	Apr 2015	Ongoing	A document entitled “Vaccine evaluation in public health emergencies – review of regulatory pathways in selected countries” is curently being drafted. This document will be submitted to the Expert Committee on Biological Standardization (ECBS)for review and advice and will be discussed with the Committee in October 2015. A brief report on the progress was presented to SAGE WG on Ebola vaccines in August 2015.

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Reports from other advisory committees	SAGE recommended appointment of appropriate programmatic and implementation expertise to IVIR-AC membership including representation of experts from low and middle-income countries.	Nov 2011	Ongoing	Since 2013 Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) includes two programmatic and implementation research members from the African Region (AFR) and the South East Asian Region (SEAR). Since 2014 IVIR-AC includes a mathematical modeler/economist from SEAR and a medical anthropologist from AFR. Currently 2 seats are vacant for health economists with experience in vaccine implementation research. Recruitment of new members is ongoing. There was a call for new members in 2015. Three potential candidates were selected to attend the June 2015 meeting. The mathematical modeler was selected to become a member but the two health economists were not selected as they did not meet the expectations. A new call for Committee Members will go out later in 2015.
Reports from other advisory committees on immunization	WHO and NIBSC should develop with other stakeholders, a business plan to assure long-term security of the development of WHO reference preparations as a global public health resource and additional efforts should be undertaken to disseminate outcomes of the committees deliberations and to explain the relevance of its work to the broader immunization community.	Nov 2006	Pending	A comprehensive review of the work of the Expert Committee on Biological Standardization (ECBS) is still pending. The review will include (but not be restricted to) consideration of communication of ECBS outcomes.This will be linked with an overriding review of Expert Committees by the department of Essential Medicines and Health Products. Discussion on a paper on the process of the review was initiated by ECBS during its October 2014 meeting; however biotherapeutic biological drugs were identified as first priority.
Smallpox vaccines	SAGE recommended that WHO initiate discussions with countries in possession of smallpox vaccine to establish mechanisms for replenishment of the WHO stockpile in case of need.	Nov 2013	Ongoing	An operational framework for vaccine donation was developed and agreed by the Global Health Security Initiative (GHSI) Medical countermeasures (MCM) task force. Discussion with the French Government for the donation of 5 million doses of vaccine are still ongoing. WHO is working on smallpox vaccine prequalification for emergency stockpile. A WHO meeting took place in Geneva 7-8 September 2015 to discuss with the National Regulatory Authorities and vaccine manufacturers what would be the minimum criteria to pre-qualify smallpox vaccines in case of re-emergence of variola virus.
Supply Chain	SAGE requested future update on approaches to prioritization within supply chain improvement plans.	Oct 2014	Ongoing	Under the umbrella of the WHO-UNICEF Immunization Supply Chain and Logistics Hub, a process has started to implement the more holistic approach to immunization supply chain improvement planning as part of the WHO-UNICEF Joint Statement that was endorsed by the SAGE. The approach builds in a methodology to prioritize strategies and activities that will have the largest impact on immunization supply chain improvements. In addition, evidence around cost-effective solutions is being compiled by the Hub which will be transformed into an Solutions Toolbox to help countries tailor and prioritize the right solutions. 5 countries have developed a supply chain improvement plan - Pakistan, Democratic Republic of Congo, Lao People's Democratic Republic, Bangladesh, and Nepal.

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Surveillance	SAGE endorsed the recommendations of the ad hoc TAG for improving the quality of the IB-VPD surveillance network and urged that the objectives of this network be more clearly defined, that collaboration with other surveillance systems and laboratory networks (i.e. the polio/measles laboratory networks) be continued, and that, where feasible, activities be linked with other programmes enhancing country capacity, including implementation of the International Health Regulations. SAGE urged greater attention to integration of data systems, which would facilitate real-time analysis and performance monitoring. SAGE also noted the opportunities for integration by building upon the enhanced capacity developed by these networks to conduct surveillance for other diseases using a similar case-definition and personnel trained in applying and adhering to rigorous surveillance protocols. Both networks should continue to share experiences with the polio surveillance network. Integration efforts must be strategically designed in ways that are logical and synergistic.	Nov 2013	Ongoing	During 2013, a global strategic review was conducted of the invasive bacterial vaccine preventable diseases (IB-VPD) and rotavirus sentinel hospital surveillance networks. During that meeting, 50 recommendations were made to advance the status of both networks. During 2014, significant progress was made to further improve the IB-VPD and rotavirus sentinel hospital surveillance networks. Network management was strengthened with the use of a Performance Management Framework to track implementation status of annual global recommendations. A major achievement was the transition to standardized, case-based reporting with quarterly data sharing plus feedback of standard process and performance indicators to sites. Data management processes continue to be improved toward having a more systematic approach in reporting, cleaning, analysing and interpreting data. The reference laboratories are appropriately supporting sites and network laboratory performance has been successfully monitored by the global external quality assessment (EQA) program as well as quality control (QC) programmes. Sentinel site and laboratory assessments have been prioritized but have not been able to include all priority sites. The most recent 2013 data available for the meeting may underestimate data quality because none of the actions taken after the 2013 strategic review are yet reflected. IB-VPD data analysis focused on assessing laboratory testing performance of culture and PCR, and found <30% of PCR results were linked into the clinical database as well as a 3-fold improved detection of pathogen by PCR over culture alone. Beginning in 2014, Regional Reference Laboratories (RRLs) will only process specimens with a unique identification number and it is thus anticipated that a larger percentage of cases will have clinical data that can be linked with RRL data. Network data has contributed to vaccine introduction decisions and the surveillance networks have been used as platforms for vaccine impact evaluations. Moving forward, the rapid introduction of Pneumococcal Conjugate Vaccine (PCV) and Rotavirus Vaccines (RV) by Member States now requires the surveillance networks to focus on improving baseline data for sites in non-vaccine using Member States and to ensure consistent surveillance practices for sites that meet inclusion criteria in vaccine-using Member States. The web-based data management tool has great potential to improve data quality and may be expanded to other vaccine preventable diseases in due course. WHO, the iTAG (informal Technical Advisory Group) and partners will work to implement recommendations to further improve the network during 2015 including to strengthen programme management: • Strengthen involvement of Ministry of Health and national EPI (Expanded Programme on Immunization) programmes; • By end-April 2015, IB-VPD specimen sharing agreements should be established between all 71 IB-VPD target hospitals and RRLs to further increase access to PCR's improved diagnostic yield; • All IB-VPD cerebrospinal fluid specimens should be tested by PCR at an RRL; • Further focus efforts and define a subset of sites where PCV and/or RV vaccine impact evaluations may be feasible due to sufficient pre- and post-vaccine introduction data; And to Improve data management and analysis: • Link clinical and laboratory data by use of unique identification numbers. Prospective data linking established by 31 Dec 2014, and sites prioritized for retrospective linking; Validation of these activities pending until June 2015. • Zero reporting to be implemented at all sites by 31 Dec 2014; In March 2015, regional activities are in progress, but zero reporting not yet been implemented. • Identify a subset of core data variables for vaccine impact assessments; • Draft guidelines for rotavirus data analysis/interpretation and assess probable bacterial meningitis data; • Finalize the web-based data management tool; • Revise site inclusion criteria: for rotavirus, reduce the number of annual stool specimens tested in vaccine using countries; for IB-VPD, include consistently performing sites that enrol fewer meningitis cases.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Tuberculosis vaccines	SAGE endorsed the establishment of a WHO TB vaccine technical expert group with representation from SAGE. An annual written report on TB vaccine developments should be provided to SAGE. SAGE would be provided with two-page summaries of progress every year. TB would only be included on the agenda of SAGE when there is a meaningful development of decision from SAGE required.	Nov 2011	Ongoing	An update on the development status of TB vaccine candidates has been received in preparation for the upcoming PD-VAC meeting. Consensus is emerging that targeting the adolescent/adult population, who carry the heaviest disease burden, will have the highest and most immediate public health impact due to reduction in transmission. A Phase IIb study with GSK's M72/ASO1E candidate is underway in 3600 HIV-uninfected, latently infected adults and may inform correlates of protection and risk, as well as efficacy to prevent activation of disease. Several other candidates are in Phase IIa, including assessment of H4/IC31 compared to BCG re-vaccination to prevent infection by Mtb (as opposed to disease) in adolescents.
Typhoid	Establish a SAGE working group on typhoid conjugate vaccines in 2016 to prepare for a SAGE review of the evidence in 2017.	Oct 2014	Pending	Following the accumulation of sufficient data, the Working Group will be established early 2016 to prepare for a SAGE review in 2017.
Un/under-immunized children	SAGE requested that WHO quickly roll out tools so that other countries can address low coverage of vaccination.	Nov 2010	Ongoing	The in-depth tool "A Guide to Tailoring Immunization Programmes (TIP) has already been developed and used by WHO-EURO (European Regional office). Currently the Univ. of Witwatersrand in South Africa has been contracted to adapt the methodology to developing countries, and less intensive consultant-based inputs. The Health Worker KAP tool has been completed and will be piloted with the assistance of JSI in Kenya. Work is ongoing on the tool to assess "Missed Opportunities". On a broader level, a companion document to the GVAP focusing on Routine Immunization, entitled "Global Routine Immunization Strategies and Practices" (GRISP) is in the final stage of drafting, and has been presented to the SAGE WG on DoV twice. In addition to a comprehensive framework of RI strategies, it highlights nine "transformative investments" to guide global partners and countries in RI strengthening.
Vaccination in humanitarian emergencies	SAGE also suggested that the framework approach to vaccine decision-making could be considered for other health interventions in emergencies.	Apr 2012	Ongoing	The Emergency Risk Management and Humanitarian Response (ERM) Department was slow in the uptake of this recommendation due to lack of staff and the high number of Level 3 emergencies. A discussion was held at the MICs Task Force meeting held in February 2015 on the possibilities of having an emergency fund for vaccines in disaster situations. The discussion resulted in a mapping of emergency funds available and gaps, which was presented in the April SAGE meeting in 2015.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccine coverage	SAGE recommended that WHO explore alternative survey methods to improve the precision, reduce the cost and improve the usefulness of survey results to national and local immunization programmes.	Nov 2011	Ongoing	To improve the precision and usefulness of survey results and to reduce the cost of surveys, the Strategic Information Group (SIG) proposes to explore 1) recent advances in sampling methodology, 2) new technologies for constructing sampling frames, supervision of field work, data collection, and analysis and 3) alternative content, collection, analysis, presentation and linkages with other data sources. An explicit description of precision, usefulness and cost of various trade-offs between alternative methods will constitute part of the exploration. An initial meeting was convened of the Department of Immunization Vaccines and Biologicals' (IVB) Informal Advisor Group on Monitoring Immunization Programme Performance through Household and Community Surveys. First meeting addressed the need to modify Demographic and Health Surveys (DHS) - implemented by ICF International; the UNICEF Multiple Indicator Cluster Surveys and the WHO Immunization Cluster Survey to accommodate changes in immunization system strategies. On 17-18 September 2012 a meeting was held with representatives of ICF and UNICEF to discuss modifications to their standard recommendations on data collection, analysis and presentation of immunization coverage data. WHO and UNICEF provided written recommendation to these agencies. An informal working group has been created to review and revise WHO guidance on measuring immunization coverage through household and community surveys. The working group met in July 2013 to agree on the scope of work, to identify initial products, and establish a plan of document production, review, pilot testing, and clearance. Draft guideline was circulated to external reviews. Protocol for pilot testing was developed and pilot testing is currently undergoing in Bangladesh. The methods will be reviewed in September by Immunization and Vaccines Related Implementation Research (IVIR) Advisory Committee. The proposed methods were reviewed in September by Immunization and Vaccines Related Implementation Research (IVIR) Advisory Committee. The methodology is currently tested in Burkina Faso and in Lao PDR. The working draft of the manual has been distributed and posted on the departmental web site(http://www.who.int/entity/immunization/monitoring_surveillance/Vaccination_coverage_cluster_survey.pdf?ua=1). A briefing workshop on the methodology for regional focal points and consultants is planned for early December.
Vaccine coverage	SAGE recommended that WHO support new research for biological specimen collection including rapid on-site diagnostics that could improve coverage and susceptibility estimates. Improved serological surveillance techniques could be integrated with existing population-based surveys such as DHS or MICS. These research topics should be included on the QUIVER (now IVIR-AC) agenda.	Nov 2011	Ongoing	As the Bill & Melinda Gates Foundation is now accepting Letters of Inquiry for the development of an easy-to-use tool that rapidly assesses the immune status of children against select vaccine-preventable diseases. Inquiries will be welcome that focus on prototype development and detailed plans for future commercialization possibilities.
Vaccine coverage	WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage.	Nov 2011	Ongoing	Currently, WHO is developing global guidelines on conducting serosurvey studies on measles and rubella and primarily to be applicable in a pre- and post-SIA (supplementary immunisation activity) setting. An expert working group has been assembled and based on the expertise in the various fields of each of the members, needed to conduct such studies, including statisticians, epidemiologists, laboratory experts, and program experts, given subtasks in developing parts of these guidelines that pertain to their respective expertise. A working draft has been circulated for comments and will be finished by the end of 2015 and will be tested subsequently in pilot studies in two different settings, pre- and post-campaign, for its applicability. These pilot studies are expected to take start Q1 2016 and will run during the entire year of 2016. Based on the outcome, the working draft guidelines will be corrected where needed and finalised. The final document is planned to be ready by end of 2016 and to be rolled out as a tool to evaluate the immune status of the target or targeted population.
Vaccine Hesitancy	SAGE encourages validation of the developed compendium of survey questions on vaccine hesitancy, which have been assessed and validated only in some high-income countries or not at all.	Oct 2014	Ongoing	Discussions with various stakeholders are ongoing (Centre for Disease Control CDC, WHO EURO, Middle Income Countries MIC task force) on the ways forward to identify partners to take on the validation of the survey quesions. The MIC task force framework was presented to SAGE during the April 2014 meeting, which highlighted the importance to advance this initiative. Currently it is being explored how to secure funding from donors in support of the listed activities and advance validation of the questions in LMIC settings.

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Vaccine Hesitancy	SAGE underlined the importance of distributing the matrix of determinants, the definition of hesitancy and the other deliverables to countries and partners.	Oct 2014	Ongoing	Discussions and presentations were held in the context of the immunization managers' meeting in the Eastern Mediterranean Region (EMR) and the African Region (AFR) Task force on immunization(TFI) meetings. A Special Issue on Vaccine Hesitancy has been published on August 18 2015 in the journal Vaccine with a series of 10 full papers plus one editorial. In conjunction, a WHO press briefing was held on 18 August to emphasize WHO initiatives addressing vaccine hesitancy. This generated much positive media coverage.
Vaccine Hesitancy	SAGE acknowledged the necessity to develop core capacities at headquarters and regional level for gaining behavioural insights that can be applied in an integrated fashion for prevention of many communicable and non-communicable diseases, as well as vaccine hesitancy. This will require the involvement of sociologists, psychologists, anthropologists, experts in social marketing, communication experts, and specific disease and vaccine experts.	Oct 2014	Ongoing	Discussions are ongoing within WHO and UNICEF and with partners on how to collectively establish core capacities in order to support and provide technical assistance to countries. For this, discussions were initiated on how to advance the establishment of a network of expertise/excellence and collaborating centres by capitalizing on currently ongoing initiatives and activities which have been established and are conducted by WHO (HQ and Regions), partners and stakeholders in the field of vaccine hesitancy. A package listing resources from a number of excellence centers which could support countries and regions has been prepared for circulation to regions and countries.
Vaccine safety	SAGE highlighted the urgent need for a safety review of other important vaccines that could be used during pregnancy.	Nov 2012	Ongoing	A sub-group of the Global Advisory Committee on Vaccine Safety (GACVS) has been launched to address vaccine safety during pregnancy. A finalized version of the GACVS report on safety of immunization during pregnancy has been made available to SAGE in November 2013 and is now available on the Global Vaccine Safety (GVS) website. A new work track was started with WHO Initiative for Vaccine Research (IVR) in order to harmonize safety monitoring during pregnancy clinical trials. WHO is a contributor to the Gates funded Global alignment of immunization safety assessment in pregnancy project that should run until the end of 2016.
Vaccine Supply	It was noted that SAGE needs to address the constraint experienced across Regions of repetitive shortfalls in vaccine supply, both for existing vaccination programmes (in particular for DTP-containing vaccines) as well as for new/emerging vaccines, and the impact on vaccine coverage in several countries. SAGE requested WHO to produce a report on the security of the supply of affordable vaccines and encouraged donors to invest in the development of new vaccine technologies that facilitate the delivery of effective, affordable vaccines to populations most at risk.	Nov 2012	Ongoing	Concerns about the ongoing shortages of traditional vaccines persist. Recent discussions with UNICEF SD (Supply Division) have indicated that a vaccine such as BCG may face supply shortages in 2015 to the extent of being unable to deliver vaccines to all countries needs, potentially prompting stock-outs. For other vaccines, including measles containing vaccines, supply is currently adequate, but largely dependent on a single manufacturer. Discussion with donors has advanced well and planning for meeting on new vaccine technologies being initiated. Internal WHO discussions are in progress. A meeting on new vaccine technologies was held in February 2014. The work on the supply of affordable vaccine is an on-going effort in which all immunization partners are engaged. WHO secretariat (EPI) is now working to develop an approach to expand timely access to supply for both traditional and new vaccines through improved demand and supply management/forecasting. A report on this area of work will be provided to SAGE in 2016.
Yellow Fever	SAGE requested WHO to revisit the IHR provisions relating to the period of validity for international certificates for vaccination against yellow fever (YF).	Apr 2013	Ongoing	The WHO World Health Assembly in May 2014 adopted an amendment to Annex 7 of the International Health Regulations (2005) (IHR), which stipulates that the period of protection afforded by yellow fever vaccination, and the term of validity of the certificate will change from 10 years to the duration of the life of the person vaccinated. This change will enter into force legally in June 2016. Until then the current IHR text on yellow fever vaccination and certificates continues to apply, and some countries may continue to request proof of vaccination or a booster within the last 10 years from travellers. As of the end April 2015, 34 countries have notifed WHO that already accepted the validity yellow fever (YF) vaccination certificate for life. The online WHO 2015 International Travel and Health (ITH) edition report on the status of YF vaccination requirements per countries.

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WHO's Vision and Mission in Immunization and Vaccines 2015 – 2030

[DESIGN: WHO Letterhead or letter-looking graphics]

Dear WHO staff and partners,

WHO's Vision and Mission in Immunization and Vaccines describes WHO's strategic focus and key roles in achieving the goals of the Global Vaccine Action Plan, across all areas of work and all levels of the organization continuing into the next 15 years.

The strategic directions described in this document are consistent with ongoing WHO reform and aligned with the Sustainable Development Goals. They reinforce WHO's longstanding role as an international leader, setting norms, establishing policies, and reaching international agreement on health priorities. They also bring forward more focused roles for WHO in providing technical assistance and managing knowledge and data.

WHO's Vision and Mission illustrates how the organization plans to evolve its critical role in immunizations and vaccines to meet the needs of future health programmes. It will be used to guide internal decisions about where to focus resources, at what level of the organization, and in which strategic directions.

WHO staff at all levels has participated in the development of this document. By sharing it with our partners and stakeholders, we hope to show how WHO will achieve its mandate over this exciting period of transition and expansion in the field of immunization.

Flavia Bustreo
Assistant Director General
Family, Women's, and Children's Health
World Health Organization

WHO's Vision and Mission in Immunization and Vaccines 2015 – 2030

Vaccines prevent disease. Vaccines avert deaths. Vaccines promote health.

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1. Preamble

Between 2010 and 2015 more than 5 million deaths[1] were averted annually thanks to vaccinations delivered around the world. This estimate does not include the impact of rotavirus vaccine and pneumococcal vaccines, for which no estimates are available. Immunization continues to be one of the most powerful and cost-effective interventions in public health.

In the past two decades, the scope of immunization has expanded significantly as new vaccines and delivery technologies have been introduced into routine immunization programmes worldwide. The same period has witnessed a proliferation of actors in the global arena that promote immunization and help vaccines reach an ever-larger number of children, adolescents and adults. The horizon is filled with prospects of new vaccines, delivery technologies and systems.

In 1974, a World Health Assembly resolution launched the Expanded Programme on Immunization (EPI) to immunize children worldwide with six vaccines. Since then, the World Health Organization (WHO) continues to act as the global authority on immunization in accordance with its constitution and obligation to its 194 Member States. In an increasingly interdependent global environment, WHO has and will continue to focus on its core roles in immunization: to set norms and standards; convene global expertise; develop, promote, and facilitate adoption of new guidelines; and monitor national and global achievements and progress.

To further articulate how these roles will evolve over the next 15 years, WHO developed a new Vision and Mission for Immunization and Vaccines for the period 2015 – 2030. This document presents the key focus areas and a series of strategic directions that define our core business for the future coinciding with the new Sustainable Development Goals era.[2]

The scope of this document includes work on immunization and vaccines taking place across all levels of WHO. A new articulation of WHO's mission, vision and strategic directions will enable the organization to better anticipate and respond to the opportunities and challenges of the immediate future. It will position WHO with the capacity and competencies needed to fulfil its mandate and streamline its core functions at global, regional and country levels. It will assist WHO in positioning itself clearly within on-going implementation of the Global Vaccine Action Plan (GVAP)[3] and prepare itself for the decade following the current GVAP: 2020 to 2030. It will also provide the basis for future global and regional plans.

This document was developed through a process that included consultations with immunization teams in all WHO regional offices and a range of meetings with other key staff in all departments engaged in vaccines and immunization work in its headquarters office in Geneva and in selected country offices. Two distinct pieces of work were undertaken to inform the work: a historical review

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[1] Based on WHO estimates of deaths averted from diphtheria, tetanus, pertussis and measles and Ehreth's estimates (EhrethJ: Vaccine 21 (2003) 596 - 600) of deaths prevented from Hib, HepB, polio and TB. Additional deaths are prevented with the increasing uptake of vaccines against *Streptococcus pneumoniae* and rotavirus.

[2] *Open Working Group Proposal for Sustainable Development Goals.* New York, United Nations, 2015 (Document A/68/970).

[3] *Global Vaccine Action Plan 2010 - 2020.* Geneva, World Health Organization, 2012.

of 40 years of EPI illustrates the main determinants for EPI successes (Annex 4) and a survey among users of WHO products and services identifies responsibilities that WHO does well and those areas that could be done equally well by partners (Annex 5). This research helped WHO identify areas where we have a unique role and comparative advantage and areas that could be phased out.

Recognizing that immunization programmes have and will continue to undergo rapid change, we shaped our mission and strategic focus areas around a set of assumptions about the environment in which immunization programmes will operate in 2030. The new environment for immunization is described below:

BOX: What will 2030 look like?[4,5]

By 2030, the immunization environment may look very different than it does today.

Countries are experiencing broad demographic and economic changes. Already, there are more people living in middle-income countries than in low-income countries. Increased economic stability will provide countries more ownership over their immunization programmes, and countries will require less technical assistance to make decisions and address problems. More countries will have sufficient capacity for regulatory affairs and prequalification at the regional and country levels, and will be less reliant on WHO's prequalification process at the global level.

The sustainable development goals will have provided direction for economic and social development. Health indicators will be broader, encompassing communicable and non-communicable diseases as well as emerging burdens from accidents and environmental threats. Prevention will continue to be important, and attention will continue to be directed to interventions that are considered cost-effective.

More vaccines will be available to protect against more diseases throughout the human life course. Immunization will likely become part of an integrated package of disease prevention strategies, meaning that immunization services will be accompanied by other services and delivered in more places, including schools, homes, and pharmacies. New, easier-to-use immunization delivery technologies may be more widely available, making it possible for non-health personnel to deliver immunization. Electronic devices and software systems will make data collection and analysis easier and more powerful, enabling managers and health staff to more efficiently identify and reach people previously missed by immunization and to tailor services to the most optimal delivery methods.

Disease elimination and eradication programmes will continue to exist, but as part of stronger health systems that have regular and reliable contact with communities, even those in remote and hard-to-reach areas. Routine and campaign immunization services will be managed in a single platform.

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[4] *Twelfth Global Programme of Work.* Geneva, World Health Organization, 2014 (http://www.who.int/about/resources_planning/twelfth-gpw/en/, accessed 9 September 2015)

[5] Chaferhoff M, Schrade C, and Suzuki E. Analysing proposals for reform of the global health architecture. London, Chatham House Royal Institute of International Affairs, Centre on Global Health Security, 2015.

More successful immunization programmes will lead to fewer people falling ill and dying from vaccine-preventable diseases, and demand for immunization may begin to drop. In such an environment, health priorities are expected to shift to the prevention and control of non-communicable diseases. Immunization services and demand for those services must be more purposefully maintained.

Fragile states will continue to exist, and the disparity between health outcomes in stable and fragile countries may continue to increase. These countries will require ongoing support to maintain reliable immunization services amongst larger age groups and more difficult-to-access populations.

2. Vision

Our vision statement presents where we want to be in the future and the impact that we intend to have on health in the world.

Our vision:

The highest attainable standard of health for all individuals and communities by preventing disease.

3. Mission

Our mission statement presents the purpose and focus of our work in immunization and vaccines over the next 15 years.

Our mission:

To support all countries to deliver quality immunization services as part of an integrated, people-centred platform of disease prevention that spans the human life-course.

4. WHO's strategic focus and cross-cutting roles

4.1 The strategic framework

Our heart and soul.

This framework is intended as a stand-alone summary of WHO's mission, vision, and strategic directions, that shape and drive the organization's work in vaccines and immunization.

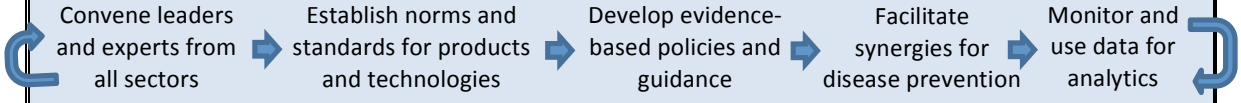
WHO in immunization:

The highest attainable standard of health for all individuals and communities through preventing disease.

Our mission:

To support all countries to deliver quality immunization services as part of an integrated, people-centred platform of disease prevention that spans the human life-course.

Our cross-cutting roles:



Proactively share information across all areas

Our strategic focus:	
"Vaccines" *Encourage and support research that is used to inform norms and standards. Identify necessary regulatory pathways to accelerate the development, licensure and introduction of new vaccines and related technologies and strategies.* **Strategic directions:** 1. Promote the development of new vaccines and vaccine delivery technologies to meet public health priorities 2. Establish norms and standards for vaccines and delivery technologies 3. Ensure vaccines and delivery technologies are of assured quality	***"Immunization"*** *Collect and share evidence that countries use to inform their choice of strategies to ensure that vaccines are available, affordable and accessible to all.* **Strategic directions:** 1. Support national immunization systems to become more effective and efficient 2. Monitor and analyse global and regional immunization data 3. Ensure the sustainability of immunization programmes 4. Apply behavioural sciences to immunization 5. Sustain immunization services in emergencies 6. Lead disease elimination and eradication efforts
Principles aligning how we work: Accountable Country-led Interconnected and interdependent Efficiency-driven Impact oriented	

4.2 The strategic directions

Our mind and body

Our strategic directions look both upstream at the development and regulation of vaccination and delivery technologies and downstream at the implementation of immunization services. These duel strategic areas were selected based on consultation across WHO regional and headquarters (HQ) offices, with input from selected country offices, and have informed our nine strategic directions through 2030.

For each strategic direction a specific approach has been defined with a view toward where we expect to be in 2030. These strategic directions and approaches are presented in Annex 1.

4.3.Roles that cut across all areas of work

Our brain

As we look to the future, we recognize the areas of work where WHO is already acknowledged—both internally and by partners—as playing a critical role across technical streams. Regardless of the area of immunization—e.g., measles elimination, outbreak response, new delivery technologies or supporting national immunization systems to become more effective and efficient—WHO's leadership in these cross-cutting roles is and will remain necessary and consistent. We also identify a few expanded roles that WHO considers both vital and important—these include adopting broader strategies for disease prevention and increasing our capacity to collect and analyse data.

The cross-cutting roles presented below describe how WHO will work over the next 15 years.

- **Convene leaders and experts from all sectors**. WHO's role in convening experts in immunization is well established and globally critical. Whether it is to convene ministries of health and immunization managers to discuss regional issues, getting all partners within the country to meet and agree on implementation plans, or bringing together global experts across a range of disciplines to recommend evidence based policy, WHO is recognized as a trusted convener at national, regional and global levels.

- **Establish standards for products and technologies.** WHO's normative role and standard-setting for vaccines, biologicals and technologies is relied upon by countries, private companies, United Nations (UN) agencies and partners to ensure that immunization products are effective, safe and suitable for all people around the world. WHO is recognized as a neutral broker and thus has a unique role to play in this sphere that is not—and some argue cannot—be filled by others.

- **Develop evidence-based policy recommendations and guidance.** WHO's role in establishing policy recommendations and guidance across all areas of immunization—from data collection to new vaccine introduction to stockpile management—remains critical for maintaining equitable, efficient and consistent immunization programmes around the world. Countries routinely look at WHO policy recommendations and guidance when developing their own strategies, programmes and implementation plans. Expert groups such as the Strategic Advisory Group of Experts on immunization (SAGE) are particularly important, as partners in bilateral agencies, foundations, and private companies refer to SAGE recommendations when planning their immunization services support and products. Similarly, the work of regional technical advisory groups is crucial to tailor policy to the specific needs and contexts of each WHO region.

- **Facilitate synergies for disease prevention.** WHO will increasingly play a key role in helping countries meet international norms, implement national health plans and identify synergies across health services that can result in more effective and efficient health systems. Providing technical guidance on programme implementation is also a critical role that WHO will increasingly address from the regional and country level.

- **Monitor and use data for analytics.** With support from Member States, academic partners and national institutes, WHO provides a nexus for the consolidation, analysis, and dissemination of data and information across all immunization and vaccine preventable disease areas. WHO will continue to validate data for quality and reliability so it can be used to inform priorities, activities and plans, and support decision-making processes at all levels. As electronic information systems begin to proliferate in developing country health systems, WHO will work with countries to extract the most useful data that can be used to make decisions and inform global and regional health strategies. WHO will also use state-of-the-art analytics and data visualization technologies to analyse data and use it to prioritize investments and develop new prevention goals.

4.4 Responsibilities of each level of the organization

Our arms and legs

Over the period 2015 to 2030, there will be a gradual shift in the critical roles of the different levels of the organization. The overall intention is to narrow the focus of HQ to areas where a global approach is required and strengthen and enhance the roles of the regional and country offices.

The table below illustrates the major roles that the global, regional, and country-level WHO offices will play. More information on the division of responsibilities is provided in Annex 2.

Table 1. Some examples of key roles for the organization at its three levels

Core Role	HQ	Regional Office	Country Office
Convene leaders and experts from all sectors	More actively involve Civil Society Organizations in setting policies and monitoring their implementation.		
Establish norms and standards for products and technologies	Promote the harmonization of international norms and standards and regulatory procedures across all countries.	Help strengthen national regulatory agencies or regional regulatory mechanisms to progressively reduce the need for prequalification systems.	
Develop evidence-based policies and guidance	Develop behavioural strategies to address hesitancy and demand.	Help tailor global strategies and support their regional implementation.	Support countries to establish their own national policies and strategies related to immunization and disease control and prevention.
Facilitate synergies for disease prevention	Identify opportunities for collaboration across health programmes to improve disease prevention services.	Facilitate inter-country and inter-regional coordination and collaboration on immunisation and elimination and control of vaccine-preventable diseases.	
		Support countries and partners' internal and external fundraising efforts, and align external assistance with country needs and priorities.	
Monitor and use data for analytics	Enable better internal and external global decision-making by sharing the best available global immunization data using analytics and visualizations.	Support inter-country collaboration to obtain quality data and conduct regional immunization and disease risk analyses.	Promote the use of new ideas and technologies (including information and communications technologies) to make data collection and use more effective and efficient.

5. Principles aligning how we work

Our pulse

WHO has identified five principles to guide our decisions and actions through 2030**.** These principles are relevant at both an individual and collective level and are meant to facilitate a shared understanding WHO's interests and goals at each level of the organization. We expect these principles to translate into behaviours that define a common culture for how those who work in vaccines and immunization at WHO approach our work and how we relate to colleagues and partners.

Our principles are aligned with the WHO reform and thus in step with on-going programmatic and managerial changes at WHO.[6] For example, the WHO reform has a stronger country-focus and introduces more rotation and mobility for human resources, which will strengthen regional and country capacity and facilitate more interaction between all levels of the organization. It will thus enhance several of the principles described below.

Accountable

- Acknowledge and take responsibility for meeting our objectives and commitments by setting and enforcing clear expectations at all levels
- Maintain high ethical and professional standards by asserting an evidence-based and independent perspective

Country-led

- Follow governments' lead and help them take ownership of their decisions and plans
- Invite country participation in regional- and global-level dialogue
- Cultivate and reinforce country-level capacity to sustain immunization achievements

Interconnected and interdependent

- Seek and foster synergies across health areas that have the potential to optimize outcomes
- Strengthen internal and external collaborations that can speed or enhance outcomes

Efficiency-driven

- Work efficiently, i.e., seek maximum results from limited resources
- Provide timely access to data and information so that all actors can react and work quickly
- Streamline processes that make it easier to collaborate with internal and external colleagues

Impact-oriented

- Draw attention to new issues, encourage ongoing learning and innovation, and actively promote successful ideas and initiatives
- Set priorities and allocate resources in alignment with the delivery of results
- Improve programme performance, so that everyone who needs vaccines has reliable access
- Promote equity in immunization

[6] *Our Reform Story*. Geneva, World Health Organization, 2013 (http://www.who.int/about/who_reform/change_at_who/strategic_vision/en/#.VfBavnjiLU4, accessed 9 September 2015).

6. The role of WHO with its partners

Our family
WHO has always worked closely with partners to set norms and standards, provide direct guidance and seek financial support for Member States. Without the ideas and contributions of partners, none of last decade's successes in immunization would have been possible.

Since the EPI launched in 1974, the number and type of partners involved in immunization has increased dramatically (see Annex 3). WHO partners in immunization include: the countries themselves (Ministry of Health, other Ministries, technical agencies), financial partners, manufacturers, UN agencies, international technical agencies, bilateral agencies and projects, and civil society organizations.

In this section, we illustrate the many ways in which WHO works with partners to help achieve our Vision and Mission in Immunization and Vaccines between now and 2030.

1. **Financial partners**

Foundations, official development agencies, and Gavi, the Vaccine Alliance have been providing financial and technical support to both countries and WHO allowing great achievements in morbidity and mortality reduction over the past decades. Ongoing support from donors complemented by increasing spending from countries themselves will ensure that recent achievements are sustained and that programmes will continue to improve in all countries.

WHO will support the work of financial partners by:
- Highlighting areas where financial and technical support is most needed
- Providing technical support to countries and defining norms, standards, policies and strategies for immunization
- Monitoring and evaluating national, regional and global programmes and strategies for immunization

2. **Manufacturers**

Providing adequate quantities of efficacious, safe and cost-effective vaccines and equipment is a prerequisite for strong programmes and an essential element in strengthening health security. Manufacturers of vaccines and immunization technologies, including those in low- and middle-income countries, are key partners for providing pre-qualified vaccines and other immunization technologies to countries.

WH*O will support the work of manufacturers by:*
- Providing guidance on how current and future vaccines and immunization technologies can be adapted to fit the needs and constraints of low-resource settings
- Developing country capacity to regulate vaccine safety and efficacy and harmonize regulatory requirements across regions

- Helping countries more accurately forecast vaccine needs and mobilize the resources required to purchase vaccines

3. United Nations agencies and global initiatives

Many UN agencies and global initiatives include immunization activities in their purview. Their collaboration is crucial to ensure that immunization is integrated across all strategies and programmes and, inversely, that immunization is a useful complement to ensure successful implementation of other health interventions.

WHO will support the work of other UN agencies and global initiatives by:

- Integrating related health and other development strategies into immunization programmes, where possible
- Improving health systems so that other health interventions benefit from strong immunization programmes
- Coordinating with other UN agencies and global initiatives to provide technical and financial support to countries
- Coordinating the production and use of quality data

4. Technical partners

The category "technical partners" covers a range of different institutions: international technical agencies and non-governmental organizations, universities and research institutes, scientific societies, and individual consultants and consulting companies.

Some of these institutions have been granted the status of WHO Collaborating Centres. This status, granted after several years of strong partnership, reinforces the link between institutions and provides stronger alignment between WHO objectives and the collaborating centres' activities.

WHO will support the work of technical partners by:

- Drawing upon their expertise and knowledge when developing WHO norms, standards and policies
- Validating and sharing monitoring and evaluation data collected from national, regional and global immunization programmes

5. Civil Society Organizations (CSOs)

Historically, the relationship between WHO EPI and civil society, including CSOs, has been relatively weak. However, civil society organizations have been increasing their involvement and support of immunization programmes worldwide and both WHO and CSOs stand to benefit from stronger collaboration and cooperation. Whereas WHO plays a leading advisory role to country governments, CSOs are often the immunization stakeholders closest to communities and populations.

As CSOs continue to expand their interest in immunization, particularly in relation to the GVAP implementation, WHO will proactively engage with CSOs and help them advocate for vaccines and immunization, support Member States and remain relevant and evolving players in global health.

WHO will support the work of civil society by:

- Involving civil society representatives as full participants in immunization programme planning, implementation, monitoring and reporting, and meetings and events.
- Normalizing the relationships between government and civil society with regards to immunization

Annex 1: Strategic areas and directions

STRATEGIC AREA: Vaccines

1.1 Strategic Direction: Promote the development of new vaccines and vaccine delivery technologies to meet public health priorities

Research and development (R&D) for new and improved vaccines and vaccine delivery technologies is central to all efforts to prevent diseases with significant morbidity, mortality and economic burden, especially in low and middle-income countries.

WHO has been involved in vaccine and delivery technology R&D for many years, facilitating productive dialogue with manufacturers and helping research institutes and manufacturers prioritize R&D investments. Over the next 15 years, WHO will continue to work with manufacturers and research institutes to recommend vaccine R&D priorities and foster the development of new technologies that can be used to meet public health priorities, such as thermostable, community-provided vaccines and needle free delivery devices.

Approach:

- Develop global agendas for R&D around vaccines and delivery technologies that address public health priorities of low and middle-income countries and formulate new research needs and promote the development of research partnerships.
- Help define target attributes and development pathways for novel vaccines/combinations and delivery technologies using preferred product characteristics (PPCs) and other guidance documents to address future implementation challenges.
- Created streamlined and accelerated development pathways for vaccines and delivery technologies by: encouraging collaboration among research centres and WHO collaborating centres, including those located in low and middle-income countries; facilitating technical support for research projects; providing expert advice on intellectual property, and facilitating technology transfer, when appropriate.

1.2 Strategic Direction: **Establish norms and standards for vaccines and delivery technologies**

One of WHO's core roles is to establish and promote global norms and standards for medicines and devices that safeguard the quality, safety and efficacy of vaccines and delivery technologies. WHO also works with countries to translate global norms and standards into regional and national regulatory practice. In 2014, the portfolio of WHO standards for biological substances extended to over 70 written standards and 300 international biological reference preparations.

Over the next 15 years, as countries begin to take on more regulatory responsibility for medicines and devices, WHO will promote regulatory convergence of international norms and standards. WHO will also seek to improve its norms and standards process so it can quickly assimilate scientific advances in production and control of vaccines and devices into the normative process.

Approach:

- Convene expert committees and promote international laboratory collaborations to set norms, standards and reference preparations and develop standards for new vaccine candidates.
- Promote the use of internationally-agreed norms and standards among all relevant international and national actors.
- Achieve convergence of international norms and standards in support of a globalized supply chain.
- Monitor scientific advances in vaccine and delivery technology production and control and translate them into evolving norms and standards.

1.3 Strategic Direction: Ensure vaccines and delivery technologies are of assured quality

Prequalification is a process established to ensure that vaccines and delivery technologies purchased by UN procurement agencies are consistently safe and effective under conditions of use by national immunization programmes. As national regulatory authorities become stronger and increasingly align their procedures with those of stringent National Regulatory Authorities (NRAs) or regional regulatory mechanisms, WHO expects that the need for the prequalification systems will gradually reduce to be used only in exceptional circumstances.

In an effort to build sufficient regulatory capacity in countries, WHO will continue to work with regional and national regulatory bodies to implement globally-accepted norms and standards so that all countries have access to safe, effective and high-quality vaccines and delivery devices.

Approach:

- Guide the development of stronger national regulatory systems.
- Expedite the registration of vaccines and devices.
- Convene expert committees to assess the degree to which vaccines and delivery technologies meet the needs of recipient countries
- Promote post-marketing surveillance of prequalified delivery technologies and vaccines to inform decision-making and any revisions to product specifications.

STRATEGIC AREA: Immunization

2.1. Strategic Direction: Support national immunisation systems to continuously become more effective and efficient

WHO's central role in immunization puts it in a unique position to set ambitious global goals and galvanize national, regional and global commitment to achieve those goals. Over the next 15 years, WHO will support Member States to provide quality immunization services as part of stronger and more integrated health systems. In this context, WHO will focus less on the provision of direct technical assistance and more on establishing necessary enabling functions that empower Member States to strengthen their own national systems.

Approach:

Seek political commitment for immunization through legislative and policy changes.

- Gain appropriate political commitment from WHO Member States to prioritize immunisation and establish common global and regional vaccine-preventable disease (VPD) control goals.
- Facilitate inter-country and inter-regional coordination on immunisation and VPD elimination and control.
- Promote in-country legislation that secures budget lines for vaccines and immunisation, requires immunization for school entry, and facilitates the equitable and universal access to and use of immunisation services in the context of the country's health system (e.g., mandates for free-of-cost vaccination, mandates for reporting vaccination data from all sectors, etc.).

Provide strategic and practical guidance to countries.

- Convene multidisciplinary global and regional advisory bodies to formulate recommendations and provide guidance on immunisation policies, strategies and practices.
- Establish and strengthen national bodies such as National Immunisation Technical Advisory Groups (NITAGs) and NRAs to promote and facilitate in-country decision-making and oversight.
- Set the global and regional agenda for, and facilitate the implementation of operational and economic research to inform decisions on disease prevention, and more effective and efficient immunisation services.
- Develop frameworks and tools to evaluate the impact of immunization on disease and socioeconomic indicators.
- Promote life course approaches to immunisation and integrate vaccination activities with broader disease-prevention efforts.

Support programme planning, budgeting and financing.

- Support the development of strategic multiyear and annual operational plans that respond to programme evaluations and are aligned with government budget cycles.
- Support Member States, as requested, with internal and external fundraising efforts and help align external support to country needs and priorities.

Involve new actors and introduce new technologies to improve implementation.

- Involve civil society and other actors in government-led health planning and in health system strengthening to promote equity and universal access to immunisation.
- Use workforce development and the adoption of new technologies, systems, and practices to support monitoring, evaluation and improvement of supply chains, service delivery, micro-planning, and in-country financial flows.

Provide guidance and tools to help countries with monitoring and evaluation, disease surveillance and Adverse Events Following Immunization.

- Support countries to establish appropriate, externally accredited surveillance laboratories and surveillance systems that provide information on the burden and epidemiology of VPDs.
- Increase the use of immunization and surveillance data to monitor immunization system performance and inform strategic, managerial, and operational decisions at national, subnational and local levels.
- Support countries to establish and/or strengthen pharmacovigilance systems to detect, investigate and respond to Adverse Events Following Immunization (AEFI) and improve vaccine safety.
- Promote the use of new ideas and technologies (including information and communications technologies, or ICT) that improve the accuracy, efficiency, and effectiveness of data collection and use.

2.2 Strategic Direction: Monitor and analyse global and regional immunization data

The collection, analysis, and use of data to monitor and evaluate national immunization programme performance from a global and regional perspective is a priority for WHO, its Member States, and immunization partners. Data analysis is also crucial for WHO and its partners to establish global/regional immunization policies and to monitor progress towards achievement of their objectives.

Over the next 15 years, WHO will continue to collect and validate coverage and vaccine management data to monitor programme performance and identify issues countries are facing. Data from surveillance systems (including disease incidence and AEFI rates) will also be used to develop global/regional immunization policies that are evidence-based and tailored to countries' needs.

Approach:

- Remain the prime source of immunization data and analytics at regional and global levels.
- Use innovative technologies to collect, interpret, share and use data while minimizing the reporting burden for Member States.

- Gather immunization data from all levels in a single global repository that WHO and partners can use to develop evidence-based global/regional immunization policies.
- Support better internal and external decision-making by disseminating accurate and timely immunization data and by using state-of-the-art analytics and visualizations.

2.3 Strategic Direction: Ensure the sustainability of immunization programmes

As the economic status of countries improves, more middle-income countries have begun to assume responsibility for their immunization programmes without or with very limited external financial resources. To date, donors and partners have provided investments to offset the cost of purchasing and implementing new vaccines and achieving more ambitious goals, however national governments with sufficient economic means are expected to maintain much larger and more complex immunization programmes over the long-term.

Over the next 15 years, WHO will coordinate with key immunization partners to help these countries achieve stronger and more sustainable immunization programmes by focusing on four key areas: enhanced decision-making capacity for immunization, increased political commitment, increased demand for immunization services and more timely access to affordable vaccine supply.

Approach

- Support countries to make timely, evidence-based decisions about vaccine policy and programme choices by building internal capacity to generate evidence and strengthening national decision-making mechanisms (such as NITAGs).
- Help countries build stronger political and legislative support for immunization programmes and secure more dependable domestic financing.
- Work with countries to improve both the reliable and timely supply of vaccines to immunization posts and maintain high demand for immunization services from the community.
- Improve vaccine price transparency and address major barriers that limit countries' access to affordable and timely supply of vaccine.

2.4 Strategic Direction: Apply behavioural sciences to immunization

In the last 40 years, most of WHO's concentration has focused on vaccine technologies and the many components required for effective service delivery, detailed planning and costing, skilled managers and vaccinators, and monitoring systems.

We are learning that while infrastructure and technologies are indeed important to the success of immunization programmes, the actors involved in immunization (i.e., caregivers, communities, health workers, logisticians, and decision-makers) and their knowledge, behaviours, and interactions are vital to achieving our immunization goals.

Despite increased recognition of the importance of these actors' roles and responsibilities, it is less clear how to facilitate and enhance their different forms of participation, especially given the interconnected exchanges between the various actors and their social context.

A field of research and practice in this area is beginning to open with new work streams emerging around vaccine hesitancy and demand generation. At the same time, we have yet to understand how behaviours, their determinants, and their connectedness collectively influence the programme outcomes we have been monitoring for decades.

A challenge remains in wholly understanding how behaviours are shaped by both constant and changing factors in immunization systems and how behaviours are then put into practice. Our focus will include an exploration of the links between the health system, frontline service providers, and the individuals and communities they serve, including factors that determine vaccine uptake such as trust and complacency. Moreover, our approach will be systematic and cross-cutting with the intent to establish a new area of technical expertise in the behavioural sciences to optimize immunization programmes.

Approach:

- Convene a network of experts around the world who can set a research agenda, synthesize and disseminate the evidence, monitor advances and manage the knowledge base around behaviours that influence the provision and demand for preventive health services.
- Develop guidance and support its application and adaptation based on the nature and context of the problem and desired objectives.
- Promote the integration of behavioural measures and indicators into routine monitoring to inform continuous learning and tailored programme implementation.

2.5 Strategic Direction: Sustain immunization services in emergencies

The need for immunizations in non-epidemic disasters is often high and specific strategies must be in place to quickly and decisively respond to such disasters.

WHO's emergency response team will provide global coordination and leadership to ensure that proven and effective vaccines are available and rapidly deployed to tackle outbreaks of diseases such as yellow fever, cholera, meningitis, Ebola, and typhoid. This effort will reduce the risk and impact of emergencies by providing efficient access to, and use of safe, effective and affordable vaccines.

Approach:

- Strengthen country capacity for preparedness and resilience to epidemic and non-epidemic emergencies, including the development of effective surveillance systems.
- Develop guidance on the use of vaccines for outbreak response and emergencies.
- Ensure that appropriate vaccines are available for all potential vaccine preventable disease epidemics.
- Maintain international vaccine stockpiles for selected diseases to ensure an equitable access to sufficient vaccine quantities at an affordable cost.

- Support vaccine development where no vaccine exists and the development of new technologies for epidemic outbreak responses and disasters.

2.6 Strategic Direction: Lead disease elimination and eradication efforts

Consistent with WHO's mission "to realize the full potential of vaccines", WHO will continue to lead efforts with key partners to eliminate Measles and Rubella, Hepatitis B and Maternal and Neonatal Tetanus and eradicate Poliomyelitis and other diseases where elimination or eradication is being endorsed as global or regional targets.

As current disease elimination and eradication efforts are achieved, WHO's role in new eradication and elimination efforts will shift from implementation to goal setting, partnership coordination, strategic development, monitoring and evaluation.

Approach:

- Lead and coordinate new eradication and elimination goals.
- Set and develop strategies to achieve global regional control/elimination/eradication targets.
- Provide training, technical support and staff supervision to enhance country capacity for specific eradication strategies.
- Support global networks of WHO-accredited public health laboratories that can diagnose and track virus movement and therefore drive implementation.
- Mobilize resources necessary for elimination/eradication.
- Establish and oversee implementation of global/regional certification criteria.
- Oversee the post-eradication agenda for diseases such as polio.
- Develop containment standards for biologicals once targets are achieved (for eradication).
- Develop stockpiles and guidance to respond to outbreaks post eradication.

Annex 2. Division of responsibilities between HQ, regional, and country offices

This section outlines the roles and responsibilities of HQ versus regions versus country office. It will be discussed and revised with input from country, regional and headquarters staff every five years.

Table 2: WHO core roles envisioned for 2030 in immunization and vaccines

	Headquarters:	**Regional Office**	**Country Office**:
Convene leaders and experts from all sectors	Convene technical experts to guide global policies and set priorities. Secure global endorsement of key policies through the World Health Assembly. Strengthen coordination between each level of WHO and between WHO and key partners. Enhance and maintain relationships with collaborating centres, universities and academic bodies. Develop advocacy strategies and tools for global and national use.	Support Member States to engage in governing bodies. Convene regional intergovernmental meetings and working groups and establish inter-regional health platforms. Engage Member States in international initiatives and coordinate with regional and sub-regional entities on their participation in global health issues. Increase visibility of immunization and WHO's role in immunization. Hold governments accountable to implement priority immunization commitments. Strengthen capacity to present scientific evidence when communicating with policymakers and communities.	Advocate for immunization of all recommended age groups in health sector plans. Strengthen government capacity to coordinate with other ministries, private sector entities and external partners in all immunization areas. Support governments to convene and coordinate health response in emergencies. Ensure that the comprehensive multiyear plan is the guiding document for health sector planning. Advocate with governments for sufficient funding for immunization programmes.
	Actively involve Civil Society Organizations in policy setting and		

	implementation discussions		
Establish norms and standards for products and technologies	Set norms and standards with input from technical experts, regional offices, and country-level representatives. Promote the convergence/harmonization of international norms and standards and regulatory procedures across all countries. Foster an environment that enables countries to oversee their own implementation of norms and standards.	Adapt norms and standards to the regional context, as necessary. Monitor the implementation of norms, standards and guidelines at country level. Build country capacity to implement global and regional norms and standards. Strengthen NRAs and regional regulatory mechanisms to progressively reduce the need for prequalification systems.	Encourage countries to apply global norms and standards and adapt them into national/sub-national guidelines and regulations. Build capacity of technical working groups at country level (e.g. NITAG) Invite contributions from countries experts in developing/updating global and regional standards. Strengthen and support NRAs.
Develop evidence-based policy recommendations and guidance.	Develop policy recommendations and support countries to achieve global goals. Develop and coordinate integrated service delivery strategies. Develop outbreak preparedness and response plans. Adapt policies to reflect changes in the health/immunization environment (e.g., demographic shifts in migration, aging populations, etc.) Develop behavioural strategies to address hesitancy and demand.	Develop, adapt, and apply policies and strategies to the regional context. Communicate with countries about policy recommendations in a timely and efficient manner. Provide technical advice to countries involved in regional policy initiatives.	Encourage countries to adopt regional and global policies and strategies. Strengthen and support NITAGs. Solicit feedback from national technical experts on global and regional policies. Advocate for immunizations and provide reference for immunization policies to be included in country cooperation strategies (CCSs).
Monitor and	Promote development	Monitor regional health	Monitor and evaluate

use data for analytics	and use of innovative data system technologies. Support regional offices in data collection and analytics. Monitor and analyse global immunization data using best available analytics and visualizations to support decision-making.	trends by aggregating, validating, analysing, disseminating health-related data. Help countries use regional data to evaluate and strengthen immunization services. Work with countries to generate and interpret data, through modelling and prediction. Provide technical support to countries to link laboratory networks with data systems.	national immunization policies and programmes. Look for opportunities for countries to share information both within and outside the country. Help countries collect and use high quality data for action. Facilitate innovation by promoting new ideas and technologies (including ICT) to make data collection and use more effective and efficient. Build capacities of national authorities to build/sustain national health observatories.
Facilitate implementation and synergies	Coordinate support given to fragile countries. Organize decentralized networks of technical experts to support different aspects of immunization (e.g., supply chain, data quality/surveys, surveillance, etc.) Identify opportunities for synergistic approaches to service delivery and develop appropriate strategies. Coordinate emergency surge capacity.	Participate in the development of CCSs. Support country implementation of international commitments and legal instruments. Lead technical collaboration in countries with no WHO presence. Strengthen technical cooperation among countries and among regions. Provide surge capacity during crisis and emergencies. Give countries more responsibility for	Ensure that immunizations are included in the CCS. Provide quality information, technical advice, best practices and updated information related to governments' immunization policies, guidelines and programme activities. Assess capacity gaps and provide training where needed. Develop strong technical capacity at country level to assist in planning, policy formulation, implementation, and leadership.

		managing decisions, technical needs, and financial needs. Engage with and coordinate technical immunization partners.	Support national coordination emergency response Support annual and multi-year immunization planning. Develop multi-disciplinary teams of immunization experts within WHO.
		Facilitate inter-country and inter-regional coordination and collaboration on immunisation and VPD elimination and control.	
		Strengthen private-sector provision of immunization.	
		Work with countries and partners to support internal and external fundraising efforts, and align external support to country needs and priorities.	

Annex 3: Matrix of the areas of collaboration between WHO and its partners

Table 1: Matrix of the areas of collaboration between WHO and all partners

+++ Critical role for the success of the collaboration
++ Important role for the success of the collaboration
+ Moderate role for the success of the collaboration

	Provide technical support to countries in collaboration with WHO	Technical support to WHO			Provide financial support to WHO	Provide financial support to countries	Prioritize research orientation
		Produce evidence	Help define norms and standards and policies	Monitor and evaluate immunization programmes			
Countries							
- MoH		+	+	+++			
- Independent Agencies	++		++				
Donors			+		+++	+++	+
Manufacturers						+	+++
UN and Global Initiatives	+++		++			+	
Technical Partners							
- International Technical Agencies	+++	++	++	+++	+		+
- Universities and Research Institutions	+	+++	+++				++
- WHO Collaborating Centres	+++	+	+	+++	+		
- Scientific Societies	++	++	+++				++
- Individual Consultants	+++		+	+			
CSOs							
- International CSOs	+	+	+	+++			
- Local CSOs	+++			+++			

Annex 4. Historic review of 40 years of Expanded Programme on Immunization

Executive summary of the desk review

In 2015, WHO commissioned a consultant to undertake a desk study of historical trends and milestones in the field of vaccines and immunization, with the aim to explore underlying factors that have contributed to progress in the 40 years of the EPI.

The study identified the following trends from the immunization coverage data:

- Global immunization coverage has improved dramatically of the past 40 years.
- Immunization systems appear to be sufficiently strong to support new vaccines and antigens being added to the EPI programme (at global level), which can result in protection against more diseases.
- The gap in coverage between the first and third dose of a DTP containing vaccine has decreased, possibly indicating that systems have become stronger.
- Equity in immunization coverage has improved and the total number of unimmunised children has decreased.
- Coverage trends differ substantially between regions.

The number of conditions that are preventable by vaccines have increased since 1974 and immunizations now prevent disease, disability and death from cervical cancer, diphtheria, hepatitis B, measles, pertussis, pneumococcal and *Haemophilus influenza* type b infections, polio, rotavirus diarrhoea, rubella and tetanus. Annual benefits from vaccination and global health improvements include around 6 million prevented deaths.

The desk study identified several factors that may have contributed to EPI progress including the standardised vaccination schedule; development and introduction of new antigens and vaccine combinations; greater equity of access between high and low income countries; and progress made towards polio eradication. With newer and additional vaccines the costs have increased but, thanks to partnerships such as Gavi, more expensive vaccines have become accessible to the poorest countries.

Technology developments and innovations relating to the cold chain, EPI management and health systems development efforts appear to have contributed to increased coverage of immunization. Initiatives such as the Universal Childhood Immunization (UCI) and other global and regional partnerships have further supported immunization improvements. WHO vaccine policy and technical guidance have also been instrumental in supporting the EPI at all levels, most notably WHO position papers and technical guidelines, recommendations from the Strategic Advisory Group of Experts (SAGE) and support by technical groups at regional and national levels.

Financial support from the global health community has been crucial to immunization improvements in developing countries. Large investments were made in the 1970s and 80s but in the 1990s, donor funding began to decline. It rose again around 2000 and now includes support from new actors such as philanthropist organizations.

The review found that WHO leadership in the EPI is widely recognised. WHO has a normative role and is seen as the technical expert organization. WHO is further recognised for its work to safeguard vaccine safety and quality and is seen as a convener of partners at all levels.

Executive summary of interviews with thought-leaders

In parallel with the desk review described above, WHO also commissioned a consultant to interview ten key informants selected by WHO as leaders or influencers in immunization. The interviews were conducted along a semi-structured question guide during March and April 2015.

In general, the informants perceived that the EPI programme was particularly successful from the late 1970s to the early 1990s. The 1990s was largely seen as a decade when donors and the health community lost interest in immunization with subsequent challenges in funding. This changed at the turn of the millennium when partners came together to create Gavi, the Vaccine Alliance and new actors entered the scene. The past decade has witnessed a positive development with substantially increased funding and several new vaccines becoming available to help countries combat their disease burden.

Key milestones identified by a majority of the informants include: the Universal Childhood Immunization (UCI), where a time-limited target of 80% immunization coverage by 1990 proved a powerful tool to focus attention and resources; cold chain innovation including the cold box and gas/kerosene fridges; the standardized immunisation schedule; training and capacity building, including the development of useful approaches, tools and guidelines such as supportive supervision, technical information sheets, coverage surveys, national programme reviews, planning tools and efforts to improve data quality.

While informants agreed about the trends and milestones, views differed substantially regarding the positive or negative effects on EPI of initiatives to eliminate or eradicate disease, most notably polio.

All informants recognised WHO's unique and instrumental role in the EPI and that without WHO, the world would not be where it is today in immunization. Informants suggested that the environment has changed since 1974, with many more actors and more funding becoming available for immunization. Informants viewed this as a positive development while recognising that this new landscape may present both opportunities and challenges for WHO. Informants were rather unanimous in their recommendation for WHO to focus on its current mandate, to be the recognised technical expert organization, to develop norms and standards (the Strategic Advisory Group of Experts (SAGE) was particularly noted), and to use its country, regional and international structures, including the World Health Assembly (WHA), to support and convene partners, including new ones. Informants underlined that WHO must work with utmost integrity and some suggested that WHO may have improve the way it communicates about its past and present achievements.

With regards to the future of the EPI, one informant suggested that there is a need for a fundamental transformation from a vaccine delivery platform focusing on immunisation coverage to a programme focusing on disease control.

Annex 5: Summary of findings from the expectations survey

What do partners expect from WHO in immunization?
Results from the expectations survey: summary

Overview
In January 2015 WHO launched a survey to understand what partners expect from WHO in immunization. The survey targeted global, regional and country level colleagues who work with WHO across all areas of vaccines and immunization—from vaccine development and prequalification, to new vaccine introduction, outbreak response and routine immunization.

In total, 35 persons responded to the survey, 56% from global level, 34% from country level and 10% from regional level. The survey was response rate was approximately 39%, which is in line with standard online survey response rates of 24 to 40%. The respondents represented non-governmental organizations (36%), other UN agencies (32%), NITAG members (13%), donors (10%) and government (9%).

The 13 open-ended questions asked for input on areas that WHO does well and what could it improve on at each level of the organization. The questions also asked respondents for their input on the major challenges that hamper WHO's performance in immunization, the areas where WHO should focus its efforts and areas of work that could be done equally well by other partners. Finally, the survey asked for input on what innovative areas of work WHO should be exploring over the coming years.

Summary of key findings
Across the board, there was consensus that WHO's key role in immunization is to develop policies. Respondents also listed surveillance, data collection, prequalification of vaccines and equipment, and global coordination as core WHO roles.

Results were more mixed on technical support and research. While some participants felt these were areas WHO should lead, others felt that that technical support, research, communications and cold chain were areas could be addressed equally well by other organizations. Respondents felt that WHO's performance in immunization is hampered by bureaucracy and a lack of focus, along with being too reliant on donor funding. In addition, WHO's personnel were seen as, in general, not being up to the task.

When asked what changes they would implement if they were in charge of immunization at WHO, respondents said they would improve coordination and collaboration with partners, improve relationships across all levels of the organization, ensure appropriate staffing and skills amongst staff, and integrate immunization activities (i.e., measles-rubella elimination, polio eradication, and routine immunization). Although less commonly than those areas mentioned above, respondents also said they would address the need for clear routine immunization guidance, strengthen surveillance, focus on resource mobilization at country level, implement the eradication strategies and change the way regions/country offices work to focus on concrete deliverables, rather than outputs.

The survey also asked respondents to identify the most innovative immunization related activity that WHO could undertake in the next 10 years. Responses highlighted the use of information technologies for impact (i.e., to improve data quality, to monitor immunization performance via SMS, to establish an electronic registry), vaccines and delivery system innovation (i.e., innovative vaccine storage and delivery strategies, more thermostable vaccines, simplified cold chain) and improving WHO itself (i.e., eradicating bad management, aligning behind one topic, and transitioning tasks to regional and country office, and eventually to ministries of health).

Global level feedback

At global level, respondents felt WHO did well at: setting policies and developing guidance, pre-qualification, SAGE, as well as convening experts and partners. They felt WHO/HQ needed to work on: coordination and coverage/data quality, developing more operational guidelines and ensuring better access to WHO information and policies.

Regional level feedback

At regional level, respondents felt WHO did well at: providing technical assistance, convening, EPI manager meetings, training, setting regional technical recommendations and managing relationships with ministries of health. They felt WHO/regional offices could improve on: coordination, being more open to working with partners, being more 'country focused' (i.e., providing more direct support to countries), being more innovative, and strengthening outbreak response and surveillance.

Country level feedback

At country level, respondents felt WHO did well at: providing technical assistance and working with the ministries of health, supporting NITAGs/Inter-Agency Coordination Committees and coordinating partners. They felt WHO/country offices could improve on: surveillance, coordination and collaboration, holding governments accountable, quality and timeliness of data, having the right human resources capacity and stronger capacity for outbreak response.

TFI Members Meeting, Sheraton, Addis Ababa, Ethiopia
June 30 to July 01, 2015
Draft Recommendations

The Task Force on Immunization (TFI) serves as the regional advisory body for immunizations and vaccine preventable diseases in the African Meeting. The first of two annual meetings in 2015 was convened in Addis Ababa, Ethiopia from 30th June to 1st July 2015. The primary goal of the meeting was to apprise TFI members on the progress made in delivering immunization services to the populations in the African Region, and thus protect the Region against vaccine preventable diseases. WHO and UNICEF members as well as TFI members and other partners provide updates on the delivery of immunization services in the African Region. The issues of communication and country ownership came out as important themes in many presentations and there was an urge to build on existing structures in country and for the increased inclusion of civil society organizations (CSOs) in program implementation. The TFI made important recommendations to guide the programme on various aspects of its operations which are noted below.

Outcome of 2015 Regional NITAG Meeting		
Noting that the number of technical advisory groups on immunization keeps growing, and the additional need to establish NITAGs in all Member States as recommended by the GVAP & the RVAP, WHO/AFRO and partners should support countries on innovative ways of establishing NITAGs, building on existing advisory bodies	WHO/AFRO	June 2016
Polio Eradication Update		
Considering the development of a regional polio legacy and the need to further strengthen the immunization systems in the African Region, TFI recommended that the key elements of polio infrastructure be retained to support Routine Immunization, and the implementation of strategies (including VPD surveillance) for the elimination and control of targeted VPDs in the post-polio eradication era in order to support the achievement of GVAP targets	WHO/AFRO	Ongoing
Overview of Immunization in Ethiopia		
Considering the encouraging level of community engagement for immunization activities in Ethiopia and noting that some countries in the Region have developed similar community structures / initiatives and have acquired valuable experiences in this area, WHO/AFRO should establish a platform for countries to share best practices in that regard.	WHO/AFRO	Ongoing
Meningitis outbreak in West Africa		
Given the emergence of other neisseria meningitidis serotypes after the introduction of the MenAfriVac® in the African Meningitis Belt Countries, WHO/AFRO should advocate for the development of affordable meningitis quadrivalent (ACYW135) conjugate vaccines.	WHO/AFRO	June 2018

WHO and partners should also advocate to GAVI to consider the inclusion of such a new vaccine (conjugate quadrivalent vaccines) in its next vaccine investment strategy.		
Noting the recent experience of meningitis outbreaks in Niger and Nigeria related to the scarce availability of polysaccharide vaccines (ACYW135), WHO/AFRO should advocate for a review of the current modalities for accessing the vaccine through the International Coordinating Group (ICG) mechanism and find ways of increasing awareness of countries in needs to use such platform.	WHO/AFRO	June 2016
Regional Strategic Plan for Immunization: Indicators Review		
Considering the fact that data quality, interpretation and use remain major issues, especially at operational levels in many AFR countries, WHO/AFRO should support member states to institute solid mechanisms within the national immunisation program and / or independent of the program, (such as the creation of expert teams/ establishing regular and structured data audit activities/ assignment of data quality focal persons/ recruitment of qualified statisticians or data managers) to implement and closely monitor data quality improvement plans.	WHO/AFRO	June 2016
In preparation to the Nov 2015 ministerial conference on immunization, and noting the high quality program data analysis presented by WHO/AFRO using administrative coverage data during the July 2015 TFI meeting, WHO/AFRO should prepare a similar, in-depth analysis of the mid-term review of RVAP using the 2014 WHO/UNICEF estimates when available.	WHO/AFRO	September/October 2015
Considering the importance of the mid-term review of the implementation of the RVAP, WHO/AFRO should allocate enough time to this topic in upcoming TFI meetings.	WHO/AFRO	December 2015
Measles elimination and rubella vaccine introduction		
Noting the importance of measles elimination goal WHO/AFRO and partners should continue to support countries to vigorously pursue ongoing efforts towards the implementation of the proven strategies (including strengthening routine immunisation, periodic supplementary immunization activities (SIAs), high quality surveillance, case management and response to outbreaks) to achieve the 2020 elimination targets	WHO/AFRO	Ongoing
Given the epidemiological shift in measles susceptibility towards the older age group in many countries if the Region, WHO/AFRO and partners should support	WHO/AFRO	Ongoing

countries to plan SIAs and response activities taking into account the local epidemiology		

In addition to the recommendations listed above, the TFI also advocated for the following ways to improve the overall operations and communications of the immunization programme in the region.

- Status of implementation of action points from previous TFI meetings
    - To optimize the inputs of TFI members and create environment for the successful implementation of the recommendations WHO/AFRO is required to give more information on the challenges encountered in trying to implement the recommendations
    - Given the increasing call of optimization of research for health, there was a call for strengthening research in Africa WHO/AFRO and TFI should explore ways of strengthening research in this region. New proposals and projects might be something to be revisited.
- SAGE April 2015 recommendations: implication for the African Region
    - Hep A and Hep B should be put on TFI standing agenda
    - Given the graduation of GAVI eligible countries and the likely withdrawal of GPEI funding, the TFI should consider ways of making vaccines available for Routine Immunization
- EPI Managers Meetings
    - Continued focus on the EPI Managers and their interactions by limiting presentations and discussions by partners. Support should be given to any structure of the agenda that would enhance listening to the people
    - Continued inclusion of TFI members in the meetings
    - To enhance TFI support for country plans WHO/AFRO should work out plans to optimize TFI inputs and constructive feedback through a peer review process
    - WHO/AFRO should communicate TFI appreciation of the invitation to participate in the EPI managers' meeting that we support them in implementing
    - WHO/AFRO should collate critical issues of importance to the EPI managers for TFI consideration
    - The recommendations from the EPI managers meetings are to the EPI managers themselves and to determine which recommendations are critical and what might be specific recommendations- perhaps have more nuanced
    - WHO/AFRO should support countries in implementing their recommendation. WHO should give feedback on the annual plan and annual progress report
- Feedback to Countries
    - Increased review and feedback from the secretariat provided to countries on cMYPs, annual reports, work plans, and all other program documents submitted
    - Increased monitoring of plans for revitalizing immunization services in Ebola affected countries
- The TFI discussed the possible inputs of the revitalized working group to the forth-coming Ministerial meeting and requested each working group to prepare briefing documents that should be 1 to 3 pages in length
- Outcome of 2015 Regional NITAG Meeting
    - Given the existence of many advisory groups on immunization in the countries there should be a hard look at the groups to see if they could be restructured, consolidated to minimize overlap and confusion
    - In recognition of the limitation of resources countries should be guided to think of innovative ways of developing a NITAG. They should consider possibility of building it up slowly

- In many countries things are written around regulations. However, partners should advise the MOH to apply their regulatory policies to guide the committees where they exist
- In terms of memberships, it was recommended that communication experts and CSO that understand how to create demand be added
- Given the need for the NITAG to be truly independent, when the TOR of NITAG is written there should be a declaration of interest which members must review to ascertain the independence of the group

- Polio eradication update
  - The plans to improve surveillance in the Region should extend Central Africa to include Lake Chad and also Horn of Africa
  - In addressing gaps in prioritized areas of concerns in the next 6-12 months and improving quality of surveillance including Madagascar, South Sudan, CAR, Niger, Cameroon, Equatorial Guinea, Lake Chad region, and Horn of Africa—including surge capacity and consultants, training of staff, and environmental surveillance. Drilling down to regions and areas of high risk and access is a problem and really focus on quality of surveillance
  - Given the urgency to find unimmunized children in high risk areas where they are at high risk or have high risk populations, weak surveillance, or weak SIAs. We are also noting the problem of cVDPV which indicates weak surveillance and weak routine immunization. We are going to ask for strengthening SIAs in terms on quality and independent monitoring as well as strengthened surveillance. There should be a report on this in the next TFI

- Revitalization of immunization services in EVD affected countries
  - In recognition of the existence of plans for the three countries, WHO/AFRO should circulate those plans and give regular updates on how well they are being implemented. TFI should monitor the progress of implementation of these plans
  - WHO/AFRO should update TFI about governments not communicating. If the governments lack adequate communication strategies for the restoration of immunization, TFI could have more feedback for government
  - TFI needs to closely monitor the research and confusion on vaccine trials and EPI program. Important for TFI to keep an eye on vaccine trial and understand the response of the community and understand if there is some confusion at the community level
  - TFI should monitor human resource issues

- Meningitis outbreak in West Africa
  - To be able to document the eruption of other serotype following the withdrawal of one serotype WHO/AFRO should strengthen monitoring
  - WHO/AFRO should articulate and document the various best practices, such as the buy in of the community and getting youth buy in
  - WHO/AFRO should endeavour to train relevant personnel in anticipation of crisis communication to counter misrepresentation in the media and deploy same as needed
  - There is a need to request a review to the current mechanism for accessing the ICG stock. There is a need to review the ICG

- TFI should work out strategically, where together with the RD, TFI could add pressure on the pricing of the vaccines

- GVAP – Regional Strategic Plan: Indicators Review
  - Given the reality that some of the targets are on track and others are not, WHO/AFRO should focus on those not on track
  - There are issues that are of great concern e.g. data quality, AFI stockouts and the stockouts will hinder our chances of achieving these goals
  - It will be useful to interrogate the big issues that may stop us, e.g. stockout and data quality issues
  - Before the Ministerial Meeting, focus on things that are not on track and are really a threat
  - Data quality and interpretation remain major issues. The monitoring of the RVAP will require the combined application of valid data from the both administrative and WHO/UNICEF estimates. Furthermore, the idea of triangulation of data on other areas like stockout versus coverage is recommended
  - TFI to review reports from the secretariat whenever WHO/UNICEF data is available
  - Identify critical issues where focus makes a difference (e.g. data quality, stockout, community participation and demand creation)
  - On demand creation, the TFI suggests a re-examination of the mid-term indicators to see if a better indicator can be identified
  - The chair of TFI and Dr Richard to prepare a consultative process to allow final development of report for Ministerial meeting

AGENDA FOR THE NEXT TFI

- The agenda for the next TFI, which is scheduled for December 3 and 4, 2015 in Brazzaville were discussed. The following agenda items were agreed upon:
  - Past TFI recommendations
    - Recommendations from last 2 meetings
    - Review over-arching list of issues that are persistently not addressed
  - Hepatitis A & B
  - Polio progress, especially with reference to:
    - Wild polio
    - cVDPV
    - IPV introduction
    - tOPV – bOPV switch readiness
  - Update on the restoration of EPI in EVD affected countries
  - Review the Regional Vaccine Action Plan (RVAP) with special focus on stockouts, immunization financing, routine immunization among special populations, unstable population, documentation etc
- Presentation on communication and demand creation by UNICEF
- Consultation with CSOs around key issues like demand creation

Technical Advisory Group on Vaccine-preventable Diseases (TAG)
XXIII Meeting
Varadero, Cuba 1-3 July, 2015

TAG 2015
Technical Advisory Group on Vaccine-Preventable Diseases

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TAG Members

Dr. J Peter Figueroa **TAG Chair**
Professor Public Health, Epidemiology & HIV/AIDS
University of the West Indies
Kingston, Jamaica

Dr. Jon K. Andrus
Executive Vice-President
Vaccine Advocacy & Education
Sabin Vaccine Institute
Washington, DC, United States

Roger Glass
Director
Fogarty International Center & Associate Director for International Research, NIH/JEFIC-National Institutes of Health
Bethesda, MD, United States

Dr. Akira Homma
Chairman of Policy and Strategy Council
Bio-Manguinhos Institute
Rio de Janeiro, Brazil

Dr. Arlene King
Adjunct Professor
Dalla Lana School of Public Health
University of Toronto
Toronto, Ontario, Canada

Dr. José Ignacio Santos
Professor
Experimental Medicine Unit
Faculty of Medicine of the National Autonomous University of Mexico
Mexico City, Mexico

Dr. Anne Schuchat*
Director
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA, United States

Dr. Anushua Sinha
Associate Professor
Rutgers School of Public Health
Newark, NJ, United States

Dr. Jeanette Vega*
Director
Chile's National Health Fund
Santiago, Chile

Dr. Cuauhtemoc Ruiz Matus
Unit Chief, Comprehensive Family Immunization — *Ad hoc* Secretary
PAHO/WHO
Washington, DC, United States

*** Not present at TAG 2015**

Acronyms

AD	Auto-Disable Syringes
AFP	Acute Flaccid Paralysis
AMR	Region of the Americas (under World Health Organization)
BCG	Bacillus Calmette-Guérin (vaccine against severe forms of tuberculosis)
BP-BM	Bacterial Pneumonia-Bacterial Meningitis
BP	Bacterial Pneumonia
BM	Bacterial Meningitis
bOPV	Bivalent Oral Polio Vaccine
CAP	Community-Acquired Pneumonias
CDC	Centers for Disease Control and Prevention of the United States
CLAP	Latin American Center of Perinatology
CRS	Congenital Rubella Syndrome
cVDPV	Circulating Vaccine-derived Poliovirus
DPT	Diphtheria-Pertussis-Tetanus vaccine
DPT3	Third dose of the Diphtheria-Pertussis-Tetanus vaccine
EMTCT	Elimination of Mother to Child Transmission
EPI	Expanded Program on Immunization
ESAVI	Event Supposedly Attributable to Vaccination or Immunization
FLASOG	Latin American Federation of Obstetricians and Gynecologists
GHSS	Global Health Sector Strategy
GPEI	Global Polio Eradication Initiative
GVAP	Global Vaccine Action Plan
HBIG	Hepatitis B immune globulin
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
Hi	*Haemophilus influenzae*
Hib	*Haemophilus influenzae* type b
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
ICG	International Coordination Group
IEC	International Expert Committee (for the documentation and verification of measles, rubella, and Congenital Rubella Syndrome elimination in the Americas)
IPV	Inactivated Polio Vaccine
ISO	International Organization for Standardization
JRF	PAHO-WHO/UNICEF Joint Reporting Form on Immunization
LAC	Latin America and the Caribbean
MCV1	First dose of the measles-containing vaccine
MIC	Middle Income Countries

MIG	Maternal Immunization Group
MNTE	Maternal and Neonatal Tetanus Elimination
MMR	Measles-Mumps-Rubella Vaccine
MOV	Missed Opportunities for Vaccination
M&E	Monitoring and Evaluation
NIP	National Immunization Program
NITAG	National Immunization Technical Advisory Group
NNT	Neonatal tetanus
NPCC	National Polio Containment Coordinator
OCV	Oral Cholera Vaccine
OPV	Oral Polio Vaccine
OPV2	Oral Polio Vaccine, 2nd dose
PAHO	Pan American Health Organization
PEESP	Polio Eradication and Endgame Strategic Plan
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
RCC	Regional Certification Committee
RF	PAHO's Revolving Fund for the Purchase of Vaccines and Immunization Supplies
RIAP	Regional Immunization Action Plan
RIVS	Regional Immunization Vision and Strategy
RSV	Respiratory Syncytial Virus
RVA	Rotavirus group A
RV1	Rotavirus type 1
SAGE	Strategic Advisory Group of Experts on Immunization (for the World Health Organization)
SH	Southern Hemisphere
SIA	Supplemental Immunization Activity
Spn	*Streptococcus pneumoniae*
SUDS	Single Use Disposable Syringes
TAG	Technical Advisory Group on Vaccine-preventable Diseases
Td	Tetanus-diphtheria vaccine
Tdap	Tetanus Toxoid Acellular Pertussis Vaccine (for adolescents and adults)
tOPV	Trivalent Oral Polio Vaccine
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
V3P	Vaccine Product, Price and Procurement Platform
VAPP	Vaccine-Associated Paralytic Poliomyelitis
WASH	A nonprofit, nonpartisan initiative dedicated to helping solve the global safe drinking Water, Sanitation, and Hygiene challenge
WHA	World Health Assembly
WHO	World Health Organization
WPV	Wild Poliovirus

Introduction

The XXIII Meeting of the Technical Advisory Group (TAG) on Vaccine-preventable Diseases of the Pan American Health Organization (PAHO) was held in Varadero, Cuba on 1-3 July 2015.The slogan for the meeting was "Bye-bye rubella! Let's go for more!" selected in recognition of the recent certification of the regional elimination of rubella and Congenital Rubella Syndrome (CRS). The objectives of this meeting were to present the Regional adaptation of the Global Vaccine Action Plan (GVAP), to review progress on several disease elimination and control initiatives and issue recommendations to address the many challenges faced by national immunization programs in the Americas.

PAHO's Assistant Director, Dr. Francisco Becerra, welcomed everyone and gave introductory remarks. Following Dr. Becerra, Dr. Peter Figueroa, was introduced as the newly appointed TAG Chair, a role he served in interim during the XXII TAG meeting after the passing of the former chair Dr. Ciro de Quadros. Dr. Figueroa is a former member of the World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) as well as a TAG member since 1991, and he will now preside as PAHO TAG Chair for the next four year term.

This XXIII Meeting of the TAG was different from past meetings in many ways. The first was that this year's TAG was the first Regional immunization meeting of its size and magnitude to be hosted in Cuba. The second was that it was the first TAG to be presided by the newly elected TAG President, Dr. Figueroa. Last but not least, this XXIII TAG Meeting was the first time the Regional Immunization Action Plan (RIAP) was officially presented to the TAG and all PAHO Member States.

This plan has been approved by PAHO's Executive Committee and will be presented to the Directing Council in September 2015. The RIAP provides an outline for the next five years, serving not only as the Regional adaptation of the GVAP but also as the official Regional Strategy and Plan of Action (2016 – 2020). The introduction of the RIAP arrives to reinforce the Expanded Program on Immunization's (EPI) foundations and provide additional guidance for meeting the ever increasing challenges faced by programs in the Region. The RIAP has four strategic lines of action: a) sustain the achievements; b) complete the unfinished agenda in order to prevent and control vaccine-preventable diseases; c) tackle new challenges in the introduction of vaccines and assess their impact; and d) strengthen health services for the effective vaccine administration. Finally, the RIAP intends to successfully guide PAHO Member States through second half of the Decade of Vaccines.

Regional Immunization Action Plan

Since the inception of the Expanded Program on Immunization (EPI) 38 years ago, countries and territories in the Americas have made significant strides in protecting their populations against vaccine-preventable diseases. Many Member States consider immunization a public good and a political priority; national immunization programs have also contributed significantly to the progress towards reaching the Millennium Development Goals.

From 2005-2013, coverage with the third dose of DPT reached a sustained 90% or higher on average in the Region; however, coverage has stagnated in recent years. Provisional data for 2014, however, shows that regional DPT3 coverage dropped to 88%[1]. As of 2013, the Americas ranked third in DPT3 coverage, when compared to other regions of the World Health Organization. The Region has remained on the forefront in the sustainable introduction of new vaccines; to date, 24 countries and territories have introduced the pneumococcal conjugate vaccine, 18 countries and territories have introduced the rotavirus vaccine and 22 countries and territories have introduced the vaccine against human papilloma virus. In 2015, the elimination of rubella and Congenital Rubella Syndrome (CRS) was officially declared and – with the exception of Haiti – neonatal tetanus is no longer a public health problem in the Region.

The work of national immunization programs protects individuals across the life cycle from deadly diseases and related suffering and the success of a program is based on strong performance across a multitude of areas, activities and strategies, including country ownership and financial sustainability by securing the political priority of the program and a legal framework for immunization, careful planning and coordination, procurement of a safe and uninterrupted supply of vaccines and injection supplies, maintenance of the cold chain, training, supervision and monitoring, epidemiological surveillance and laboratory capacities, and communication and social mobilization. The efforts of national immunization programs also do not happen in isolation; they are instead an integral part of national health systems and contribute to the achievement of universal health coverage.

Upcoming immunization challenges facing the Region are numerous and include: certifying the elimination of the endemic transmission of measles; adding a dose of the injectable polio vaccine and switching from the use of tOPV to bOPV, in accordance with the Polio Eradication and Endgame Strategic Plan, 2013-2018; overcoming a limited global supply of certain biologicals, identifying better strategies to reach vulnerable populations at the local level and improve coverage and improving the quality of immunization data and its use for decision-making and strategic intervention.

In order to provide strategic guidance to confront these challenges and achieve technical excellence, an overarching regional framework for immunization is critical. Over the last eight years (2007-2015), PAHO's Regional Immunization Vision and Strategy (RIVS) – approved by the 50th annual Directing Council through Resolution CD50.R5 – has served this purpose, as the strategic roadmap for national immunization programs across the Region.

In 2010, the global health community began work on the Decade of Vaccines Collaboration, with the goal of establishing the global vision for national immunization programs through the year 2020. This participatory, multifaceted effort culminated in the development of the Global Vaccine Action Plan (GVAP), which was subsequently endorsed by the World Health Assembly in May 2012 through resolution WHA65.17. As part of this process, it was established that all regions of the World Health Organization would be responsible for adapting the GVAP to fit their own specific and unique contexts.

In October 2012, the contents of the GVAP were presented to the TAG and it was reaffirmed that the Region would move forward in tailoring the global goals and strategies to the fit the needs of Member States in the Americas; this new Regional Immunization Action Plan (RIAP) will extend the RIVS framework when it expires in 2015 as the strategic document for immunization in the Americas. During the TAG meeting in July 2013, an additional presentation was given on the GVAP framework for

[1] Provisional data as of 26 June 2015.

monitoring, evaluation and accountability; this framework set forth a global structure for regular monitoring of the GVAP at all levels of implementation, including global, regional and national levels.

In anticipation of the transition from the RIVS to the GVAP adaptation for the Americas, the PAHO Secretariat has developed a proposal for the Regional Immunization Action Plan (RIAP) that was presented during the 156th session of the PAHO Executive Committee in June 2015. The RIAP will now be presented at the 54th Directing Council in September 2015 for the consideration of all Member States. The draft proposal was the product of a wide consultation process over the past year. The proposed strategies, objectives and monitoring framework were developed considering PAHO's Strategic Plan 2014-2019, as well as other regional and global level action plans, including the Polio Endgame. Within the Region, EPI managers and PAHO immunization focal points have provided feedback to align the document with the current challenges faced at the national level to move the immunization agenda forward. Other key partners have provided additional comments on the targets and monitoring framework proposed.

Through its four strategic areas of work, the RIAP 2016-2020 aims to provide Member States with the justification, guiding principles, objectives, and monitoring and evaluation (M&E) frameworks to enable national immunization programs in the Region to align successfully with the GVAP and implement strategies to ensure that all citizens of the Americas will benefit from immunization, regardless of where they are born, who they are, or where they live, until 2020 and beyond. The RIAP also encourages countries to take a more active role to achieve universal health coverage and address inequities and social determinants of health to ensure the protection of all individuals against vaccine-preventable diseases.

Recommendations:

- TAG commends countries for the significant achievements and health gains of their immunization programs, in particular the certification as the first Region to have eliminated rubella and the Congenital Rubella Syndrome.
- At the same time, TAG notes with grave concern the decrease in DPT3, Polio3 and MCV1 coverage in the Americas at national, subnational and municipal levels in recent years. Therefore, TAG calls on countries and PAHO to recommit themselves to universal immunization coverage, based on the principles of equity and solidarity, in the context of achieving universal health coverage for all.
- The TAG endorses the Regional Immunization Action Plan as the overarching regional framework to realize the vision of well-integrated, comprehensive immunization programs in the countries of the Americas.
- TAG urges Member States and PAHO to sustain health gains, prevent the reintroduction of controlled or eliminated diseases, and successfully implement the RIAP.
- TAG recommends that the health benefits, economic benefits, and cost-effectiveness of immunization in the Americas be clearly documented for policy makers, so that they fully appreciate the compelling case for investing in national immunization programs and how these benefits are linked to achieving GVAP goals.
- TAG urges PAHO to develop a communication strategy, in order to better educate the people in all sectors of society of the Americas regarding the value of immunization, to promote the demand for vaccination and its recognition as a social responsibility, and the consequences of not sustaining high coverage in terms of lives, disease, and costs.

- TAG urges Member States to identify unvaccinated populations and reach them through prioritizing the most vulnerable, including populations living in remote, peri-urban and/or border areas and belonging to special social groups (i.e. indigenous communities) in order to diminish inequities in health.
- TAG urges Member States to analyze their own data at the national, regional and local level in order to generate strategies to strengthen the routine immunization program and monitor the implementation of the RIAP/GVAP.
- TAG urges PAHO to identify ways to provide technical assistance and mobilize additional funding to support country efforts to implement the RIAP/GVAP, with an emphasis on improving coverage from the local to the national level and introduce new vaccines, where the evidence indicates. TAG urges Member States to assure adequate resources to strengthen the foundation of NIPs.

Global and Regional Initiative for Polio Eradication Update

In May 2012, the 65th World Health Assembly adopted a landmark resolution declaring the completion of poliovirus eradication a "programmatic emergency for global public health." In response, the WHO Executive Committee approved the *Polio Eradication and Endgame Strategic Plan 2013-2018 (PEESP),* which provides a detailed approach and concrete timeline for complete polio eradication.

There has been significant progress at the global and regional level in the implementation of the four key strategic objectives: 1) detect and interrupt all poliovirus transmission; 2) strengthen immunization systems, introduce the inactivated polio vaccine (IPV), and withdraw oral polio vaccines (OPV); 3) certify the eradication and containment of all polioviruses; and 4) assure that the polio investment will benefit other long term public health goals.

Progress made on the implementation of the PEESP objectives at the global level

In 2014, 359 cases of paralytic polio due to wild poliovirus (WPV) were reported, 95% occurred in the three endemic countries: Pakistan, Afghanistan and Nigeria. Pakistan notified 85% of the total confirmed cases. 19 cases occurred in 6 countries that were previously free of polio. Nigeria has not reported any wild poliovirus cases since 24 July 2014.

The South-East Asia Region, which includes India, was certified a polio-free Region on 27 March 2014. With this achievement, 80% of the world's population now lives in polio-free regions. However, the continued detection of cVDPV type 2 in environmental samples from Nigeria and Pakistan and polio cases caused by cVDPV type 2 have been detected in Pakistan in December 2014, and in Nigeria, with onset on 16 May 2015 are of concern.

The last case of WPV-type 3 was notified in Nigeria in November 2012. Since then, WPV-type 1 has caused all polio cases.

Strong progress towards polio eradication has been seen in 2015, with more and more children in the remaining endemic countries now fully protected from lifelong polio paralysis and in turn a declining number of global WPV cases. However, coverage levels are still not optimal, especially in insecure and politically unstable areas. As long as the disease remains anywhere, children everywhere are at risk.

On 5 May 2014, the WHO Director General declared the international spread of WPV a public health emergency of international concern and issued temporary recommendations on measures to reduce the risk of international WPV spread, like managing the event as a national public health emergency and vaccinating travelers from affected countries. The temporary recommendations were extended in August 2014, November 2014, February 2015, and April 2015. Currently, Pakistan is the only country exporting the virus, a significant improvement from 2014.

To comply with the guidelines of the PEESP, all countries in the world will need to introduce at least one dose of IPV in their routine immunization program by the end of 2015, in preparation for the switch. Currently, all countries have committed to do this, and introductions are underway, with almost 20% of all scheduled introductions already completed. The constrained IPV supply will be the major challenge in meeting this target.

The switch or the replacement of all trivalent oral polio vaccines (tOPV), which contain vaccine-poliovirus types 1, 2 and 3, to bivalent oral polio vaccines (bOPV), which contain vaccine-poliovirus types 1 and 3, is tentatively scheduled to occur in April 2016 during a two-week window that will be defined by SAGE in October 2015. SAGE recommended the switch because WPV type 2 has not been detected since 1999, and now tOPV generates more risks than benefits and undermines global polio eradication. Around 90% of polio cases due to cVDPV and a third of all vaccine-associated paralytic poliomyelitis (VAPP) cases are caused by poliovirus type 2.

As of 1 May 2015, 87 (45%) of the 194 WHO Member States already use IPV in their routine immunization schedules, 103 (54%) have formal commitment to introduce IPV in 2015, and 4 (2%) countries have informally indicated plans to introduce IPV in 2015.

All of the 156 countries and territories in the world that currently use tOPV should be preparing national plans for the switch following the WHO guidelines. A draft plan should be ready by the end of July and finalized by September 2015.

The WHO has a global action plan (GAPIII) to minimize poliovirus facility-associated risk after polio eradication that includes the containment of all polioviruses: wild, VDPV and Sabin. This containment plan is sequential and will begin with the containment of WPV-type 2 by December 2015, followed by the containment of Sabin poliovirus type 2 by July 2016. The final containment of all wild poliovirus is tentatively planned for 2019 before bOPV cessation. All Sabin polioviruses type 1 and 3 will be contained after the interruption of bOPV.

Countries are developing a plan to ensure that investments made during polio eradication will continue to benefit other development goals in the long term. Careful planning is essential to ensure that lessons learned during polio eradication, as well as the assets and infrastructure built in support of the effort, are transitioned responsibly to benefit other development goals and global health priorities.

Progress made on the implementation of the PEESP objectives at the regional level

The Region of the Americas reported the last case of polio in 1991 and was certified as a polio-free Region in 1994. In the last 20 years since the certification of eradication, the Region has had only one outbreak of circulating vaccine-derived poliovirus (cVDPV), which occurred in Haiti and the Dominican Republic, between 2000 and 2001.

To maintain polio eradication, countries should continue the surveillance of acute flaccid paralysis (AFP) cases in children under 15 years because AFP surveillance is considered the gold standard in polio

surveillance. Additionally, countries should implement strategies to achieve and maintain high vaccination coverage against this disease. However, the Region of Americas is not achieving all of the surveillance quality indicators. Similarly, vaccination coverage varies among countries, only 15 countries reach 95% or more of polio coverage and regional coverage has been declining in recent years.

Environmental surveillance could complement AFP surveillance in high risk areas. The Region of the Americas is considering the feasibility and opportunity costs of implementing environmental surveillance in a couple of countries. However, due to the high resource demand of implementing these activities, a careful cost-benefit analysis should be carefully considered.

The notification rate of at least 1 case of AFP per 100,000 children under 15 years has been achieved every year since 1986; the percentage of cases with adequate stool samples obtained within 14 days of the onset of paralysis, which should reach at least 80%, has varied from 73% to 79% over the last 10 years; and the percentage of AFP cases investigated within 48 hours after notification, which should reach 80%, declined in 2013 (61%) and has increased again in 2014 (75%), although not reaching the recommended target. During 2014, only two countries in the Region met these three indicators: Mexico and Nicaragua.

Regional vaccination coverage against polio, which reached 94% in 2011, has declined over the past three years, falling to 87% in 2014. In 2013 and 2014, most countries did not reach polio vaccination coverage of 95% and several countries in the Region had coverage under 90%.

To fulfill the guidelines of the PEESP, and in preparation for the switch from tOPV to bOPV, the countries of the Region will be introducing at least one dose of IPV by the end of 2015 in their routine immunization program as part of a sequential schedule: IPV followed by OPV. To date, of the 46 countries and territories of the Americas, 15 are already using IPV in their routine immunization programs and 30 have official commitment to introduce IPV by the end of 2015. To date, only Curacao maintains the plan to introduce IPV in January 2016.

Following OPV2 cessation, there will be a relatively higher, but time-limited, risk of the emergence of cVDPV and for this reason, all countries must maintain sensitive surveillance systems in order to rapidly detect and interrupt any circulating poliovirus.

The countries of the Region have received guidelines to develop switch plans and should have already started working on their plan to ensure that all requirements for a safe switch will be met. Additionally, as another important step in preparation for the switch, countries must implement a containment plan for polioviruses, according to the guidelines that have been adapted for the Region.

To verify that requirements for the adequate containment of poliovirus and final destruction of the tOPV following the switch have been met, the countries of the Region should form National Certification Committees composed of independent experts in different areas of public health. PAHO has formed a new Regional Certification Committee (RCC), which met for the first time in June 2015.

Regional plan for poliovirus containment

The Americas Region (AMR) completed Phase I of containment of wild poliovirus infectious or potentially infectious materials in 2010. Phase I was conducted in 42 countries and territories, following WHO guidelines, under AMR RCC guidance, and with the support of PAHO as secretariat.

Of 59,898 laboratories/institutions surveyed, 4,673 (7.8%) were classified as high risk, 11,549 (19.3%) as medium risk, and 43,676 (72.9%) as low risk of a facility-associated reintroduction of poliovirus into the polio-free community. At the end, 12 countries reported to have infectious or potentially infectious material of wild poliovirus, 3 of them (Colombia, Cuba and Panama) destroyed their material and 9 countries (Argentina, Brazil, Canada, Chile, Costa Rica, United States, Guatemala, Mexico and Trinidad) notified the decision to retain these materials, expecting final WHO recommendations.

On 29 December 2014, the WHO global action plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of OPV use was delivered. The 3rd edition of the Global Action Plan (GAPIII) aligns the safe handling and containment of poliovirus infectious and potentially infectious materials with the PEESP.

Achieving this goal requires implementation of safe handling and containment of polioviruses to minimize the risks of a facility-associated reintroduction of virus into the polio-free community.

The global strategy to minimize poliovirus facility-associated risks consists of risk elimination by destruction of poliovirus materials in all but certified essential poliovirus facilities and bio-risk management of such facilities by strict adherence to required safeguards.

Risk elimination in non-essential facilities is achieved through the destruction, or a transfer to essential poliovirus facilities, of infectious and potentially infectious WPV and OPV/Sabin virus-containing materials. Destruction applies to all materials potentially contaminated with any type or strain of WPV or OPV/Sabin poliovirus, or where the presence of polioviruses cannot be ruled out.

In April 2015, a small working group meeting was convened in Washington, DC to review and discuss the adaptation of the containment plan for the Americas. Two issues were extensively considered: 24 years without AFP cases caused by wild poliovirus and OPV use in most of the countries.

Aligned with the Global Action Plan, the Regional GAPIII is being implemented in three phases linked to national and international milestones in polio eradication.

Phase I: Regional and global readiness coordination

Phase I is ongoing until conditions for the global readiness of OPV2 withdrawal have been met.

Key activities to be done during this phase are:

- National laboratory survey, and inventory of polioviruses (wild, vaccine) and potentially infectious material;
- Destruction of unneeded wild poliovirus materials, that includes VDPV;
- Transfer of needed wild poliovirus materials to essential poliovirus facilities;
- Destruction of unneeded vaccine poliovirus type 2 materials;
- Transfer of needed vaccine poliovirus type 2 materials to essential poliovirus facilities;
- Destruction of unneeded samples potentially containing poliovirus materials;
- Transfer of needed samples potentially containing poliovirus materials to essential poliovirus facilities;
- Governments, institutions, and polio facilities are informed about the upcoming need for poliovirus containment; and
- Designated essential poliovirus facilities obtain certification for containment.

Phase II: Poliovirus type 2 containment period

Phase II commences as soon as the criteria for global readiness of OPV2 withdrawal are met, and continues until certification of global WPV eradication. The trigger for setting a definite date for global OPV2 withdrawal (tOPV-bOPV switch) will be the absence of all persistent cVDPV2 for at least six months.

This phase has two parts, addressing the containment of WPV or OPV2/Sabin2:

Phase IIa: Containment of all wild poliovirus (WPV)

- All WPV are contained in certified essential facilities.
- All samples potentially containing wild poliovirus materials are contained in certified essential facilities.

Phase IIb: Containment of OPV/Sabin type 2 (OPV2/Sabin2) polioviruses

- All OPV2/Sabin2 polioviruses are contained in certified essential poliovirus facilities.
- All samples potentially containing vaccine type 2 poliovirus materials are contained in certified essential facilities.
- Safe handling of new samples potentially containing poliovirus material in non-essential laboratories.

Phase IIb commences within three months of OPV2 withdrawal (tOPV-bOPV switch).

Phase III: Long-term poliovirus containment

Phase III commences when global WPV transmission has not been detected for three years and just prior to certification of global WPV eradication.

Phase IIIa: Containment of all wild polioviruses

- All WPV are contained long-term in certified essential poliovirus facilities, with enhanced primary safeguards.
- All samples potentially containing wild poliovirus materials are contained in certified essential facilities, with enhanced primary safeguards.

Phase IIIb: Containment of all OPV/Sabin (OPV/Sabin) polioviruses

- All OPV/Sabin polioviruses are contained long-term in certified essential poliovirus facilities.
- All samples potentially containing vaccine poliovirus materials are contained long-term in certified essential facilities.

Phase IIIb commences within three months of bOPV cessation (bOPV cessation is planned one year after certification of global WPV eradication).

Findings from studies on IPV-OPV sequential schedules in the Americas

Based on the WHO recommendation that all countries in the world introduce at least one dose of IPV in their routine immunization schedules by the end of 2015, in preparation for the switch from tOPV to

bOPV, studies were conducted in Latin America to assess the immunological response to sequential vaccination schedules of IPV followed by bOPV. The main results of these studies indicate that:

1. One dose of IPV at 2 months of age or later provides seroconversion in 80% of children vaccinated with an additional 10% of children presenting immunological memory in case of exposure to wild or vaccine virus.
2. Two doses of IPV provide seroconversion in 100% of vaccinated children.
3. As for intestinal immunity, two doses of IPV decreased the peak and duration of poliovirus excretion, in response to the monovalent type 2 oral polio vaccine challenge.
4. bOPV is equivalent to tOPV in seroconversion to serotypes 1 and 3 with protection in >95% of children after 2 doses. The bOPV proved to be safe, with no evidence of serious or moderate adverse events supposedly attributable to the vaccine.

Recommendations:

- All countries should have a comprehensive national switch plan developed by July 2015 and should introduce at least a single dose of IPV by the end of 2015 in order to ensure a safe switch from tOPV to bOPV.
- Countries should achieve and maintain high vaccination coverage with IPV >95% in every district and municipality. They should strengthen AFP surveillance for the early detection of polio cases caused by cVDPV or WPV. The risk of polio outbreaks caused by cVDPV2 after discontinuing use of tOPV will remain for a limited time during the transition period. After the switch from tOPV to bOPV, countries should apply at least one dose of IPV followed by two doses of bOPV, to ensure full immunity.
- Countries that have not already formed a National Certification Committee should do so as soon as possible in order to fulfill the requirements and demands of the Global and Regional Certification Commissions.
- Countries should be prepared to follow TAG recommendations on the introduction of a second IPV dose as soon as the available IPV supply is sufficient.
- TAG reaffirms that the containment of poliovirus is needed in order to protect the achievement of poliovirus eradication. TAG endorses the Regional Action Plan for containment of poliovirus that is aligned with GAP-III.
- TAG invites all countries to designate a national polio containment coordinator (NPCC).
- TAG encourages countries to carefully document the national poliovirus inventory according to the recommendations outlined in the containment plan.
- TAG reaffirms that countries must define the poliovirus essential facilities that will satisfy the GAP-III requirements to be classified as certified essential facilities.

Monitoring Immunization Progress in the Americas with the PAHO/WHO-UNICEF Joint Reporting Form (JRF)

Background

PAHO/WHO and UNICEF jointly collect information on the structure, policies, performance and impact of national immunization programs every year. Since the 1980's, PAHO has collected immunization data using the EPI Tables, initially several times a year and then every six months. Historically, WHO and

UNICEF have also collected immunization data. These organizations completed this data collection on separate timelines, despite the fact that each organization requested similar information from countries. Beginning in 1998, WHO and UNICEF merged their data collection and processing exercises through a Joint Reporting Form on Immunization (JRF) and in 2005, PAHO adapted the EPI tables to merge them with those of the WHO/UNICEF JRF. The structure and content of the JRF is now defined jointly by WHO headquarters and its regional offices (including PAHO), as well as by UNICEF, and is reviewed every 2 years; the last JRF review took place in September 2014.

The JRF is a tool used for a comprehensive data collection process. Ultimately, the objective of this process is to obtain accurate, up-to-date data on the progress of immunization programs from all WHO/UNICEF Member States globally and disseminate information to all immunization stakeholders. The data reported through the JRF is the official information source from countries and is available on the web at www.paho.org/immunization/data. It is also disseminated in at least three of PAHO's printed publications: the Immunization Newsletter, the annual brochure "Immunization in the Americas" and in immunization country profiles. Similarly, WHO and UNICEF use JRF data to produce six annual publications, articles and reports with worldwide distribution.

The process of completing the JRF also aids countries in standardizing, organizing and producing useful data for the management of their own immunization programs, as well as in evaluating the progress made. At the regional level, the data collected through the JRF helps PAHO identify the strengths and challenges faced by its Member States. This data also contributes to the formulation of regional immunization strategies, including prioritizing areas of technical cooperation with countries.

At the 2012 World Health Assembly, all WHO Member States endorsed the Global Vaccine Action Plan (GVAP) and its monitoring and accountability framework. During the 2015 Directing Council, PAHO Member States will be asked to consider the adoption of the Regional Immunization Action Plan (RIAP), which is the adaptation of the GVAP for the context of the Americas. The RIAP will provide a regional roadmap for achieving immunization goals at both the regional and global (GVAP) level. The JRF will be the official data source for monitoring the implementation of the RIAP and the progress towards achieving the targets set forth at both the regional and global level.

While the JRF offers a standardized structure and process for reporting against key indicators, this data is only useful in as far as the country-level reporting is complete, adhering to high-quality standards and submitted in accordance with the regional and global level deadlines. Late submissions and incomplete reporting result in significant data gaps and misinformation, which may impede informed policymaking and development of regional and global strategies. In the Americas, only 20 countries and territories submitted their 2015 JRFs by April, the official cutoff for submissions. An additional 20 countries and territories completed the submission process for JRFs during the months of May and June (as of 25 June); however, two countries still have not submitted their reports for this period. These delays affect the regional and global deadlines for reporting. Beginning in 2015, PAHO has made efforts to produce automated country reports from the JRF data to provide a feedback loop to countries as a means of validation.

Other challenges related to reporting inconsistencies and missing data can also have repercussions, including more delays in the publication of official data at the regional and global level, incorrect conclusions from the data and, in general, the dissemination of misinformation. In the worst case

scenario, analysis of some indicators becomes impossible due to poor quality and/or missing data points. Examples that illustrate some of these challenges in terms of JRF data are presented in the following sections, related specifically to vaccination financing data and overall vaccination coverage.

Monitoring sustainable financing for immunization in the Americas

For nearly two decades, PAHO Member States have routinely reported their expenditures on vaccines and vaccination supplies. More recently, countries have reported on the operational budget and execution for immunization services, including recurrent costs such as salaries, maintenance of vehicles and cold chains, social mobilization activities, to name a few. Historically, Member States have matched expenditures against the same planning categories used for the annual plans of action and draw from official budget execution reports. Since 2006, the WHO-UNICEF JRF has included six immunization expenditure indicators.

Four indicators are expressed in absolute values (US$ or local currency):

- Total expenditure on routine immunization, including vaccines
- Government expenditure on routine immunization, including vaccines
- Total expenditure on vaccines - used for routine immunization
- Government expenditure on vaccines only - used for routine immunization

Two indicators expressed in percentages (%):

- Percentage of routine immunization expenditure financed by government
- Percentage of vaccine only expenditure used for routine immunization - financed by government

The overall objective of these indicators is to indicate the extent to which countries are moving towards financial sustainability and greater country ownership, while introducing new vaccines and increasing universal access to immunizations. While countries in the Region and elsewhere have consistently reported against these six indicators, analysis reveals that the operational definition of the indicators and understanding of their use has changed over the years, resulting in challenges both for the countries reporting and the regional and global levels using the data to monitor trends. The WHO and PAHO are committed to supporting countries in their understanding, estimation, and use of immunization expenditure data, in order to track progress towards sustainable financing. PAHO has developed guidance for categorizing expenditures in the annual plans of action, which should ideally facilitate how expenditures are reported. Also, some countries have received support from PAHO to estimate the cost of immunization services, including the health systems shared costs – though, these expenditures should not be included in the official JRF expenditure indicators.

The GVAP has given high priority to country ownership and financial sustainability of immunization programs. In its accountability and monitoring framework, “domestic expenditures for immunization per person targeted” is one of the key indicators to monitor progress toward government commitment to NIPs. These indicators are becoming more strategic and increasingly used to evaluate and to inform immunization policy at the global, regional and country levels. Interest in improving the quality and completeness of fiscal data has increased since 2000 as governments in the Americas and elsewhere have substantially increased their investment in expanding immunization services, both in terms of the populations targeted and the vaccines offered. For example, the proportion of total available financing from government sources has on average reached 90% or more, and in most years surpassed 99% during the period between 2009 and 2013. The increase in total financing with origin from domestic (do

we mean national government?) revenue sources indicates a strong push in the Region towards sustainability for the program. Despite the absolute large incremental hike in resource needs, governments have consistently been able to source their programs with national funds.

However, the current quality, timeliness and accuracy of immunization and vaccine expenditure data for the full range of countries in the Region are weak and vary considerably among countries and reporting year. Errors, inconsistencies, and missing data are frequently identified when compiling and analyzing the data in time series. There are a number of issues that have contributed to reporting problems, including the limited clarity and understanding of the indicators and instructions; difficulty in accessing actual expenditure data; and lack of capacity, skills and incentives to collect, estimate, validate, and report the correct data. These limitations are hindering efforts to assess progress towards sustainable financing objectives and to make financing and strategic decisions based on strong evidence at the global, regional and country levels.

Immunization coverage trends in the Americas

With the approval of the GVAP's M&E framework, the World Health Assembly established a series of four immunization coverage indicators on which progress should be reported annually. These indicators were adapted for the Region and incorporated into the RIAP. Based on preliminary JRF data received for 2014 (from 40 out of 42 countries and territories), regional results for these indicators are listed below:

1) Number of countries reporting national average coverage of at least 95% with DPT3 in children less than 1 year of age.
    - Preliminary reported regional DPT3 coverage for 2014 was 88%, compared with 90% in 2013. Looking at overall trends, reported regional DPT3 coverage has steadily decreased over the last four years. In 2014, 15 out of 40 countries and territories reported national DPT3 coverage greater than 95%; 20 countries and territories reported coverage between 80% and 94%; and three reported coverage between 50 and 79%.

2) Number of countries reporting coverage of at least 95% in each district or equivalent with DPT3 in children less than 1 year old.
    - When examining equity in coverage at the subnational level, 42% of all municipalities in the Region reported coverage of at least 95% for DPT3 in 2014; this was a decrease in comparison to 2013 (46% of all municipalities).

3) Number of countries and territories that have a dropout rate below 5% between the first and the third dose of DPT.
    - Across the Region, in 2014 the DPT dropout rate was below 5% in 22 countries and territories. Seven countries reported negative dropout rates, or having administered more third doses than first doses of DPT.

4) Number of countries and territories with coverage of at least 95% for DPT3 sustained for three or more consecutive years.
    - Twelve countries or territories reported coverage of at least 95% over the last 3 or more years (2012 – 2014); in contrast, over the last three years, 23 countries and territories have never reported national DPT3 coverage greater than 95%. Additionally, three countries reported a drop in DPT3 coverage greater than 5%, when comparing 2013 to 2014.

The combination of the decreasing trend in reported regional DPT3 coverage, with decreases in the percentage of municipalities reporting coverage over 95% is of great concern. Given that viruses such as measles, rubella, and polio continue to circulate in other regions of the world, stagnant or decreasing coverage in the Americas places the immunization achievements of the entire Region at risk and requires collective action in order to confront.

Recommendations:

- PAHO should work with countries to identify obstacles encountered in the proper completion of the JRF and to streamline the reporting and data collection processes.
- In turn, TAG calls on countries to improve the quality, completeness and timeliness of JRF reporting, as the JRF is the official tool for reporting against global and regional immunization program targets in the GVAP and RIAP.
- TAG encourages countries to routinely assess the financial sustainability of their programs, using the tools in the JRF and other tools from PAHO, such as COSTVAC and the expenditure tracking tool in the quarterly Plans of Action Reporting of Expenditures.
- PAHO should develop training materials and distribute specific guidance on the data sources and methods required for correctly collecting data used in the JRF, using new technologies where applicable.
- PAHO should further the dissemination of JRF data and systematize the production of immunization country profiles.

Update of the PAHO Revolving Fund in the Global Context

Improving Member States' understanding of the challenges of vaccine markets is important to maintain the focus of PAHO and Member States towards actions that can ensure access to sufficient quantities of vaccines on a timely basis and at lower prices. In addition, understanding the rationale of global efforts and initiatives related to vaccine access will help Member States comprehend the importance and recognize the value and uniqueness of the PAHO Revolving Fund.

Timely and sufficient availability

Vaccine markets are unique and unlike other pharmaceuticals. Vaccines are more prone to manufacturing failure, and thus require high quality manufacturing standards with resulting regulatory oversight and costs. Production timelines are often lengthy and require considerable and careful advance planning. The limited number of manufacturers restricts the global supply base of some vaccines, which also does not promote competition to reduce prices.

Despite challenges in the vaccine market, the PAHO Revolving Fund has successfully ensured the sufficient availability of the majority of vaccines procured in the last 2 years. However, there are still some significant challenges. For example, for some vaccines, there is a very limited global supply base with no more than 3 or 4 suppliers, with no new entrants in the market expected. Such is the case with the BCG, DPT and Yellow Fever vaccines. For others, such as vaccines containing acellular pertussis, the supply base is not robust and there have been production problems from the manufacturers.

To address these challenges, PAHO has taken different approaches, depending on the issue. PAHO has moved its bid solicitation process to earlier in the year, so that manufacturers can be notified and plan

production months in advance to the first deliveries. PAHO has been working with Member States to encourage them to consider different supply base conditions in their decisions on whether to include particular vaccines in their immunization programs. In addition, for vaccines such as BCG and DPT, based on market insight, the Revolving Fund implemented a different procurement approach and issued a three-year tender in order to increase market attractiveness for manufacturers and ensure long term commitment to fulfill the needs of PAHO's Region. With a vision to enhance the regional supply base of strategic vaccines, the PAHO Revolving Fund has expanded eligibility for some vaccines with marketing authorization and lots released by some regional National Regulatory Agencies. PAHO will continue encouraging developing country vaccine manufacturers in order to enhance supply of WHO pre-qualified vaccines that meet PAHO Revolving Fund quality standards for the Region.

Careful preparation and anticipation of demand forecasts from countries and territories is necessary to support PAHO's procurement strategy. PAHO has made missions to Member States to jointly review demand forecast processes and to identify improvement opportunities for the tools used.

Vaccine prices

Vaccine prices represent significant financial challenges for Member States, as the total vaccine cost to fully immunize a child against 12 vaccine-preventable diseases is US$63.80[2]. Most of this cost represents new vaccines – particularly pneumococcal conjugate (PCV) and rotavirus vaccines. The PCV vaccine alone is US$47.40, which accounts for 75% of the total vaccine cost of immunizing a child; and the rotavirus vaccine is US$13.00, which represents 20%. The introduction of the HPV vaccine adds an additional financial challenge.

Unfortunately, there is little to no real competition in the new vaccine markets for PCV, rotavirus, or HPV vaccines. There are no more than two WHO prequalified manufacturers for any of these products, and no new entrants expected in the short term; and market competition is a key driver to lower prices. For example, the pentavalent (DTP-HepB-Hib) vaccine is available at significantly lower prices than it was six years ago as a result of an increased number of WHO prequalified manufacturers, currently seven. This competition has led to a sharp drop in prices.

The PAHO Secretariat continuously seeks opportunities to access vaccines at lower prices in order to support the sustainability of Member State immunization programs, and its opportunity to keep expanding the protection against other preventable diseases for the populations.

Counting on the commitment of solidarity and support from PAHO Member States during a long negotiation process, the PAHO Secretariat, with support of partners, reached agreements with both HPV vaccine manufacturers to secure lower prices for the participating countries and territories in the Revolving Fund. PAHO is encouraged that, as a result of these agreements, the use of this vaccine should be brought to scale in the Region. Dialogue, partnership, and commitment of solidarity from PAHO Member States have made this success possible.

Global initiatives in regards to vaccine access

[2] Based on 2014 PAHO Revolving Fund Prices and considering the following vaccines: BCG, polio, penta (DPT-Hib-HepB), MMR, PCV, and Rotavirus.

Countries beyond our Region are exposed to the same challenges of the vaccine markets as the countries in our Region. The difference is that countries in our Region have access to the Revolving Fund and have solved different financial, procurement and regulatory challenges, which the countries in other regions still face. Pooled vaccine procurement initiatives in other regions have been considered or implemented but without achieving the expected results so far.

In May 2015, the World Health Assembly (WHA) agreed to a resolution that urges Member States to increase transparency around vaccine pricing, explore pooling the procurement of vaccines, among other aspects. This endorsement will support the ongoing and future global efforts to increase access to affordable vaccines for middle income countries.

Currently there are two global efforts led by the WHO including PAHO, with the support of partners. These efforts are "The Vaccine Product, Price and Procurement (V3P) system[3]" to increase vaccine price transparency. So far PAHO RF, UNICEF and 34 countries, most from the European region, are sharing vaccine prices. Despite the limited number of countries participating, the impact of the PAHO Revolving Fund with regards to access to lower prices can be seen in the V3P.

The second effort, endorsed by SAGE in April 2015, is known as the Middle Income Countries (MIC) Strategy. The Strategy focuses on enhancing political will and appropriate domestic financing; strengthening evidence-based decision-making; access to timely and affordable supply; and, enhancing systems and delivery capacity. Within the framework of the MIC Strategy, PAHO will explore opportunities to synergize procurement approaches with developing countries in other WHO Regions.

At the end of 2014, 41 countries and territories had acquired vaccines, syringes, and supplies through the Revolving Fund. The Fund offers 45 vaccines and 19 types of vaccination supplies. Total purchases over the past year have been in the order of US$573.3 million. Given the global vaccine market dynamics, global efforts mentioned, and the relevance of the pooled vaccine procurement approach in the Americas, the Revolving Fund has emerged as an example of a successful mechanism for several international organizations and other WHO regions.

Recommendations:

- TAG recognizes the PAHO Revolving Fund as a unique contribution to the success of the immunization programs in the Americas, and that it represents a model for consideration by other Regions.
- TAG lauds the collective effort of countries participating in the Revolving Fund to ensure access to an affordable and sustainable supply of vaccines for the people of the Americas.
- TAG encourages PAHO to update countries on vaccine markets and implement proactive responses to specific vaccine issues.
- Successful negotiation of affordable prices requires, among other aspects, that all countries provide accurate forecasting of vaccine needs. Therefore, TAG strongly recommends that countries ensure the development of increasingly accurate demand forecasts and the prompt payment against the orders. PAHO should support countries in the process of demand planning and monitoring.
- TAG encourages PAHO to support global efforts to improve access to affordable vaccines, including regional pooled procurement initiatives.

[3] http://www.who.int/immunization/programmes_systems/procurement/v3p/platform/en/

Update on Maternal Immunization

Maternal immunization refers to immunization prior to pregnancy, during pregnancy, and in the post-partum period (for both the mother and the newborn), in order to provide protection to the mother-child binomial. Maternal immunization has the potential to impact early childhood morbidity, and in some cases, mortality. Infections such as respiratory syncytial virus (RSV), influenza, and pertussis are associated with adverse outcomes in young infants – i.e. prior to commencement or completion of primary infant immunization series. Gains in reducing global childhood mortality have mostly been outside the neonatal period. Approximately 40% of global childhood deaths occur in the neonatal period. Many of these deaths are due to infections that can be prevented through existing or potential maternal vaccines.

One reason maternal immunization has gained attention in recent years is the potential to leverage the antenatal care platform. It is a core component of the new immunization model, which transitioned from child immunization to immunization of the whole family. The establishment of a routine maternal immunization platform represents a new paradigm that includes the universal use of influenza, tetanus and pertussis vaccines and consideration of the use of other relevant vaccines in the near future.

To date, in all LAC countries, the tetanus-diphtheria-containing vaccine is recommended for all women of childbearing age; in 27 LAC countries influenza immunization is indicated for pregnant women; and, the pertussis-containing vaccine is indicated for pregnant women in 11 LAC countries in outbreak situations

PAHO Maternal Immunization Working Group (PAHO MIG)
In February of 2015, PAHO convened a PAHO Maternal Immunization Working Group (PAHO MIG) in Washington, DC with key maternal immunization and infectious disease experts from multiple institutions, with the aim of developing a PAHO field guide on Maternal Immunization and to provide ongoing technical guidance on maternal immunization to the PAHO Technical Advisory Group (TAG).

The PAHO MIG includes representatives from WHO, CDC, Emory University, CLAP, FLASOG, the Expanded Program on Immunization (EPI) – Honduras, EPI – Argentina, Cincinnati Children's Hospital and the Universidade Santa Casa de Sao Pablo.

The PAHO MIG is currently reviewing the content to be included in the guide, which will provide information on the integration of immunization and prenatal care services, vaccine safety and effectiveness, decisions on implementation or expansion of coverage of existing available vaccines (such as seasonal influenza, tetanus and pertussis), M&E, and communication strategies and tools for different target audiences.

Vaccine safety
Maternal immunization is critical for the health of both mothers and babies. The demonstrated safety of maternal vaccines, as well as the management and communication of adverse events constitutes a critical strategy for the success of the maternal immunization platform in the PAHO Region. The PAHO Maternal Immunization Guide will address this important issue and provide countries with practical

communication tools and guidance for different audiences (obstetricians, pregnant women, general population, and media).

Integration of immunization and antenatal care services
A key aspect highlighted throughout the guide is the integration of health services. An integrated and comprehensive service delivery has the potential to generate demand, strengthen routine immunization services, and improve the coverage of integrated activities. NIP's and other reproductive, maternal, neonatal and child health (RMNCH) interventions will benefit integration at the service delivery level, since it make the most efficient use of scarce resources, such as health workers, and respects the burden on families associated with travelling to health facilities. It also implies that more mothers and children will receive these integrated health services.

As part of these integration efforts, PAHO's Immunization Unit is working closely with the Latin American Center of Perinatology (CLAP) to expand their Clinical Perinatal Record to include more maternal immunization-related variables that will allow for regional analysis, progress follow-up, and eventual adverse events.

Maternal immunization schedule
The PAHO field guide contains a revision of maternal immunization, covering all SAGE and TAG-recommended vaccines (preconception, during pregnancy and postpartum), and the vaccines that could be given to pregnant women in special situations, including travel to endemic areas of diseases preventable by maternal immunization, exposure, and outbreaks. It also includes newborn immunization during the first 24 hours of life (BCG and hepatitis B).

Recommendations:

- TAG congratulates PAHO for taking the lead in the development of an integrated maternal immunization platform, including guidelines and a maternal immunization schedule.
- TAG encourages PAHO to finalize this line of work to provide guidance to countries on maternal immunization, including information on vaccine safety and risk communication necessary to its successful implementation. PAHO should foster a model where immunization is part of an integrated platform of care for pregnant women and newborns.
- TAG reaffirms existing recommendations for the universal use of influenza vaccine among pregnant women and the use of Tdap among pregnant women where indicated by pertussis outbreak among young infants.

Update on the Status of Measles, Rubella, and Congenital Rubella Syndrome Elimination

On the 22nd and 23rd of April, 2015, the International Expert Committee (IEC) for Measles and Rubella Elimination in the Americas reviewed epidemiological evidence presented by PAHO/WHO Member States and determined that the Region had eliminated the endemic transmission of rubella and Congenital Rubella Syndrome (CRS). The last confirmed endemic rubella case was reported in February of 2009 in Argentina, while the date of birth of the last confirmed CRS case was August 26, 2009 in Brazil.

To accomplish this goal, PAHO developed a rubella and CRS elimination strategy, aligned with the measles elimination strategies. This strategy calls for the (1) introduction of a rubella-containing vaccine into routine vaccination programs for children aged 12 months, reaching ≥95% coverage in all municipalities; (2) implementation of a one-time mass vaccination campaign among adolescents and adults, in an estimated range of 15-49 years of age ("acceleration campaigns) and periodic follow-up campaigns among children aged 5 years; and (3) the integration of rubella surveillance with measles surveillance and the implementation of CRS surveillance.

Since 2010, 57 imported rubella cases have been reported in eight countries: Argentina (4), Brazil (1), Canada (17), Chile (1), Colombia (2), French Guyana (1), Mexico (2) and the United States (29). Regarding CRS, 4 imported cases have been reported in Canada (1 in 2011) and United States (3 in 2012). In 2015, no imported cases of rubella or CRS have been reported.

The IEC also noted that, in the near future, it hopes to be able to declare the Region free of measles. Endemic measles transmission had been interrupted in the Region in November 2002. Nevertheless, in recent years, imported cases from other regions of the world have produced significant measles outbreaks in several countries. The total count across the Americas of imported cases from 2003 to 2014 reached 5,086 cases, most of which occurred in 2011 (n=1,369) and 2014 (n=1,824). In 2015, a total of 543 cases have been reported[4] mainly in Brazil (n=161), Canada (n=195), Chile (n=7), Mexico (n=1), Peru (n=4) and the United States (n=175).

During the April meeting with the IEC, Brazil presented the current epidemiological situation of the sustained measles outbreak affecting the states of Ceara and Pernambuco. After updating the figures through the weekly measles bulletins, the number of confirmed cases reached 1,109[5] for the period 2013-2015. The outbreak remains active in the state of Ceara (n=855), specifically in the municipalities of Fortaleza (n=395) and Caucaia (n=87). Adolescents and adults remain the most affected group by this outbreak (44.4%), followed by children aged 6-11 months (24.8%). For this reason, Brazil started vaccinating children aged >6 months in 2014 (dose zero) and continued administering the first and second doses at 12 months and 15 months. The genotype identified was D8. Slow but continuous transmission ("drop by drop" transmission) showcased failure to implement an aggressive and quick outbreak response, as well as the presence of several unvaccinated individuals dispersed in areas with reported high vaccinated coverage.

In late February 2015, Ceara implemented a mop-up vaccination campaign targeting individuals aged 5-29 years in Fortaleza and Caucaia. The campaign may be extended to additional municipalities (n=20) in order to get ahead of the virus. Strong political commitment is being demonstrated at all levels (federal/state/municipality) to halt the current epidemic within the next 60 days, as strongly recommended by the IEC in April 2015. However, despite improvements, the outbreak continues, with rash onset of the last confirmed case on 2 June 2015.

Today, endemic measles virus transmission has been re-established in Brazil, as virus circulation has persisted for over 24 months in the country, and there are still cases under investigation (n=35)[6].

[4] Data as of epidemiological week 26, 2015 (ending on 4 July 2015).
[5] Data as of epidemiological week 25, 2015 (ending on 27 June 2015).

[6] Data as of epidemiological week 24, 2015 (ending on 20 June 2015).

Regional framework for sustaining elimination

Following the Resolution CSP28.R14 issued at the 28th Pan American Sanitary Conference in September 2012, the IEC tasked PAHO at its last meeting to provide guidance on how to monitor the progress towards the sustainability of measles, rubella and CRS elimination. To this end, PAHO is developing a framework to monitor the sustainability, to ensure alignment between the activities that will be implemented among PAHO's Member States. This framework will build on the vast experience gained in all countries and therefore will propose complementary surveillance and vaccination activities (i.e. active case finding) to add to existing evidence in the documentation of the absence of measles and rubella cases in the Region. The sustainability of measles and rubella elimination should be annually monitored in each country, following a standardized process.

Several technical consultations were held for defining the surveillance indicators, including a working group meeting with renowned country experts and PAHO's immunization focal points, which took place in Bogota, Colombia on June 2-3, 2015. The working group underscored the need of having complete, reliable, timely and consistent surveillance data. To this end, it was proposed to replace the indicator that collects information on the number of surveillance sites reporting weekly with, indicators to monitor the number of municipalities reporting suspected measles and rubella cases as well as the number of countries reporting measles-rubella weekly data to PAHO. Finally, the working group recommended that countries adopt and use PAHO's confirmed case definition for measles and rubella, and the CRS suspected case definition.

Following recommendations from TAG in 2014 requesting that PAHO carefully study the transmission patterns and age-distribution of cases in the recent measles outbreaks, PAHO presented this data, in particular evidence from recent outbreaks in Brazil, Ecuador and the United States, to the June 2015 technical consultation working group members. Based on this evidence, the working group agreed to continue recommending vaccination against measles (one or two doses depending on the age) for all individuals over 6 months of age living in areas with documented measles virus circulation.

Recommendations:

- TAG recognizes the efforts of Brazil in the face of the ongoing outbreak of measles. Nonetheless, TAG urgently calls on the Government to take decisive measures to end the outbreak of measles in Ceara. Following the last confirmed measles case in Ceara, the government will need to document the interruption of measles virus circulation in the affected areas, in accordance with the verification criteria established by PAHO.
- TAG urges countries to fully implement the currently recommended surveillance indicators, in order to have a sensitive and timely surveillance system, which produces reliable and consistent data.
- TAG recommends vaccinating infants 6-11 months of age in outbreak situations. (This dose will be considered to be a "zero dose"). These infants should then receive the first dose of measles-rubella-mumps (MMR) containing vaccine when they reach 1 year of age, and a second dose according to the country's national schedule, preferably at 18 months of age.
- TAG strongly recommends that WHO-Geneva raise progress towards the global elimination of measles as a resolution at the next World Health Assembly (WHA), to strengthen the commitment of the other regions in achieving the goals of the Global Vaccine Action Plan (GVAP).

Update on HPV Vaccination in the Americas

As of June 2015, 23 countries and territories in the Americas have introduced the vaccine against human papillomavirus (HPV) in their publicly funded immunization programs. An estimated 85% of a typical birth cohort of adolescent girls (6.5 million girls) has access, by policy, to HPV immunization in the Americas. Data on the actual vaccination coverage is not available for all countries that have introduced the HPV vaccine. Where available, these data show that coverage is at best 85% for the first dose and lower for the subsequent doses.

The pace of countries introducing the HPV vaccine appears to have decreased in the Americas. Although seven countries introduced the HPV vaccine in 2013, only three countries did so in 2014. Six additional countries had intended to introduce it in 2014, but, but did not. Compared to the subregions of North America, the Southern Cone and the Andes, fewer countries in Central America and the Caribbean have introduced the HPV vaccine. Concern about whether the country can afford HPV vaccination is the main reason why national authorities have postponed new introductions. Nonetheless, PAHO, with support of partners, reached agreements with both HPV vaccine manufacturers to secure lower prices for the participating countries and territories in the Revolving Fund. This agreement — together with the implementation of a 2-dose extended immunization schedule for adolescents aged <14 years (recommended by both TAG and SAGE) — should, in the next few semesters, ease concerns about the affordability of HPV vaccination. Economic analyses unequivocally show that HPV vaccination is a cost-effective intervention.

Evidence from active surveillance and large epidemiological studies demonstrate that the HPV vaccine is safe. Regrettably, large strata of the public, the media, and even health professionals have an opposite, incorrect perception. This situation came to a dramatic manifestation in August 2014 in a town of the Caribbean coast of Colombia, where an outbreak of mass psychogenic illness occurred. HPV vaccination was expanded in Colombia in 2013 to include all girls aged 9–18 years; in the affected town, a significant number of girls received their second dose in March–April 2014. Between May 28 (outbreak onset) and mid-September, 2014, 457 patients presented at the town's hospital with two or more of the following signs/symptoms: headache, paresthesia of the lower or upper limbs, respiratory distress, chest pain and fainting. Of those patients, 444 (97%) were girls aged 9–19 years. Although some girls went to the hospital several times, all case-patients recovered quickly without sequelae. The epidemic curve shows several clusters of cases over the 3.5-month period. The community initially attributed the illness to an alimentary intoxication and later to pesticide fogging. However, the largest cluster of cases occurred between August 18 and 28, 2014, when the community eventually attributed the illness to HPV vaccination and national media quickly covered the story. In the town, there are 21 schools; 60% of the cases related to 6 schools. Highest attack rates were observed for girls living in urban neighborhoods and attending public school. The outbreak may have started in a school, due to a psychologist who had labor complaints; an aspiring local politician, a group of lawyers interested in collectively representing the patients against both the state and the vaccine manufacturer, and representatives of the Spanish association of the "HPV vaccine victims" converged in August to fuel the outbreak. A similar, albeit much more limited outbreak occurred on September 4, 2014, in a school in Brazil. After the administration of the second dose of HPV vaccine, 11 girls fell ill and were taken to emergency rooms; all recovered quickly and were discharged. The Colombian and Brazilian outbreaks of mass psychogenic highlight the importance for health professionals and authorities to be aware of the possibility of mass psychogenic illness related to HPV vaccination or the administration of any other vaccines. In addition to a quick

recognition of these events, the response needs to be deliberate and carefully balanced because both dismissing and overreacting will fuel the potential outbreak.

HPV vaccine is safe and efficacious. Mounting evidence also shows that HPV immunization programs are effective in reducing HPV infections and precancerous cervical lesions among young women. HPV immunization programs can curb the burden of cervical cancer and possibly other HPV-related cancers within a generation in the Americas. Availability of the vaccine through publicly-funded programs, unambiguous programmatic efforts to achieve and maintain high vaccination coverage, and acceptance of the HPV vaccine by the public and media will be key ingredients to achieving such potential.

Recommendations:

- TAG applauds the efforts of the PAHO Revolving Fund to negotiate lower HPV vaccine prices for Member States to accelerate regional uptake of this vaccine.
- TAG urges countries that have not introduced the HPV vaccine as part of their vaccine preventable disease and cervical cancer prevention platforms to accelerate their decision-making process and to take full advantage of two-dose extended immunization schedules and the favorable HPV vaccine price offered through the PAHO Revolving Fund.
- Countries that have already introduced an HPV vaccine should strengthen their efforts to determine vaccination coverage at the subnational and national levels, and to use these data to solve barriers to and misperceptions related to HPV vaccination.
- TAG requests that PAHO document the experiences and lessons of countries that have introduced the vaccine and make them available to other countries.

- TAG notes the findings from the Global Advisory Committee on Vaccine Safety (GAVCS) that affirm the safety of the HPV vaccine. PAHO should disseminate these findings and work with countries to develop easily understandable information on the safety and effectiveness of this vaccine in the prevention of cervical cancer.

New Vaccines Surveillance Update

Sentinel surveillance of bacterial pneumonia and meningitis (BP-BM), and rotavirus was implemented in Latin America and the Caribbean (LAC) in 2005. There are 12 countries (Bolivia, Brazil, Ecuador, El Salvador, Guatemala, Haiti, Honduras, Nicaragua, Panama, Paraguay, Peru, Venezuela) and 37 sentinel sites for BP-BM, and there are 18 countries (same countries as BP-BM, but also Chile, Colombia, Dominican Republic, Guyana, Saint Vincent and Grenadines, Suriname) and 79 sentinel sites for rotavirus surveillance. Since 2009, the World Health Organization (WHO) has implemented the global sentinel surveillance network for invasive bacterial diseases and rotavirus and LAC is part of this network.

The objectives of the sentinel surveillance are to:

1. Describe the epidemiology of the diseases monitored.
2. Estimate the burden of disease to support the introduction of new vaccines.
3. Monitor the impact of vaccination on the epidemiology of these diseases.

Regarding the epidemiology of these diseases, the information gathered from surveillance has been important for the development of studies and data analysis that show how the distribution of the disease has changed after the introduction of vaccines, especially in the countries that had data before vaccine introduction.

The basic criteria for a sentinel site to be considered a consistently performing site include: the enrollment of cases for all 12 months of the year, the enrollment of at least 100 suspected cases per year for meningitis and rotavirus, and at least 500 for pneumonia.

The percentage of positivity for *Streptococcus pneumoniae (Spn)* in BP has shown a downward trend since the beginning of the surveillance in 2007. However, of the identified positive cases, the highest percentage still corresponds to *Spn*, representing over 70% of isolates from investigated cases in all of the years of surveillance. The surveillance of BP has enabled the reporting and investigation of 127,000 hospitalized pneumonias, 75,000 pneumonias with a radiological pattern that were most likely bacterial, and 56,000 blood samples which included 852 *Spn* or Hi positives for approximately one million hospitalized children.

In addition, the sentinel surveillance of BM has enabled to capture a total of 5,000 meningitis cases, of which 2,000 (49.2%) were classified as most likely to be bacterial and 285 were confirmed either as *Hib* (58; 20.4%), *Hi* not b (20; 7.0%), *Neisseria meningitidis* (39; 13.7%) or *Spn* (168; 58.9%).

However, the sentinel surveillance of BP-BM has a number of challenges that are important to consider. First, the identification of the total of hospitalized Community-Acquired Pneumonias (CAP); the accurate reading of chest X-rays, which classify the cases as probable for BP or not; obtaining blood samples or pleural fluid; and the culture and identification of these organisms.

Proper identification of hospitalized CAP, training in chest X-ray readings, the monitoring of sampling, culture, and identification procedures are key aspects in the proper functioning of this surveillance system.

Today, with regards to surveillance, the implementation and the use of molecular techniques, such as the Polymerase Chain Reaction (PCR), will be important for the proper identification of these pathogens.

Regarding rotavirus surveillance between 2005 and 2013, there have been a total of 256,643 hospitalizations for diarrhea reported and investigated, 136,040 suspected cases for rotavirus diarrhea, 104,068 stool samples collected, and 30,984 positive rotavirus cases. A downward trend in the percentage of identified cases of rotavirus diarrhea has been shown (percentage <0.001), with a reduction of 40% between these years. Some major challenges that have yet to be met with regards to rotavirus surveillance include the need to standardize sample selection for genotyping and linking case-based data to genotype data.

Recommendations:

- TAG recognizes that the success of sentinel surveillance depends upon the timely and complete reporting of data, and as such, countries should assure that the performance criteria defined by WHO/PAHO are met.
- TAG thanks countries for their participation in the Regional network and for the progress in monitoring the epidemiology of rotavirus and pneumococcal disease in the Region. Countries

that have not implemented sentinel surveillance should consider doing so, using global and regional guidance on quality.

Missed Vaccination Opportunities

Strategic Objective 3 of the Global Vaccine Action Plan (GVAP) calls for the benefits of immunization to be distributed equitably to all people. PAHO, in its Regional Immunization Action Plan, shares this goal. PAHO and other partners have helped LAC countries implement plans of action to raise immunization coverage in vulnerable municipalities. Countries are encouraged to determine local causes of under-vaccination and to implement interventions to overcome barriers in achieving high vaccination coverage.

In response to recent country requests for assistance in conducting Missed Opportunities for Vaccination (MOV) studies with the goal of increasing immunization coverage in vulnerable municipalities, PAHO is publishing a standardized methodology to evaluate MOVs in children aged <5 years in primary and secondary health facilities and to evaluate the vaccine-related attitudes and knowledge of health workers. The methodology was adapted from the original WHO methodology published in 1988 and other immunization studies implemented in the Region, and takes into account the best practices in immunization surveys from LAC.

Based on a review of available data, PAHO developed the study methodology and two questionnaires: one to measure MOVs in children aged <5 years and one to evaluate the knowledge, practices, and attitudes of health workers. A guiding principle for the inclusion of information to be collected was its usefulness in the field and its potential for identifying corrective measures. The method was designed such that both questionnaires would be implemented on the same day at the same health facility, with the first being administered by interviewers to caregivers of children aged <5 years and the second being anonymously completed by individual health workers. The methodology seeks information from a broad range of participants and is designed to evaluate health practices in visits intended for vaccination and in those sought for other reasons (i.e. well child check-ups). Caregivers of children aged <5 years are eligible to participate following a visit to a health center for any reason. Healthcare professionals who do not routinely administer vaccines, including those who work in nutrition and well child clinics, may also be included in the health worker surveys.

The methodology allows for a cross-sectional evaluation of MOVs. Because the evaluation serves as an operational tool for the identification of MOVs in municipalities that do not meet target coverage levels, quota sampling rather than probability sampling is recommended. Geographical areas (municipalities) are first selected based on coverage rates, indices of unmet basic needs, and other indicators. Health facilities are then selected, taking into account the proportion of the population residing in rural versus urban areas and the proportion of patients who use hospitals versus primary care centers

In October 2012, the Dominican Republic piloted the updated methodology using the methodology and questionnaires written in Spanish. In 99 health centers in low-coverage municipalities, 1500 parents and guardians of a child aged <5 years were interviewed and 398 healthcare professionals completed the health worker survey. Of 782 opportunities for 527 eligible children to receive needed vaccines, a total of 262 MOVs were observed. To evaluate the completeness, implementation and understanding of the methodology, PAHO professionals participated in all stages of the evaluation. Implementation was considered successful: the assessment was feasible to implement in two weeks, target sample sizes

were obtained, and a large proportion of health workers participated, recognized the findings as problems in their health facilities, and proposed solutions to these problems.

To implement the assessment, a country must adapt the questionnaires and MOV algorithm to its vaccination schedule. The methodology provides guidelines to aid investigators in determining eligibility, timely doses, and windows of opportunity. The country should then select an implementation team. Implementation teams should consist of a general coordinator, supervisors, interviewers, and data entry personnel (if data are collected using paper forms), and the inclusion of a statistician in the study team is recommended. The team may be composed of non-immunization health professionals, or the country may hire an independent polling company or an academic institution to conduct the assessment. Training sessions for team members, a pilot test, and procedures to ensure data quality are required. Before implementing the study, investigators must ensure that it will be conducted according to national regulations for the use of health data. Investigators are encouraged to conduct univariate and stratified analyses to identify factors associated with MOVs and under-vaccination in the surveyed population, with the understanding that the results are not generalizable to the entire country as sampling is non-probabilistic.

The final step is the preparation of reports that facilitate the design of specific strategies to reduce MOVs. The first report should be brief and highlight major findings for national health authorities and partners where applicable; and another more detailed report to be presented to the subnational and national EPI managers, and to those in charge at the local level.

As the results were presented in the Dominican Republic to both national and subnational EPI managers, and subnational officials, many of whom are responsible for immunization services in evaluated health centers, they suggested interventions and helped ascertain underlying factors related to identified barriers. Moreover, the inclusion of local-level immunization officials in the MOV assessment increases the involvement and commitment of the officials who are ultimately responsible for implementing interventions.

Lastly, countries should document studies they conduct on MOVs and under-vaccination. The limited number of published studies in developing countries, particularly in LAC, that evaluate immunization programs, validate coverage data, or assess the effectiveness of interventions is well known. Among other benefits, increased documentation of operational studies on immunization will help countries establish a baseline for progress, advocate for increased political commitment and external funding, promote evidence-based decision-making, and share experiences with the rest of the immunization community.

Recommendations:

- TAG commends the work of countries to identify and remove barriers, to vaccination with the aim of achieving high vaccination coverage at all levels.
- PAHO, in conjunction with other partners, will continue to review studies regarding the regional causes of under-vaccination.
- PAHO should make information available on the best practices to reduce missed opportunities for vaccination, describing how successful interventions are developed, cost-effectively implemented, monitored, and evaluated.

- Countries should document interventions and repeat this type of study, ideally with a costing component, in three to five years, to evaluate whether the interventions implemented were successful in reducing MOVs and contributed to more equitable immunization coverage rates.

Progress toward Regional Neonatal Tetanus Elimination

Background

In 1989, the World Health Assembly adopted a resolution calling for the elimination of neonatal tetanus (NNT) throughout the world by 1995 and the resolution was endorsed by the PAHO Directing Council. Ministers of Health of PAHO Member States initiated specific program activities to eliminate neonatal tetanus with support from PAHO and a variety of international agencies.

To achieve maternal and neonatal tetanus elimination (MNTE), the WHO recommends that countries reinforce the reliable surveillance of NNT cases, promotion of clean delivery services, routine immunization of pregnant women, and conduct supplemental immunization activities (SIAs) for women of childbearing age. The WHO defines global elimination as an annual rate of <1 case of NNT per 1000 live births at the district level.

Haiti is the only country in the Region of the Americas that has not yet achieved maternal neonatal tetanus elimination. In 2015, Haiti has estimated 11,447,951 inhabitants with 10 health departments and 140 health communes.

Progress toward Neonatal Tetanus Elimination in Haiti

Haiti has made substantial progress towards neonatal tetanus elimination and has implemented specific activities in order to achieve this goal by the end of 2015. In 2012, Haiti did a thorough data review of all communes and identified that all 140 communes were considered high-risk for NNT. In addition to vaccinating pregnant women during routine immunization activities, three rounds of Td-SIAs were conducted in the 140 communes to immunize all women of reproductive age, irrespective of their previous vaccination status in 2013, 2014 and 2015. These SIAs resulted in at least 80% of Td2+ vaccination coverage in 131 of the 140 communes.

Haiti also integrated NNT surveillance into AFP, measles/rubella, diphtheria and pertussis case-based surveillance in 2013. Thirteen cases of NNT were detected in 2013 with 3 communes reporting > 1 case per 1000 live births; in 2014 and to-date in 2015 only 3 and 4 cases, respectively, of NNT were detected, and every district is reporting < 1 case of NNT per 1000 live births.

Strong technical, logistical and financial support from partners (UNICEF, CDC, Brazilian Cooperation and PAHO) and high vaccination coverage during the Td-SIAs have been key factors in the progress towards NNT elimination.

However, despite the progress made, some challenges remain. There is a lack of human and financial resources to implement the necessary activities and percentage of clean deliveries, and Td routine immunization coverage is low. In 2014, the percentage of clean deliveries averaged 29%, ranging from 12% to 60% in the 10 health departments; and 54% of communes achieved less than 50% routine immunization coverage.

All maternal and neonatal tetanus elimination activities in Haiti depend on funding from partners. The main challenge is to mobilize funds in order to reach at least 80% of Td2+ vaccination coverage for pregnant women during routine immunization, integrate NNT community-based surveillance into NNT surveillance, and improve clean deliveries and practice proper umbilical care.

Recommendations:

- Elimination of NNT in Haiti is critical to achieving regional vaccine-preventable disease elimination targets. TAG urges the country to pursue the measures proposed towards NNT elimination, with support of the partners and special attention to the sustainability of these actions as an integrated approach. These proposed measures include:
    - Implement mop-up immunization activities for communes with <80% of Td2+ vaccine coverage during Supplemental Immunization Activities.
    - Review performance of maternal and neonatal tetanus elimination activities for each commune for specific actions.
    - Integrate neonatal tetanus community-based surveillance in order to reinforce NNT surveillance.
    - Set up survey of vaccine coverage for Td-SIA.
    - Invite the external assessment team in 2016 for validation of Maternal Neonatal Tetanus Elimination.

Dengue Vaccine Development Update

Over the last three decades, the burden of dengue has steadily increased in the Americas. In 2014, 1,178,506 cases of dengue were reported in 47 countries and territories in the Region. Of these, 16,044 cases (1.4%) were serious and 677 (0.06%) patients died. Reported cases are estimated to represent only one tenth of all clinically apparent dengue virus infections of the Region. In addition to the relevant human suffering that these figures represent, they are also a clear indication of the burden that dengue puts on national health care services and economies. Dengue virus transmission has occurred in all countries of the Americas, except for Canada, continental Chile and Uruguay.

A dengue vaccine is viewed as a valuable additional tool for integrated dengue prevention and control. Five candidate vaccines are currently in clinical development and they are all tetravalent, i.e. intended to protect against the four dengue viruses (DENV1–4). Table 1 summarizes the characteristics and development phase of these candidate vaccines.

Table 1: Dengue Candidate Vaccines in Clinical Development, July 2015

Sponsor (Candidate Vaccine Name)	Candidate Vaccine Principle	Clinical Development Phase	Number of Doses (Schedule in Months)
Sanofi Pasteur (CYD-TDV)	Live-attenuated viruses (chimeric yellow fever virus vaccine 17D strain expressing pre-membrane and envelope proteins of DENV1–4)	III (in follow-up, Asia and Latin America)	3 (0,6,12)

	[CYD-TDV]		
Takeda (DENVax)	Live-attenuated viruses (chimeric attenuated DENV2)	II (Colombia, Puerto Rico, Singapore, Thailand); III (planned for 2015)	2 (0,3)
US NIAID/ Butantan (TV003)	Live-attenuated viruses (full-length DENV 1, 3, 4 plus mutagenesis-directed chimeric DENV2)	II (stepwise, Brazil; Thailand), III (planned for 2015, Brazil)	1 (N/A)
GSK/ Biomanguinhos/ Walter Reed Hospital (DPIV)	Inactivated purified whole viruses	I (two trials in USA and Puerto Rico, respectively)	2 (0,1)
Merck (DEN-80E)	Sub-unit envelope protein expressed in an insect cell system	I (Australia)	3 (0,1,2)

In 2014, the results of two phase III trials of a live attenuated chimeric tetravalent dengue vaccine (CYD-TDV) carried out in Asia and Latin America were published. These results are the first ever published efficacy data for any dengue vaccine. The two trials include 10,278 children and adolescents aged 2–14 years of five countries of Asia and 20,875 adolescents aged 9–16 years of five countries in Latin America. Outcomes are consistent between the two trials. The overall efficacy for dengue was 57% in Asia and 61% in Latin America; efficacies for severe dengue and dengue hospitalizations were higher. While the CYD-TDV candidate vaccine is immunogenic for all four dengue virus serotypes, efficacy varies by serotype (lowest for DENV2, intermediate for DENV1, and highest for DNEV3–4). Also, efficacy was lower for younger participants and for participants without measurable antibody titers before the first vaccine dose was administered. The trials in Asia and the Americas are ongoing with an overall follow-up of 6 years, which is important to validate the results of the first 25 months of the trials.

As the clinical development of dengue vaccines advances, the strengthening of dengue surveillance is critical. Between November 2013 and June 2015, PAHO jointly with eight countries and supported by the Sabin Vaccine Institute developed a generic surveillance protocol intended for implementation in all countries of the Region. This protocol achieves three significant advances in particular:

- First, it translates the inherently clinical case classifications of the 2009 WHO “Dengue Guidelines for Diagnosis, Treatment, Prevention and Control” (dengue and severe dengue) into operative definitions that can be used in an epidemiological surveillance system. The agreed upon definitions now focus on probable (clinically compatible cases with a laboratory result suggestive of a dengue infection) and confirmed cases; the generic protocol standardizes in details, like definitions.
- Second, sentinel surveillance comes to complement country-wide passive surveillance. As opposed to systems developed so far for other vaccine-preventable diseases, the sentinel surveillance would not be based on a single institution—typically a hospital of the second or third level. Specifically, it is proposed to set up a “sentinel area” within each country, a well-defined locality within which the spectrum of dengue manifestations is recorded in detail in a hospital and in the health centers that refer patients to that hospital. Within a sentinel area, data from epidemiological, entomological and environmental surveillance are also to be integrated to guide overall prevention and control measures.

- Third, seven performance indicators have been defined to monitor the performance of the epidemiological surveillance. These indicators will contribute to a harmonized implementation of dengue surveillance in Latin America and the Caribbean. The indicators are: timeliness of the periodic report from the lower administrative level; virus typing in areas with ongoing transmission; information quality for the reported cases (minimum set of case data complete); lethality; incidence; proportion of severe dengue; predominant dengue virus serotype; infested household and Breteau indexes. Each indicator is defined in a format that standardizes it based on 10 attributes.

The generic protocol for dengue surveillance is being adapted to the national conditions and is implemented without major constraints in the majority of the eight countries that contributed to its development, including large countries like Brazil and Mexico. This fact indicates that the implementation of the protocol is feasible and that it should be acceptable to all the countries of the Americas. In addition to contributing to dengue prevention and control, the implementation of the protocol will also provide evidence for the decision-making related to dengue vaccine introduction and for the impact evaluation of dengue vaccination activities**.**

Recommendations:

- TAG recommends that the countries swiftly implement an integrated approach to reduce dengue transmission, providing training on diagnosis and clinical case management, emphasizing vector control, and improving awareness so that people know how to protect themselves and their communities from mosquitoes as stated in the World Health Assembly Resolution (2015).
- While the burden of dengue in the Americas is significant, TAG notes there is insufficient evidence to make a recommendation on vaccine introduction at this time. TAG is committed to evaluating timely new evidence as it becomes available and countries should do the same over the coming months in their own national decision-making processes.
- In coordination with other initiatives, PAHO's ProVac Initiative should support national level decision-making regarding dengue prevention and control, through the use of economic evaluations grounded in local data.

Update on National Immunization Technical Advisory Groups (NITAGs)

In the early years of the Expanded Program on Immunization (EPI), the World Health Organization (WHO) recommended a set of inexpensive vaccines that provided direct protection against six diseases. Global and regional recommendations on the routine use of these traditional vaccines quickly led to their adoption at country-level. Today, vaccines available to prevent pneumococcal disease, rotavirus diarrhea and cervical cancer as well as other second generation and new vaccines in the pipeline have promised to save even more lives. However, many country-specific factors influence how these vaccines are valued relative to other competing priorities in the immunization program and broader health sector. Therefore, the World Health Organization (WHO) has recommended that countries establish National Immunization Technical Advisory Groups (NITAGs) to provide objective and scientific advisory guidance to ministries of health regarding their national immunization policy decisions. NITAGs have an important role in developing recommendations regarding national vaccination schedules, introduction

of new vaccines and immunization strategies (i.e. boosters, school based vs., health facility based delivery, etc.).

WHO developed guidance for the establishment and the strengthening of NITAGs in 2008. This guidance was adapted to the Region and published in 2010 for countries the Americas. The XX TAG recommended that immunization programs in the Americas accelerate the strengthening of NITAGs in countries with functional committees, including the development and adoption of standard operating procedures and increased investment in evidence generation at country-level. The TAG also encouraged countries to rapidly establish NITAGs where they currently did not exist. Since 2010, a set of common indicators to track the progress of NITAG establishment and strengthening has been incorporated into the WHO-UNICEF Joint Reporting Form (JRF). A functional NITAG has been defined as one that meets all of the six following process indicators:

1. Legislative or administrative basis for the advisory group
2. Formal written terms of reference
3. At least five different areas of expertise represented among core members
4. At least one meeting per year
5. Circulation of the agenda and background documents at least one week prior to meetings
6. Mandatory disclosure of any conflict of interest

The Global Vaccine Action Plan (GVAP) and the proposed PAHO Regional Immunization Action Plan (RIAP) has set a goal of all countries having an active and functional NITAG by 2020. Member States of PAHO have made steady progress in establishing NITAGs and strengthening these advisory bodies to fully support a transparent and credible decision-making process for vaccine policy. By 2014, 23 countries in the Latin America and Caribbean Region had established NITAGs, which cover 93% of the regional population. Most recently, countries such as Guatemala and Peru have reestablished committees that were non-active for some years. However, only 17 of the 23 countries meet all six criteria for a well-functioning committee proposed by WHO/PAHO. Also, there are still a few large-population countries that have yet to establish committees.

PAHO has provided technical assistance in the form of trainings and facilitation of technical exchanges between committees since the 1990s. In the past five years, 12 countries have worked with PAHO to revise their terms of reference (TOR) and standard operating procedures (SOP). Argentina published their revised TORs in *Vaccine* as a brief report last year in an effort to share with other countries. As of 2014, 22 of the 23 countries that report an active NITAG have formal terms of reference. Though, the systematic declaration of conflicts of interests by core members is still absent in some countries. Four of the 23 countries with NITAGs do not meet all six indicators for a well-functioning NITAG because these committees have not introduced these procedures. Still, the number of national-level decisions backed by NITAG recommendations in the Region indicates that governments generally recognize the value of NITAGs in ensuring a credible, transparent and evidence-based process for decision-making.

This process is only possible with the presence of a strong executive/NITAG secretariat within the national immunization programs. The executive/NITAG secretariat is responsible for the preparation of the technical content and evidence inputs required for the committees' deliberations. In this sense, since 2004, PAHO ProVac Initiative has assisted countries in the development of evidence inputs for vaccine policymaking, primarily vaccine cost-effectiveness and impact data. These studies have been an important input into decision-making for new vaccine introduction. 14 countries have completed

analyses and presented results from them to their national authorities and in May of this year much of this data was published in a special issue of the journal *Vaccine*.

Important advances in strengthening the process for evidence-based immunization policy at the country-level in the Region have been made. To sustain this progress and achieve the goals set forth for this decade, countries will need to continue their commitment to strengthening their committees and establishing them where they do not yet exist. The English-speaking Caribbean is a special case where countries in this sub-region have generally worked as a sub-regional block towards harmonized policies for immunization. This model is unique in the world and the governments in this sub-region may consider strengthening the formality of this model.

Recommendations:

- TAG reiterates the independent advisory role of NITAGs and encourages all countries in the Americas to formally establish these committees, considering the guidance developed by PAHO.
- Where NITAGs already exist, they need to be guided by independent experts using the scientific evidence available to make recommendations with a transparent and structured process.
- In the English-speaking Caribbean, there are existing sub-regional collaborations on immunization policy development. PAHO should support countries in a coordinated effort to formalize this technical advisory structure.

Update on Cholera and the Oral Cholera Vaccine Stockpile

Reversing a gradual decrease observed from year to year, the number of cholera cases reported in Haiti during January—May 2015 was greater than the numbers for the same periods of 2014, and was similar to that of 2012 and 2013. Between January 1 and May 31, 2015, 17,107 cholera cases, 13,312 hospitalizations (78% hospitalization rate), and 139 deaths (0.8% case-fatality rate) were notified: these figures are, respectively, 3, 4 and 5 times greater than 2014. During the same period, the Haitian Ministry of Public Health and Population registered outbreak alerts in 8 of 10 country departments, an indication of an intense and widespread circulation of *Vibrio cholerae* O1 at the community level. The increase in cumulative incidence from 2014 to 2015 is observed for both the age group of children aged <5 years and that of people aged ≥5 years; however, the cumulative incidence in children is now twice higher than that of the older age group, whilst it was equal at the beginning of the epidemic.

During January–May 2015, 273 suspected cholera cases and 10 cholera-related deaths were reported in the Dominican Republic. Similarly to Haiti, the number of suspect cases represents a 76% increase compared to the same period of 2014, likely as a consequence of the cholera dynamics occurring in the neighboring country. In January 2015, the Canada International Health Regulations National Focal Point communicated the confirmation of cholera in an individual with history of travel to Cuba; no other cholera cases have otherwise been reported in 2015 related to Cuba. Fourteen cholera infections were registered in 2014 in Mexico (13 infections in the State of Hidalgo, and one in the State of Querétaro); no new cholera infection has been reported in Mexico since January 2015.

To address the possibility of cholera becoming endemic in the island of Hispaniola, attempts are being made to elucidate whether the causative agent of cholera has established an environmental reservoir in the surface waters of Haiti. Comparing the period from April 2013 to March 2014 to the previous 12-month period, researchers who use 15 sentinel sites in one Haitian Department found a four-fold

increase in the number of water samples containing culturable *V. cholerae* O1 (9% vs. 2%); the number of sites with ≥1 positive sample rose to 58% from 20%. The authors suggested that seasonal water temperatures and precipitation likely drove those increases. The burden of diarrheal disease in Haiti is also being better documented, at least among children. In a prospective cohort of 1,245 school-children of a locality, gastrointestinal illness caused 278 visits per 1,000 children. The most common diarrheal pathogen was enteroaggregative *Escherichia coli* (17% of children with diarrhea), followed by *Vibrio cholerae* O1 and norovirus (both 7%).

TAG discussed the use of the oral cholera vaccine (OCV) in October 2012 with a focus on the island of Hispaniola. As part of a regional initiative towards the elimination of cholera transmission on the Island, TAG recommended deployment of the OCV in Haiti to mitigate the cholera burden in the short and medium term, until significant and sustainable advances are achieved in infrastructure for drinking water supply and sanitation. TAG's recommendations were adopted in the "National Plan for the Elimination of Cholera in Haiti, 2013–2020," which the Haitian Government issued in February 2013. TAG reviewed again the situation in July 2014 and reinforced previous recommendations to maintain WASH as a fundamental pillar to the comprehensive approach towards an overarching goal to eliminate cholera transmission. TAG also reaffirmed that vaccination is one of possible short-term actions toward the achievement of the long-term elimination goal.

In the past few years, reactive deployments of the oral cholera vaccine have been documented for both feasibility and effectiveness. The feasibility and administrative coverage of the first round of vaccination in Haiti done by two non-governmental organizations in 2012 at a rural and urban site were reviewed at the previous TAG meeting. In 2013, the Haitian Ministry of Public Health and Population, with support from PAHO and UNICEF, implemented a second round of vaccination for 120,000 people of two towns. A survey of 925 households found that two-dose coverage was 63% and 77%, respectively. Coverage was 68% and 82% in children aged 1–4 years, 78% and 84% in children and adolescents aged 5–14 years, and 56% and 71% in persons aged ≥15 years. Dropout between first and second dose was smallest among younger children and somewhat higher in adults. Among adults, the coverage was higher among female participants than male participants. The main reason for not being vaccinated was the absence during the daytime hours, when the vaccine was offered. In August-September 2014, a third vaccination round occurred; 300,000 additional people were vaccinated.

The effectiveness of OCV deployments has now been assessed. Within 6 months of the reactive vaccination in two prefectures of Guinea (June–October 2012), a matched case-control study found 87% effectiveness (95% CI: 57–96%). Incomplete vaccination had 43% effectiveness (not significant, −84–82%). A similar study carried out between October 2012 and March 2014 evaluated the effectiveness of the cholera vaccine campaign that a non-governmental organization had carried out in April–June 2012 in the rural area of Haiti. Effectiveness was 58% (13–80%) based on certified vaccination and 63% (8–85%) based on self-reported vaccination. The results are compatible to those of a large cluster-randomized trial in an endemic area of Calcutta, India, which showed 65% effectiveness for five years after vaccination. Evaluations are ongoing to assess the effectiveness of a single dose (preferable especially in a reactive deployment) and its cost-effectiveness compared to two-dose series. As a counterpart to effectiveness, one needs to consider that the impact of vaccination eventually depends on the level of cholera incidence when vaccinated —impact will be higher when vaccinated at higher incidence, such as in the case of reactive vaccination.

The global OCV stockpile was launched in late 2013. It is managed as a rotating fund by the International Coordinating Group (ICG), of which WHO is a member and functions as Secretariat. Until June 2015, 17 requests from 10 countries (including one request from Haiti) were accepted and 1.8 million doses were

deployed. In spite of the increased use, global OCV production has not kept pace with the demand, essentially because of lower than expected yields in the production of most used vaccine. Hence, OCV availability in the global market remains limited.

Recommendations:

- TAG reiterates its previous recommendations to maintain WASH as a fundamental pillar to the comprehensive approach toward the overarching goal of eliminating cholera transmission in the Island of the Hispaniola.
- Haiti should follow previous TAG recommendations that were included in the "National Plan for the Elimination of Cholera in Haiti, 2013–2020." As part of this implementation, Haiti may continue to require cholera vaccination.
- As information on the impact of cholera vaccination in Haiti remains limited, TAG recommends studying the effectiveness of future OCV deployments.

Impact of Rotavirus Vaccination in the Americas

The rotavirus disease is caused by rotavirus group A (RVA). It is an important public health problem, associated with severe diarrheas in children aged <5 years at the global level. It affects mostly children aged 3 to 36 months. The clinical spectrum is wide, going from asymptomatic infection to severe dehydration, choc and death. The disease is characterized by sudden diarrhea, vomit and fever. The disease is typically more severe than other diarrheas and is associated with dehydration and hospitalization.

An estimated 95% of children aged between 3 and 5 years will be affected by rotavirus. Incidence peaks during the fall and winter months in countries with temperate climates. According to WHO, rotavirus diarrhea leads to 453,000 deaths annually in children aged <5 years. In Latin American and Caribbean countries (LAC), before the introduction of the vaccine, there were 75,000 hospitalizations, one million medical visits and 10 million rotavirus diarrhea cases.

As of June 2015, 17 countries (Argentina, Brazil, Bolivia, Colombia, Dominican Republic, Ecuador, El Salvador, Guatemala, Guyana, Haiti, Honduras, Nicaragua, Mexico, Panama, Peru, Paraguay, and Venezuela) and one territory (Cayman Islands) in LAC have introduced the rotavirus vaccine, meaning that 92% of the birth cohort live in countries with vaccination schedules that include the rotavirus vaccine. There are two vaccines available: the monovalent human rotavirus vaccine G1[P8] (RV1 Rotarix®, GSK), and the pentavalent bovine-human, reassortant vaccine G1-G4[P8] (Rotateq®, Merck). The monovalent vaccine requires two doses (at 2 and 4 months) and the pentavalent three doses (at 2, 4 and 6 months). The PAHO's TAG recommends completing the schedule and vaccination by the first year of age; however countries should continue making efforts to administer rotavirus vaccines on their routine immunization schedules, at the recommended ages.

Regarding vaccine effectiveness, a meta-analysis (De Oliveira et al, 2015) found that RV1 varied, depending on the control group, between 63.5% and 72.2%. The effectiveness was higher in children <12 months ranging from 75.4% to 81.8%. In children aged >12 months it ranged from 56.5% to 66.4%. In Brazil, there was an estimated reduction of 130,000 hospitalizations and 1,500 deaths from diarrhea

in a period of three years following vaccine introduction (Do Carmo et al). Other impact studies in El Salvador, Nicaragua and Panama showed a reduction of 48% (Yen et al, 2011), 23% (Orozco et al, 2009) and 37% (Molto et al, 2011) respectively in hospitalizations for diarrhea. There are many rotavirus vaccine effectiveness and impact studies in Latin America and all have consistently shown that the vaccine significantly reduces hospitalizations and death from diarrhea. It is estimated that approximately 8,600 deaths due to rotavirus were avoided in 2013 in the 15 countries that have introduced RVA in LAC.

Recommendations:

- TAG encourages all countries to introduce the rotavirus vaccine, in accordance with their epidemiological contexts, considering the current evidence demonstrating high vaccine effectiveness, cost-effectiveness and enormous impact in reducing morbidity and mortality from diarrhea in general and rotavirus diarrhea, specifically in the Americas.
- Countries should continue to assess the impact of RVA in order to adequately monitor the prevalence of circulating strains and changes in the epidemiological profile of the disease.

Influenza Vaccination in Tropical Areas

Background

Influenza virus illnesses and their complications contribute significantly to morbidity and mortality in the Americas. It is estimated that 40,880–160,270 influenza-associated deaths occur annually in this region. Timely and effective vaccination remains the best available measure to prevent severe influenza illness. Contrarily to countries from temperate zones in the Americas for which influenza seasons are well-defined, and thus allow for an optimal planning of vaccination, countries from the American Tropics, situated between the Tropic of Cancer and Tropic of Capricorn, that concentrate the great majority of Latin American and Caribbean countries have had difficulties characterizing the seasonality of influenza viruses circulation.

Progress in influenza vaccine use

There is considerable use of seasonal influenza vaccines in the Americas. As of 2014, 40 out of 44 countries/territories in Latin America and the Caribbean (LAC) have policies for influenza vaccination that reflect the most recent World Health Organization and TAG recommendations. Vaccination policies target most frequently healthcare workers and the elderly (in 38 countries), followed by individuals with chronic conditions (in 35 countries), pregnant women (in 27 countries) and healthy children (in 25 countries) or children suffering chronic conditions (in 5 countries). It is worth noting that vaccination of pregnant women has substantially increased, with seven countries targeting this group in 2008 to 27 in 2014. Vaccination coverage estimates reported in the region vary widely reflecting difficulties related to data quality and completeness, absence of precise denominators for vaccine coverage estimation and other operational challenges to completing vaccination schemes among vaccine-naïve children <9 years.

Progress in assessing influenza vaccine performance

With such widespread and high uptake of influenza vaccines in the LAC region, it is important to assess its performance in real-life settings. To date, there have been very few reports of vaccine effectiveness and impact from the region. This gap in knowledge makes it difficult for countries currently using the vaccine to sustain or expand investments to recommended target groups. Influenza vaccine effectiveness can vary widely between seasons, due to numerous factors including the match between the vaccine strains and circulating viruses, the adequacy of vaccine availability and timing, and host

factors such as prior exposure to influenza viruses and to the vaccine, and the health status of the vaccine recipient. Thus, it is necessary to evaluate vaccine performance systematically and annually. Moreover, considering these yearly fluctuations in vaccine effectiveness, a valid evaluation of the impact of an influenza vaccination program would require information from various influenza seasons. In order to maximize the effect of vaccines, vaccination efforts should be concentrated prior to the highest concentration of influenza cases in the country. Late vaccination may only have limited benefits considering possible waning immunity and decreasing vaccine effectiveness as influenza viruses undergo antigenic changes.

Progress in defining seasonality of influenza virus circulation in the American Tropics

In recent years, countries in the American Tropics especially Central America such as El Salvador, Colombia, Cuba and Costa Rica, have made adjustments to their vaccination policies based on recent seasonality analyses. Using influenza surveillance data, secondary data, and varying methods, these analyses have led to changes in the vaccine formulation from the Northern Hemisphere to the Southern Hemisphere (SH) formulation and in vaccination timing from November to April-May. A review of antigenic characterization data from Central America also suggested that the SH formulation corresponded to the most updated formulation available before the start of influenza seasons. Of 33 predominant antigenic virus strains identified in Central America during 2002–2014, 21 (64%, 95% CI 47%–80%) matched the SH recommendations and 24 (73%, 95% CI 58%–88%) matched the Northern Hemisphere recommendations.

Recommendations:

- TAG recognizes the progress of countries in strengthening influenza surveillance and expanding vaccine use across the region.
- TAG also congratulates countries on making evidence-based changes to their vaccination policies, including changes regarding timing of influenza vaccination programs and most appropriate vaccine formulation.
- TAG urges countries to continue generating evidence on disease burden, seasonality of influenza virus circulation, vaccine effectiveness and impact, using national data sources and appropriate methods.
- TAG also recommends continuing the current strategies in place, vaccinating intensively prior to the peak of highest burden of influenza illness, optimally reaching very high vaccination coverage through a single campaign. Influenza vaccine should then continue to be offered to the unvaccinated through the routine health services throughout the influenza season.
- TAG recommends that large countries carry out sub-regional seasonality analyses or stratify analyses by microclimates in order to inform vaccine use as needed.

Transitioning to the Use of Auto-Disable (AD) Syringes

Background

Injections are one of the most common health care procedures. Sixteen billion injections are administered annually worldwide and only five to 10 percent of these injections are provided by health care workers for the administration of a vaccine.

Safe injection practices, in the field of immunization, prevent the possibility of diseases like hepatitis B, hepatitis C, HIV from being transmitted, and the occurrence of events supposedly attributable to

vaccination or immunization (ESAVI). In addition to promoting occupational health to workers in the health services, safe injection practices reduce the environmental risk to communities. Another aspect to consider is that the practice of safe injection, one of the key components of vaccine safety, is a measure that guarantees the progress being made by immunization programs and therefore has a significant impact on global vaccination coverage.

In 1999, the WHO, United Nations Children's Fund (UNICEF) and United Nations Population Fund (UNFPA) issued a joint policy declaration[7] on the use of self-deactivating syringes (AD) in immunization services. This declaration recommended that all countries adopt this document and implement the use of self-deactivated syringes in immunizations by the end of 2003.

According to this policy, this recommendation was based on the possible reuse of single-use syringes and needles, a practice that poses a high risk to public health. The community at large is also at risk when used injection equipment is not safely discarded. Self-deactivating syringes lower the risk of disease transmission from person to person because they cannot be reused, since they have a mechanism that disables the syringe from further use.

The WHO policy is focused on the use of self-deactivating syringes, which are pre-qualified after a review process of the dossiers. The WHO and the International Organization for Standardization (ISO) have developed quality standards[8].

The countries of LAC continue utilizing single use disposable syringes (SUDS), purchased through the PAHO Revolving Fund (RF), for their immunization programs. The quality of syringes and needles provided by the PAHO RF are verified through laboratory tests. In addition, PAHO also supports countries in building the testing capacity of the countries to carry out their own quality testing and verification.

The current recommendations regarding safe injections from PAHO's Technical Advisory Group (TAG) XIII meeting, held in Canada in April 1999[9], are:

- The only way to ensure that used injection equipment is not reused is solely through the use of auto-disable syringes.
- All health workers should be informed on the danger posed by recapping a used needle.
- All countries using or introducing single use disposable syringes for vaccine administration should secure the funds to purchase: sufficient syringes, sufficient safety boxes for disposing used syringes and needles, supervision to document safe syringe disposal, and for the adequate collection/incineration of used injection equipment.

[7] This joint policy revises and replaces the document WHO-UNICEF policy statement for mass immunization campaigns, WHO/EPI/LHIS/97.04Rev.1.It is issued by the World Health Organization, Geneva, Switzerland (Department of Vaccines and Biologicals), the United Nations Children's Fund (UNICEF) Programme Division, New York, USA and UNICEF Supply Division, Copenhagen, Denmark) and the United Nations Population Fund, New York. This policy is also the adopted practice of the international Federation of Red Cross and Red Crescent Societies in their operations.

[8] Standards for auto-disable syringes (ISO 7886-3; 7886-4), Performance specifications E8/DS1 and DS2 – OMS.

[9] TAG Recommendations, Meeting XIIII in Canada, April 1999

- PAHO should support studies to develop new technologies in the administration of safe injections.

In line with WHO policy, PAHO has begun promoting the use of self-deactivating syringes. The acquisition and use of these AD has been taking place in a progressive manner according to the ability of countries. Prior to introducing ADs, each country has to train health care workers in the handling and proper use of the new syringe designs. PAHO has informed all managers involved in the vaccination process on the benefits gained by the safety of the patient and the health professionals. Based on the training in the proper use of AD syringes and good safe injection practices, countries have partially begun introducing AD syringes into their programs. By 2005, only 5 countries had incorporated the use of ADs into their program. By 2015, 14 countries were using ADs for certain injections. Currently, 2 countries are using only AD syringes. Other countries have purchased a mix of AD syringes and conventional SUDS.

The benefits of using AD syringes are:

1. Reduction in the risk of re-use, thereby improving the safety of the patient, the health workers, as well as safety of the community.
2. The AD syringes come with a single scale, according to the administered dose for each vaccine, thereby reducing the risk of administering more or less dose-specific dosage of the vaccine.
3. There is less dead space in the hub of the needle, resulting in less vaccine remaining in the hub; therefore there is less vaccine wastage.

PAHO has strengthened the mechanisms for procurement syringes, not only in the review of documents and verification of compliance with the established requirements by the providers, but PAHO also performs quality verification through testing under specific standards of manufacturing, design and quality.

PAHO's priorities are:

- To promote the practice of safe injections as a component of vaccine safety.
- Introduction of new technologies, like self-deactivating syringes.
- Ensure syringe quality.
- Develop capacity in countries for verifying quality assurance.
- Training in risk management, management of new technology, waste disposal of sharps.
- Provide technical cooperation in following-up good safe injection practices in disposing of sharps.
- Provide technical assistance to countries to assess syringe quality, as well as develop and implement a national policy for safe injection.

PAHO, through the EPI and the RF, acquires an average of 188,224,000 syringes annually. 69% are single use disposable syringes and 31% are self-deactivating syringes for EPI programs in the Region. To ensure the quality, effectiveness, and safety of syringes and other products used in the immunization programs, PAHO's Comprehensive Family Immunization Unit (FGL/IM) conducted an analysis of the processes for planning, procurement and distribution, the use of injection equipment and disposal for both types of syringes. The resulting analysis shows the need to establish an action plan to validate compliance with the international standards of quality, safety, and the WHO guidelines for these products, as well as develop the institutional capacity in developing countries for testing and verifying product quality.

Recommendations:

- TAG recommends that, by the end of 2020, all countries should only use auto-disable (AD) syringes for immunization.
- Training must be conducted before introducing new AD syringe technology.
- Countries should plan the training, supervision and sensitization activities with assistance from PAHO.
- All countries should follow and strengthen good injection safety practices and the management of safe waste disposal operations.
- All countries using standard syringes or introducing AD syringes for vaccine administration should seek funding for:
  - The purchasing of sufficient syringes and safety boxes to safely dispose of syringes and sharp materials.
  - The documentation of safe syringe disposal.
  - The proper collection/incineration of used injection equipment.

Control /Elimination of Hepatitis B in the Americas

Hepatitis B virus (HBV) infection is a leading cause of infectious disease mortality worldwide with an estimated 4 million new HBV infections and 780,000 deaths annually. It is preventable with vaccination.

The World Health Organization (WHO) estimates that worldwide more than 2 billion people are infected with HBV, of whom 240 million have a chronic infection. Most HBV-related morbidity and mortality result from complications of chronic infection: cirrhosis and hepatocellular carcinoma (HCC). It is estimated that 15-25% of people with chronic HBV infection will die prematurely from HBV-related cirrhosis or HCC.

The risk of chronic infection is inversely related to the age at infection. Chronic infection develops in up to 90% of infants infected during the perinatal period, 20-60% of young children infected in the post-perinatal period through five years of age, and in <5% of children, adolescents, and adults with infections acquired after five years of age. Globally, two-thirds of HBV-related deaths result from infection acquired in the perinatal and early childhood period, underscoring the need routine infant hepatitis B immunization, with the first dose administered at birth, as the cornerstone of a hepatitis B prevention strategy.

Regionally, HBV infection is not distributed homogeneously. The prevalence of chronic infection as measured by the seroprevalence of the hepatitis B surface antigen (HBsAg) among 5-9 year old children in the Americas varies from low (<2%) in Brazil, Canada and the USA to low-intermediate (2-4%) in Argentina, Chile, Colombia, and Mexico to high-intermediate (5-7%) in Bolivia, Ecuador, and Peru. Within a country there may be ethnic, geographic, and socioeconomic, and differences in the prevalence of the infection.

The WHO is currently developing a 2016-2021 Global Health Sector Strategy (GHSS) on viral hepatitis, with the plan to submit it to the 69th World Health Assembly in 2016. The GHSS responds to specific

requests included in resolution WHA67.6 of 2014, asking WHO to assess the feasibility of elimination of HBV infections as public health problems.

The WHO is promoting the elimination of HBV infection by the year 2030. The feasibility of HBV elimination was determined through modeling studies. The results of these studies were used to set the targets that include eliminating HBV by 2030 through a combination of high routine 3-dose infant vaccination coverage, high birth dose coverage, and the scale up of treatment services for persons with chronic HBV infection. Elimination of mother to child transmission (EMTCT) of HBV infection is considered a milestone on the road to HBV elimination. Of note, the Region of the Americas is committed to a Dual Elimination Initiative for mother to child transmission of HIV and syphilis.

Three doses of the hepatitis B vaccine, with the first dose administered within 24 hours of birth and the remaining doses given per the recommended schedule, can prevent approximately 95% of cases. Currently, WHO and SAGE recommendations to reduce perinatal and early childhood transmission emphasize the importance of a birth dose of hepatitis B vaccine administered within 24 hours of birth, followed by two or three doses to complete the series. Hepatitis B immune globulin (HBIG) prophylaxis in conjunction with HBV vaccination may offer minimal additional benefit to newborn infants whose mothers are HBsAg positive, particularly if they are also hepatitis B “e” antigen (HBeAg) positive. However, the use of HBIG is not feasible in most countries due to program logistics (lab-based screening program to identify HBsAg-positive mothers) and due to the supply and cost of HBIG.

In the Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection, launched in 2015, the WHO recommended treatment of pregnant women with tenofovir, but no recommendation was made for the routine use of antiviral therapy to prevent mother-to-child-transmission of HBV.

In the Americas in 2014, regional coverage with three doses of the hepatitis B vaccine among children less than one year of age was 90%. However, only 18 of 44 countries and territories in the Region currently include a birth dose of the hepatitis B vaccine in the national infant immunization schedule (source: WHO/UNICEF Joint Reporting Forms).

Given that the WHO is considering the elimination of HBV as a goal for 2030, the Americas should consider regional and country level control strategies, with an overall strategy of high 3-dose vaccine coverage, the implementation of birth dose vaccination and treatment of chronic HBV infection, and leading to the elimination of HBV mother-to-child transmission as a milestone towards HBV elimination.

Recommendations:

- **Coordination**
  - PAHO should continue the inter-programmatic work that brings together the maternal and child health services units, the Latin American Center for Perinatology (CLAP), the Comprehensive Family Immunization Unit, HIV/AIDS/STI/TB and Hepatitis Unit, Occupational Health Unit, Legal Office, among others, in order to support Member States in their evaluation of the feasibility of HBV elimination as a public health problem. PAHO should also support developing strategies, and identifying gaps that need to be addressed in order to achieve this goal by 2030.

- **Vaccination and monitoring**
  - TAG reminds countries to introduce the birth dose of the hepatitis B vaccine, i.e., the first dose within 24 hours after birth, in countries that have not already introduced it.
  - Countries should monitor the administration of the birth dose within 24 hours of birth and reach at least 80% coverage, in all countries.
  - Countries should document prevalence of hepatitis B infection among pregnant women and strengthen hepatitis surveillance.
  - TAG reiterates previous recommendations on hepatitis B vaccination for children, healthcare workers, and other high-risk groups.
  - PAHO and countries should evaluate the current status of hepatitis B control and the feasibility of hepatitis B elimination, so that TAG can assess their progress and the feasibility of eliminating hepatitis B at the regional level.

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Sixth Meeting of the South-East Asia Regional Immunization Technical Advisory Group (SEAR-ITAG)

Conclusions and recommendations
New Delhi, India, 15–19 June 2015

DRAFT

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Contents

Acronyms

AES	acute encephalitis syndrome
AEFI	adverse events following immunization
AFP	acute flaccid paralysis
bOPV	bivalent oral polio vaccine
CRS	congenital rubella syndrome
cVDPV	circulating vaccine-derived poliovirus
EPI	expanded programme on immunization
EVM	effective vaccine management
EVSM	effective vaccine store management
GAVI	Global Alliance for Vaccines and Immunization
GIVS	Global Immunization Vision and Strategy
GMP	good manufacturing practices
GVAP	Global Vaccine Action Plan
HPV	Human Papilloma Virus
IBVPD	Invasive Bacterial Vaccine Preventable Diseases
IPV	inactivated polio vaccine
IRI	intensification of routine immunization
ITAG	Immunization Technical Advisory Group
LJEV	live Japanese encephalitis vaccine
MCV	measles-containing vaccine
MCV1	first-dose of measles containing vaccine
MNT	Maternal and Neonatal Tetanus
mOPV	monovalent oral polio vaccine

MR	measles and rubella vaccine
MRI	Measles Rubella Initiative
NCC	National Certification Committee
NIDs	national immunization days
NIP	National Immunization Programme
NRA	national regulatory authority
NITAG	National Immunization Technical Advisory Group
NUVI	new and underutilized vaccine introduction
OPV	oral polio vaccine
PMS	post-marketing surveillance
RI	routine immunization
RC	Regional Committee
RCCPE	Regional Certification Commission for Polio Eradication
SAGE	Strategic Advisory Group of Experts
SEAR	South-East Asia Region
SIA	supplementary immunization activity
TCG	Technical Consultative Group
tOPV	trivalent oral polio vaccine
UNICEF	United Nations Children's Fund
VDPV	vaccine-derived poliovirus
V_3P	vaccine product, price and procurement project
VMA	vaccine management assessment
VPD	vaccine-preventable disease
WHO	World Health Organization
WPV	wild poliovirus

1. Introduction

The Sixth Meeting of the World Health Organization's South-East Asia Regional Immunization Technical Advisory Group (SEAR-ITAG) was held from 15 to 19 June 2015 in New Delhi, India.

The SEAR-ITAG is a regional technical expert group, established by the Regional Director for providing advice on all aspects of immunization, vaccines and vaccine-preventable disease (VPD) prevention, control, elimination and eradication. It comprises experts from disciplines such as programme management, communicable diseases/vaccine preventable diseases control, virology, epidemiology, and immunization. It meets annually with the participation of national expanded programme on immunization (EPI) managers and national surveillance focal points and partners to review the progress on increasing and sustaining immunization coverage, surveillance performance, programme issues, and matters related to vaccine quality assurance, and provides guidance to countries on ways to improve and sustain overall high-quality performance.

The terms of reference for the ITAG are as mentioned below.

- Review the Regional and Member State policies, strategies and plans for the control, elimination and/or eradication of VPDs, especially for polio eradication, measles elimination, rubella/congenital rubella syndrome (CRS) control, and Maternal and Neonatal Tetanus (MNT) elimination.
- Provide guidance to the setting of regional immunization priorities for immunization and vaccines.
- Make recommendations on the framework for development of national immunization policies as well as operational aspects of their implementation, and also provide framework and approaches to periodic evaluation and strengthening of routine immunization (RI) services and systems.

- Advise Member States on the appropriate choices of new vaccines and recommend optimal strategies for their introduction, including technical guidance for monitoring and impact evaluation of new vaccines once introduced into national immunization programmes.
- Promote and provide technical guidance for the implementation of high-quality VPD surveillance, including laboratory networks for surveillance.
- Advise Member States on regulatory requirements to ensure quality and safety of vaccines used in a national immunization programme.
- Provide guidance on public private partnerships.
- Identify and advise on appropriate implementation research topics in immunization and vaccines, and review the conduct and the results of such research projects.

The meeting was chaired by Professor Gagandeep Kang with Dr Robert Linkins as rapporteur on days 1 and 2, and Dr Elizabeth Jane Soepardi as rapporteur on days 3, 4 and 5. Other ITAG members in attendance were Professor Sanath Lamabadusuriya, Dr Charung Muangchana, Dr Yasho Vardhan Pradhan, Professor Mohammod Shahidullah and Professor Saw Win. In addition to SEAR-ITAG members, other participants included members of National Committees for Immunization Practices (NCIPs) of Member States, Members of the Strategic Advisory Group of Experts (SAGE) representing the South-East Asia Region, national EPI programme managers and national surveillance focal points from all 11 countries, representatives from WHO headquarters, the Regional Office for South-East Asia and WHO country offices' immunization focal points, the Regional Office for the Western Pacific, United Nations Children's Fund (UNICEF) headquarters, the South Asia and the Eastern Asia and Pacific Regional offices, country offices and a number of other local and global partners and stakeholders.

The Director of Family, Gender and Life Course, Dr Arun Bhadra Thapa, opened the meeting.

2. Objectives

Immunization-related areas are very well funded, but almost disproportionately so by private foundations and global alliances, who increasingly wield influence on policy and strategy matters at global, regional and country levels. The substantial funding available has encouraged the proliferation of multiple stakeholders beyond the traditional stakeholders. There is an increasing and constant need for ensuring coordination and coherence in the development and implementation of immunization policies. Additionally, there are time-bound immunization and disease eradication/elimination/control targets that attract intense scrutiny by stakeholders. Thus it is essential for regular oversight and monitoring of the programme by a regional advisory body and for periodic course correction. In this Region, the SEAR-ITAG meeting is the mechanism that supports this role.

The primary objectives of this meeting were as mentioned below.

(1) To review status of performance of national EPI programmes in relation to disease eradication/elimination/control targets (including Implementation of the recommendations of the Fifth SEAR-ITAG Meeting conducted in August 2014).

(2) To address and seek guidance on ways to effectively address the following technical areas of importance to this Region.

I. Progress towards achieving regional and global immunization targets, including review of the Global Vaccine Action Plan (GVAP) areas.

II. The status and progress of regional efforts to meet the goal of eliminating measles and controlling rubella and CRS by 2020.

III. The risks to the polio-free status in the Region, the strategic actions being taken, which should be taken to mitigate the risks and the five readiness criteria for the withdrawal of the type 2 component of oral polio vaccine (OPV) and the potential actions required for each criteria (including for inactivated polio vaccine (IPV) introduction), in preparation of the withdrawal for the type 2 component of OPV.

IV. Progress made towards MNT elimination, the MNT elimination status in countries, areas already validated current maintenance strategies and present action plans to reach the goal and the MNT elimination status in countries or in subnational areas where elimination has not yet been validated and in areas already validated.

V. Experiences and lessons learned on issues related to new and underutilized vaccines, Japanese encephalitis (JE), rotavirus gastro-enteritis (RVGE) and invasive bacterial vaccine preventable diseases (IBVPD) and Human Papilloma Virus (HPV) infections.

VI. Currently available country level influenza surveillance information and consensus on defined criteria for decision-making to introduce seasonal influenza vaccines for high-risk groups.

VII. The status of adverse events following immunization (AEFI), vaccine product, price and procurement project (V3P), vaccine pharmacovigilance and national regulatory authority (NRA) capacity-building initiatives.

VIII. Issues around data quality related to VPDs.

The main outcomes are related to these areas, with advice for countries and stakeholders on the most appropriate way forward.

3. Conclusions and recommendations of the Sixth SEAR-ITAG

Progress has been made in immunization activities in SEAR since the last ITAG Meeting, held in August 2014. The countries in the Region are well positioned to take the lessons learned and apply best practices to their respective national immunization programmes.

I. Measles elimination and Rubella control

The ITAG is encouraged by countries' commitment to the regional goal of Measles Elimination and Rubella/CRS Control by 2020. The ITAG clearly recognizes that with the integrated measles and rubella strategy, and the use of a combination vaccine (measles and rubella vaccine (MR) or MMR), rubella/CRS will also be eliminated. Nevertheless, the ITAG believes that the current efforts in the Region, specifically the timing of national, wide age-range MR campaigns and introduction of measles and rubella containing vaccine into the routine schedule, are inadequate to achieving the 2020 goals. To this end, the ITAG will monitor a number of interim milestones that must be met to ensure that the Region meets the measles elimination and rubella/CRS control goal by 2020:

(1) By the end of 2015:

(a) All countries to have a nationally approved plan to eliminate measles and control rubella/CRS by 2020 and share with SEARO.

(b) All countries to have detailed plans with timelines to achieve, maintain and verify at least 95% population immunity against both measles and rubella in all age cohorts.

(c) Nationwide case-based surveillance for measles and rubella to be fully operational in all countries except for **India** and **Indonesia,** which will continue to expand case-based surveillance following wide age-range campaigns.

(d) All countries to report case-based data at least monthly to the "WHO country office and WHO SEARO" in line with reporting requirements. All countries to submit an annual report to SEARO on (i) the susceptibility profile of populations to measles and rubella; (ii) plans to cover the immunity gaps shown; and (iii) subnational risk assessments of measles.

(e) All countries to have adequate access to a proficient national and reference laboratory, and to ensure that laboratory data are linked with case-based epidemiological data.

(f) A Regional Verification Commission will have been established and a National Verification Committee will be established in every country.

(g) SEARO to develop and publish Regional surveillance guidelines and surveillance indicators for measles and rubella.

(2) By the end of 2016:

(a) All countries in the Region to have implemented an RI schedule of two-dose measles-rubella containing vaccine preferably by the end of the second year of life, but no later than the third year of life.

(b) Those countries conducting immunization campaigns against both measles and rubella to conduct an evaluation to assess whether 95% coverage at the second administrative level was achieved and outline plans to address remaining immunity gaps.

(3) In addition, the ITAG:

(a) Commends **Nepal** for providing MR immunization to high-risk populations affected by the tragic April 2015 earthquake and requests **Nepa**l to report on the status of surveillance and immunization services post April 2015 earthquake at the 2016 ITAG.

(b) Encourages **Myanmar** to follow the implementation of their high-quality MR campaign (which was conducted in the first quarter of 2015), with a national coverage survey and to report back results at the 2016 ITAG meeting.

(c) Would like to review at the 2016 meeting the progress on the national MR campaign and the continued expansion of the measles/rubella laboratory-supported case-based surveillance from **India** and **Indonesia**.

(d) Requests **Sr**i **Lanka** to report back, at the 2016 ITAG, findings from the EPI Review with special emphasis on measles and rubella activities.

(e) Requests a report from the Regional Verification Committee at the next ITAG meeting in 2016.

(4) Related to the MR laboratory network, the ITAG recommends by the end of 2015:

(a) **Timor-Leste** to enhance its current laboratory to "proficient" status in order to support measles/rubella case-based surveillance.

(b) All countries to collect adequate specimens to characterize measles and rubella genotypes and share information with WHO in a timely fashion. These data should be linked to EPI case-based data to enable identification of chains of transmission.

(c) WHO proficient or nationally recognized laboratories be compliant with WHO standards to support CRS surveillance.

(5) Related to the MR laboratory network, the ITAG recommends by the end of 2016:

(a) To verify interruption of indigenous transmission and identify imported and import-related cases, measles virus genotypes to be characterized in at least 80% of chains of transmission.

(6) For countries with established CRS sentinel surveillance, the ITAG recommends by the end of 2015:

(a) To have a plan in place to conduct an evaluation of the CRS surveillance system (may include retrospective review of data from the reporting sites).

(b) To use CRS data in conjunction with case-based rubella data to monitor the progress of the rubella control programme.

(c) To report rubella laboratory and epidemiological data to the WHO country and Regional offices monthly.

(7) Monitoring progress towards rubella and CRS control:

(a) In addition to the laboratory-supported case-based measles rubella surveillance systems, countries to consider adopting additional surveillance mechanisms to monitor programme progress, such as age-stratified serosurveys for rubella.

II. Polio eradication

The ITAG congratulates immunization, surveillance and polio laboratory teams of Member Countries of the South-East Asia Region and their national governments for maintaining polio-free status for more than four years since the last case, due to wild poliovirus (WPV), was detected in January 2011. The ITAG takes note of and endorses the actions being taken by national governments to maintain high population immunity against polio, achieve certification standard surveillance and preparedness for outbreak response in all countries. The ITAG also recognizes the support and guidance provided by the donors and partners, and the important contributions of the National Certification Committees for Polio Eradication (NCCPE) and the South-East Asia Regional Certification Commission for Polio Eradication (SEA-RCCPE).

Despite this enormous achievement, the ITAG notes the risk of WPV spread following an importation as well as the risk of emergence of circulating vaccine derived polioviruses (cVDPV) in the Region. The ITAG is concerned with the persistently low oral polio vaccine (OPV3) coverage through RI in **India**, **Indonesia, Myanmar and Timor-Leste.** This has resulted in an immunity gap in children less than five years in **Indonesia, Myanmar and Timor-Leste**. The gaps in **India** have been addressed by conducting polio supplementary immunization activities (SIAs). The challenges remain in maintaining acute flaccid paralysis (AFP) surveillance indicators in **Sri Lanka and Timor-Leste**. The ITAG notes that an EPI and VPD surveillance review has been conducted in **Timor-Leste** and that a review is planned in **Sri Lanka** later this year.

The ITAG also notes the Region's progress towards achieving the objectives of 'Polio Eradication and Endgame Strategic Plan 2013-2018' including plans for IPV introduction and the preparedness for the globally synchronized withdrawal of type 2 component of OPV by switching from

trivalent oral polio vaccine (tOPV) to bivalent oral polio vaccine (bOPV). The ITAG acknowledges the challenges involved with the withdrawal of type 2 component of OPV and appreciates the efforts being made in the Region to overcome these challenges, including the recent dry run exercise conducted in **India** from which numerous important lessons have been learned. The ITAG also notes the efforts being made to ensure availability of licensed bOPV for use in RI post-switch; a plan for effective management of tOPV stocks; plans for containment of all type 2 polioviruses as per Global Action Plan III (GAP III); verification of elimination of WPV type 2; and outbreak response plans to manage any type 2 poliovirus outbreaks. The ITAG notes the plans of the Region for expansion of environmental surveillance to supplement AFP surveillance in order to ensure early detection of imported WPVs and emerging vaccine-derived polioviruses (VDPVs), and as a tool to monitor Sabin virus isolation after cessation of use of type 2 component of OPV. Despite a recommendation made during the 2014 ITAG, environmental surveillance has not started in **Bangladesh** and expanded in **Indonesia**.

The ITAG supports the most recent recommendations of the SAGE, SEA-RCCPE and the Global Polio Laboratory Networks.

(8) ITAG recommends that:

(a) All countries should continue their efforts to achieve/sustain certification-level AFP surveillance and polio immunization performance.

(b) **India, Indonesia, Myanmar, and Timor-Leste** should urgently address the issue of persistent low polio immunization coverage through RI. These countries should also conduct one to two national/subnational polio SIAs with tOPV in 2015/early 2016 to close potential immunity gaps prior to the withdrawal of type 2 component of OPV.

(c) Considering the significant movement of population between India, Nepal and Pakistan, subnational polio SIAs targeting high-risk populations and areas should be conducted in **Nepal** in the second half of 2015/early 2016. **India** should follow guidance from its national level expert advisory body for polio SIAs. Efforts should be made to

synchronize the polio SIAs in India, Nepal and Pakistan to the extent possible.

(d) Consideration should be given to conducting seroprevalence studies in countries with low routine OPV3 coverage to assess seroprevalence against polioviruses as a part of risk assessment. While conducting polio seroprevalence studies, consideration should also be given to using the opportunity to assess immunity against other vaccine preventable diseases.

(e) **Timor-Leste** should fully implement the recommendations of the EPI and VPD surveillance review that was conducted in March 2015. The findings of the upcoming EPI and VPD surveillance review in **Sri Lanka** should be shared with the ITAG when ready and **Sri Lanka** should fully implement the recommendations emerging from the review for strengthening AFP surveillance. Timor-Leste and Sri Lanka should share an implementation report one month prior to the ITAG meeting in 2016.

(f) In view of the continued transmission of poliovirus in Pakistan and Afghanistan, and the consequent potential for poliovirus importation to the Region, all countries should conduct risk mitigation activities including cross-border vaccination activities and introduce and monitor polio vaccination for travelers to/from polio infected countries.

(g) **Bhutan, India, Indonesia, Myanmar, Sri Lanka, Thailand and Timor-Leste** should ensure that at least one dose of IPV is introduced in their EPI schedule before the switch from tOPV to bOPV.

(h) All countries should urgently begin planning for the withdrawal of type 2 component of OPV (tOPV to bOPV switch). The national switch plans, with timelines, should be finalized and submitted to WHO-SEARO no later than September 2015.

(i) In preparation of the switch, all countries should begin urgent actions for an inventory and effective management of their tOPV stocks to ensure that there are no stock-outs

of tOPV before the switch and that residual tOPV stocks after the switch are small.

(j) Mechanisms for tOPV recall at the time of the switch and the destruction and the monitoring/validation of this process after the switch should be in place in all countries as a part of the national switch plan.

(k) Countries that self-procure OPV, namely **India, Indonesia, Nepal, Sri Lanka and Thailand** should immediately start the process of bOPV procurement to meet the needs of this vaccine after the switch.

(l) **India** should expedite the process of licensure of label and package insert change for bOPV use in RI and complete this at the earliest.

(m) All countries that have not yet done so, should expedite the licensure process of bOPV as soon as possible. In the absence of this process being completed before the switch date, countries should consider using bOPV based on WHO prequalification.

(n) Countries should expedite activities towards achieving laboratory containment phases 1 and 2 required to be completed before the switch as per GAP III. As such, it is crucial that active national polio laboratory containment coordinating bodies are in place and required resources are in place.

(o) Environmental surveillance should be expanded to additional sites in **India and Indonesia** and initiated in **Bangladesh and Myanmar** in 2015. **Nepal, Timor-Leste and Thailand** should consider initiating environmental surveillance in 2016.

(p) The NCCPEs of all countries should remain active until global certification. Certification activities should continue as per recommendations by the SEA-RCCPE.

(9) The ITAG recommends that SEARO:

(a) Supports countries with activities in preparation for the withdrawal of type 2 OPV including IPV introduction, development of switch plans, licensure of bOPV, containment of polioviruses as per GAP III, expansion of environmental surveillance and development of protocols for outbreak preparedness.

(b) Continues to regularly monitor the surveillance and immunization performance of all countries, assist countries with subnational risk assessments and support country risk mitigation activities.

(c) Continues to function as Secretariat to the SEA-RCCPE and support countries in meeting poliovirus laboratory containment requirements as per GAP III.

(d) Conducts a workshop on "Expedited Approval of Licensure of Vaccines" before the end of 2015 to facilitate availability of a licensed bOPV before the switch.

(10) The ITAG recommends that Partners (WHO, UNICEF, Rotary, NGOs, professional bodies and other stakeholders):

(a) Work with countries that have not yet introduced IPV to ensure that the vaccine is introduced before the tOPV to bOPV switch.

(b) Support development of national plans for the tOPV to bOPV switch in all countries by September 2015.

(c) Recognize that comprehensive resource and advocacy support is still required after certification, to prevent complacency and shifting priorities to other public health requirements and to meet polio endgame requirements towards global eradication and certification.

III. Maternal and neonatal tetanus elimination

The ITAG notes the global and regional progress towards MNT elimination. The ITAG congratulates **India** on its recent validation of neonatal tetanus elimination. As of April 2015, MNT elimination has not been validated in 22 countries globally including 4 provinces in **Indonesia**. If the control

measures planned in these areas in **Indonesia** are fully implemented, the ITAG is confident that the country will complete MNT elimination activities in 2015 and thus be eligible for validation in 2016.

The ITAG notes that vaccination is one of multiple strategies used to achieve MNT elimination, which also includes health facility-based deliveries, presence of skilled birth attendants, clean deliveries and safe cord care practices.

The ITAG reminds national programmes and partners that MNT elimination strategies are a means of reaching women that are usually unreached and thus offers opportunities for comprehensive health service delivery (EPI, maternal and child health, basic newborn care) to contribute to reducing maternal and neonatal mortality.

The ITAG fully realizes that sustaining MNT elimination requires vigilance and addressing risks and gaps related to access, coverage and quality of health care for all communities and welcomes the operational guidelines, developed by the global MNT Elimination Initiative.

(11) The ITAG recommends that:

(a) **Indonesia** and relevant partners continue to place high priority on implementing necessary actions to eliminate MNT by the end of 2015 in the remaining areas.

(b) all countries and areas that have achieved elimination should conduct annual district-level risk assessment to identify low-performing areas in terms of sustaining elimination and implement appropriate corrective actions, with WHO and UNICEF participation as appropriate.

(c) where applicable, countries should review their plans to maintain elimination status. These should include optimizing immunization schedules to ensure full and early protection against tetanus through childhood or adolescent booster doses (e.g. through school based immunization programmes) for recommended five doses in both sexes and adding diphtheria protection through shift from Tetanus Toxoid to tetanus/diphtheria toxoid containing vaccines.

IV. Vaccine Quality and Management

NRA Strengthening

In line with 2014 WHA resolution 67/20, the ITAG recognizes that effective regulatory systems for vaccines and medicines are an essential component of health system strengthening and contribute to better public health outcomes. Furthermore, it recognizes that regulators are an essential part of the health workforce, and that inefficient regulatory systems themselves can be a barrier to access safe, effective and quality vaccine and related medical products. The ITAG reiterates that strengthening regulatory systems will promote access to affordable vaccines and related medical products with assured quality, safety and efficacy. The ITAG recognizes that India, Indonesia and Thailand are the only countries in the region which manufacture WHO prequalified vaccines and have NRAs which have been assessed by WHO as functional. .

(12) The ITAG recommends that all Member States:

(a) Ensure that NRAs actively participate in:

(i) monitoring AEFI surveillance;

(ii) effective vaccine management (EVM) assessments to enforce Good Distribution and Good Storage Practices;

(iii) working with National Immunization Programmes (NIP), WHO, UNICEF and other key partners to develop capacity to implement EVM assessment recommendations.

(b) The ITAG recommends that **Bangladesh and Myanmar, the countries that are locally manufacturing and using selected vaccines in their national programmes,** invest significantly in their NRAs in order to comply with international/WHO standards for functional NRAs, such that their vaccines are of assured quality.

(13) The ITAG recommends that SEAR:

(a) Supports capacity-building of NRAs on accelerated licensing procedures/collaborative procedures to ensure timely introduction of vaccines (e.g. bOPV).

(b) Continues to encourage and facilitate intercountry cooperation as an effective means of using existing capacity and building capacity at the same time.

Vaccine availability and quality

In line with the 2015 WHA resolution on the GVAP, the ITAG recognizes the importance of competition to reduce prices. The ITAG further recognizes that there is the need to expand the number of manufacturers in developing countries that produce WHO-prequalified vaccines and thus create a competitive market. The ITAG notes with concern the global shortage of BCG and combined measles-rubella vaccines.

(14) The ITAG recommends that countries:

(a) Enhance interactions between NIP managers and vaccine producers at all appropriate levels – national, regional and global – to provide manufacturers with accurate and timely information on vaccine demands and to address current vaccine shortages especially for basic vaccines.

(b) Explore mechanisms of cooperation that promote Regional access to an assured quantity and quality of vaccines at an affordable price, such as the ASEAN Initiative on Vaccine Security.

(c) With limited NRA capacity, continue to use exclusively WHO prequalified vaccines for their immunization programmes.

(15) The ITAG recommends that SEAR:

(a) Works with WHO/headquarters to facilitate dialogue with manufacturers and NRAs to explore solutions to increase local/regional production of vaccines through providing access and knowledge about specific technologies, e.g. for

pandemic influenza vaccine and delivery systems of hepatitis B birth dose.

AEFI

(16) The ITAG recommends that countries:

(a) Prioritize strengthening quality AEFI investigation to ensure and maintain the highest level of public trust in the national immunization programme.

(b) Share AEFI data with vaccine manufacturers through NRA and NIP to consolidate vaccine safety profile with newly introduced vaccines.

(17) The ITAG recommends that SEAR:

(a) Finalizes the manual for field investigation of AEFI and facilitate implementation at country level.

V. New and underutilized vaccines, Japanese Encephalitis, Rotavirus gastro-enteritis, invasive bacterial vaccine-preventable diseases and human Papilloma virus infection

New and Underutilized Vaccines

The ITAG notes that SEAR countries have achieved reasonable progress in adding vaccines to their national immunization schedules in recent years. All countries have introduced Hepatitis B vaccine and **Democratic People's Republic of Korea, Indonesia, Maldives and Thailand** have achieved high coverage with timely birth dose of Hepatitis B vaccine. Ten out of 11 countries of SEAR (except **Thailand**) have introduced Hib vaccine as pentavalent vaccine since 2008. **India** has completed its Hib introduction in 20 States/Union Territories in the first quarter of 2015. Among other vaccines, **Bangladesh, Democratic People's Republic of Korea, Maldives** and **Nepal** have introduced a supplemental dose of IPV and all other countries are planning to introduce IPV by 2016 as per the polio endgame plan. **Bangladesh** and **Nepal** have introduced Pneumococcal Conjugate Vaccine. Bhutan has introduced HPV vaccine nationally.

Japanese Encephalitis

The ITAG takes note that the quality JE/ acute encephalitis syndrome (AES) surveillance data are inadequate to make evidence-based decisions for JE control and prevention in some countries. Hence, the ITAG makes the following recommendations which include a number of those previously made in 2014. Furthermore, the ITAG notes that guidance and tools to use country level data for designing policies and strategies for JE control & prevention including JE vaccine introduction are urgently required.

(18) The ITAG recommends:

(a) Countries to integrate JE vaccination into national immunization schedules in at-risk areas in all SEAR countries (except Maldives) where JE is a public health priority. Even where the number of JE-confirmed cases is low, vaccination should be considered if there is a suitable environment for Japanese encephalitis virus transmission, i.e. presence of animal reservoirs, ecological conditions supportive of virus transmission, and proximity to other countries or regions with known JE Virus transmission.

(b) The National Immunization Technical Advisory Groups (NITAGs) to consider the recommendation, in (a) above, from the WHO position paper on JE vaccines published in February 2015 while making decisions.

(c) **Bangladesh, Indonesia and Myanmar** to conduct desk reviews of available national data to define the magnitude of the problem and develop comprehensive plans for JE control and prevention and report on progress to the ITAG in 2016.

(d) **Bhutan and Timor-Leste** to define the high-risk areas for JE and strengthen laboratory-based JE surveillance.

(e) **India** should collate more evidence on the need and justification for adult JE vaccination and share it with the ITAG, facilitating guidance for other JE endemic countries in the Region.

(f) **Nepal, Sri Lanka and Thailand** NITAGs/NCIPs should further collect data to determine the need and rationale for booster doses of JE following primary immunization and share with the ITAG for further refining the recommendation in this area.

(19) The ITAG recommends that SEARO:

(a) Continues to support Member States to improve the surveillance data quality by:

(i) Assisting with reviewing their JE/AES surveillance data quality and the use of the data for determining the disease burden.

(ii) Supporting Global Alliance for Vaccines and Immunization (GAVI)-eligible countries in the Region that are interested in introducing JE vaccines to prepare applications, develop and implement robust vaccine introduction plans.

(iii) Systematically reviewing the needs of Member States and finalizing a comprehensive action plan for effective JE control in the Region for presentation to the ITAG in 2017.

Rotavirus Gastroenteritis, Invasive Bacterial Vaccine-Preventable Diseases (IBVPD)

The ITAG congratulates Member States for establishing sentinel site surveillance for IBVPD and Rotavirus gastroenteritis with and without the support of WHO. The ITAG takes note of the plans to expand this surveillance platform to include other VPDs such as typhoid. The ITAG also underscores the fact that the sentinel site assessments for performance have revealed deficiencies in the quality of surveillance.

(20) The ITAG recommends that:

(a) All countries that are conducting IBVPD and rotavirus surveillance take steps to improve the quality of surveillance. Countries that receive WHO support and have had sentinel surveillance site assessments should

improve quality of surveillance as per the indicators of the performance management framework.

(b) All countries that are conducting IBVPD and rotavirus surveillance with WHO support report case-based data to the WHO country office in a timely manner.

(c) The **Indian** surveillance network of IBVPD and rotavirus gastroenteritis surveillance which is not supported by WHO is also encouraged to provide data to WHO country office and WHO SEARO is requested to facilitate the participation of the **Indian** surveillance network in all activities of the Regional network.

HPV Infection

HPV vaccine has not been introduced widely in the SEAR. The ITAG recommends that country NITAGS review the importance of the HPV in their countries. **Bhutan** introduced HPV vaccine nationwide for 9–13 year-old adolescent girls and **Sri Lanka** will be introducing HPV in 2017. **Bangladesh** and **Nepal** are planning to conduct HPV vaccination demonstration programmes in preparation for nationwide introduction.

(21) The ITAG recommends that:

(a) **Bangladesh** and **Nepal** utilize planned HPV vaccination demonstration programmes as pilots to launch comprehensive cancer control activities and coordinate or integrate, as appropriate, with adolescent and reproductive health programmes. The two countries are requested to share lessons learned in the ITAG by 2017.

(b) Other countries in SEAR considering introduction of HPV vaccine, as appropriate, consider a coordinated strategy that includes education about risk reduction behaviours for HPV infection, establish and/or strengthen screening programmes and treatment for cervical cancer in order to achieve comprehensive cervical cancer control and plan, where possible, to deliver HPV vaccination in close collaboration with other adolescent health programmes.

(c) For countries that have not planned either HPV demonstration programmes or national introduction programmes, develop plans to collate evidence on disease burden and cost-effectiveness studies and present the evidence to their national NITAGs to make an informed decision on vaccine introduction.

VI. Seasonal influenza

The ITAG recognizes that there has been progress made on seasonal influenza activities since the ITAG meeting in 2014. The ITAG notes that influenza surveillance and seasonal influenza vaccination is a key component of pandemic preparedness and response. The ITAG also notes that opportunities exist for the Regional Office and Member States to strengthen influenza surveillance, determine the burden of disease and enhance regulatory capacity-building in relation to influenza vaccines. The ITAG congratulates the Regional Office for identification of Member States for targeted support and capacity enhancement in influenza laboratory diagnosis, provision of technical assistance to improve laboratory assisted surveillance and taking the leading role in collating existing evidences and planning burden of disease studies and economic analyses of seasonal influenza vaccines. The ITAG also underscores the importance of efforts of Member States in SEAR in the identification and implementation of specific activities to improve influenza surveillance and also starting to plan for collating and reviewing existing evidence for identification of information gaps for establishing policies and strategies for influenza vaccination.

(22) The ITAG recommends that countries:

(a) Regularly assess the performance of the laboratory-supported surveillance networks to determine risk groups, seasonality of the disease and the annually circulating influenza strains. Regular review of data by NITAGs/NCIPs will contribute to the improvement of surveillance quality and use of data for decision-making.

(b) Through NITAGs consider seasonal influenza vaccination as well as pandemic preparedness in their national immunization strategies.

(c) Report the progress of influenza surveillance and immunization activities to the 2016 ITAG.

(23) The ITAG recommends that SEARO:

(a) Coordinates global pandemic preparedness with the other WHO Regions.

(b) Supports seasonal influenza surveillance activities and assessment of impact of vaccination with other partners.

VII. Data quality

The ITAG notes that the lack of quality immunization data is an impediment to monitoring and improving immunization programme performance. The ITAG notes the use of the available subnational data and not just data from national surveys can result in better national coverage estimates. Hence, it makes the following recommendations which include several made in 2014:

(24) The ITAG recommends that countries:

(a) Namely, **Indonesia, Myanmar and Timor-Leste** conduct in-depth data quality assessments to validate immunization coverage estimates and report on progress to the ITAG in 2016.

(b) All countries that are currently doing so, should continue to share subnational data with SEARO. The ITAG encourages **India** and **Thailand** to develop mechanisms to receive and share subnational data with SEARO.

(c) Engage the NITAGs/NCIPs in monitoring data quality and the implementation of the data quality improvement plans.

(d) That apply for GAVI health system strengthening grants to utilize the opportunity to include support to strengthen their immunization information systems, including coverage monitoring, VPD surveillance, and AEFI monitoring, in their proposals.

(25) The ITAG recommends that SEARO supports countries to:

(a) Disseminate all the new data quality assessment guidelines, tools, and mobilize resources to assess and improve data quality.

(b) Meet the GAVI data quality requirements (in relevant GAVI-eligible countries).

(c) Continue to review the quality of the immunization data provided to SEARO and provide feedback to Member States.

Way forward

The ITAG requests WHO SEARO to provide an annual report on the progress towards reaching the recommendations. The report will be provided to all ITAG members at least one month prior to the annual ITAG meeting that includes the following:

(1) Country-specific reports that include:

(a) table of MR related timelines and activities, the susceptibility profile of populations to measles and rubella, including plans to cover the immunity gaps shown, subnational risk assessments of measles, performance indicators, SIA schedule and coverage data;

(b) updates on the implementation of the tOPV to bOPV switch, environmental surveillance activities in relevant countries and review of serosurveys.

The ITAG requests that the ITAG 2016 agenda includes sessions on: typhoid, cholera, hepatitis B, Hib and school based immunization.

4. Conclusions

The Sixth Meeting of the SEARO-ITAG launched the tenure of the newly appointed ITAG. In addition to the ITAG members, respective MoH EPI Managers, VPD surveillance focal points and WHO country Focal Points contributed to the meeting. The other participants in this meeting included

members of NCIP of Member States, SAGE members representing the Region, WHO headquarters, Regional Office for South-East Asia and representatives from WHO country offices, UNICEF regional and country offices and a number of other local and global partners and stakeholders. The inclusion of the larger partnership allowed for more transparency and identification of challenges and synergies across the partnership. The general consensus was that this inclusion of all stakeholders was both productive and efficient and so the Secretariat has concluded that this format would be followed next year as well.

Full report and annexes can be found on the SAGE website

WORLD HEALTH ORGANIZATION

REGIONAL OFFICE FOR THE WESTERN PACIFIC

English only

MEETING REPORT

24th MEETING OF THE TECHNICAL ADVISORY GROUP ON IMMUNIZATION AND VACCINE-PREVENTABLE DISEASES

Convened by:

WORLD HEALTH ORGANIZATION
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SUMMARY

The Technical Advisory Group (TAG) on Immunization and Vaccine-preventable Diseases in the Western Pacific Region was established in 1991 with the following terms of reference:

1. to recommend, in coordination with the Regional Certification Commission, technical issues regarding sustaining the poliomyelitis-free status of the Western Pacific Region and global certification of poliomyelitis eradication;
2. to review the epidemiological situation in the Western Pacific Region and recommend appropriate goals, targets, strategies and surveillance indicators, and monitor progress towards the reduction of vaccine-preventable diseases, including the control and elimination of measles and maternal and neonatal tetanus;
3. to recommend suitable strategies and processes for the introduction and integration of new vaccines into the Expanded Programme on Immunization (EPI), including methods of monitoring progress for the diseases concerned;
4. to recommend suitable strategies for sustaining high-quality national immunization programmes in the Western Pacific Region, including management, vaccine supply, cold chain and the safety of injections;
5. to strengthen, in coordination with the Inter-agency Coordinating Committee, the active involvement of all institutions, national and international organizations, and political leaders concerned with immunization and vaccine-preventable disease control efforts in sustainable programme activities, including participation at the meetings of the Technical Advisory Group on EPI and Poliomyelitis Eradication and Inter-agency Coordination Committee meeting; and
6. to advise the WHO Regional Director for the Western Pacific Region on the above points.

Since 1991 TAG has met annually to review the progress of the immunization programme in the Western Pacific Region and provide guidance on establishing and achieving immunization goals. The 24th TAG meeting was held in Manila, Philippines, from 8–12 June 2015. The meeting was attended by five TAG members, five temporary advisers, 23 participants from 15 countries and areas, 27 representatives from partner organizations, and WHO staff from headquarters, the Regional Office for the Western Pacific and country offices.

After the Global Vaccine Action Plan 2011–2020 was approved by the World Health Assembly (WHA) in 2012, the Western Pacific Region developed a Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific. In 2014, the sixty-fifth session of the Regional Committee for the Western Pacific endorsed the Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific in resolution WPR/RC65.R5. The 24th TAG focused on reviewing progress towards the implementation of the regional framework. Topics included achieving targets and programme indicators for the polio endgame; measles, rubella, and maternal and neonatal tetanus elimination; and hepatitis B control. Discussions were also held on the acceleration of Japanese encephalitis (JE) control in the Western Pacific Region, introduction of affordable new vaccines, immunization supply chain systems, and the use of quality vaccines. The meeting also covered work towards the new regional immunization coverage goals that aim to ensure equity in immunization services to reach unreached target populations and improve data quality.

1. INTRODUCTION

1.1 Meeting organization

The meeting was attended by five Technical Advisory Group (TAG) members, five temporary advisers, 23 participants from 13 countries and areas, 40 representatives from partner organizations, and WHO staff from headquarters, the Regional Office for the Western Pacific and country offices. The timetable of the meeting is provided in Annex 1. The list of participants is included in Annex 2.

1.2 Meeting objectives

The objectives of the meeting were:

1) to review progress, identify critical issues and discuss key actions to achieve regional immunization goals and strategic objectives as specified in the *Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific*; and

2) to identify opportunities to enhance collaboration and coordination among immunization partners to support countries in implementing the *Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific*.

2. PROCEEDINGS

Full report of the proceedings can be found on the SAGE website

3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Measles and rubella elimination

A. Measles Elimination

TAG congratulates the three countries – Brunei Darussalam, Cambodia and Japan – that were verified in March 2015 as having achieved the interruption of endemic measles virus transmission for a period of at least 36 months; these countries joined the four countries and areas that were verified in March 2014 – Australia, Macao SAR (China), Mongolia and the Republic of Korea.

TAG notes that the regional measles incidence (per one million population) significantly increased from 5.9 in 2012 to 17.7 in 2013 and 44.0 in 2014. This increased incidence of measles virus transmission can be attributed to: (i) resurgence of endemic transmission in endemic countries; (ii) large-scale outbreaks following importation in countries with low or no recent documented measles transmission; and (iii) multiple importations in countries that have achieved or are approaching interruption of endemic measles virus transmission.

TAG notes the changing epidemiology and age distribution of measles cases observed in recent outbreaks, with decreased incidence among children targeted for vaccination and increased incidence among infants too young to be vaccinated, as well as among adolescents and adults. This age pattern may be expected when vaccination has prevented measles cases among children in age groups targeted through routine and supplemental immunization activities and immunity gaps remain in older persons.

As of June 2015, all except four countries (the Lao People's Democratic Republic, Papua New Guinea, Solomon Islands and Vanuatu) in the Region have introduced a routine second dose of measles-containing vaccine (MCV2).

TAG acknowledges that a highly proficient laboratory network with strong quality assurance provides laboratory confirmation and genotyping evidence to the measles and rubella elimination programme in the Western Pacific Region, which can better inform immunization strategies.

TAG notes that for the countries that have verified measles elimination, genotype evidence supports the interruption of endemic measles virus transmission.

B. Rubella Elimination

TAG acknowledges that a regional rubella elimination goal was endorsed by the Regional Committee for the Western Pacific in October 2014 as one of eight regional immunization goals specified by the Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific. TAG notes that rubella-containing vaccine has now been introduced or will soon be introduced (Papua New Guinea, Vanuatu and Viet Nam) into the routine immunization programmes of all Member States.

TAG notes that many countries in the Region have been utilizing the measles elimination platform and strategies to accelerate or initiate activities for rubella elimination. Several countries in the Region have made significant progress toward rubella elimination recently and have set target years for achieving elimination (e.g. 2020 for Japan and Mongolia). The Global Vaccine Action Plan 2011–2020 has established the goal of achieving measles and rubella elimination in five of six WHO regions by 2020.

To support countries in the Region to develop a national policies, plans and strategies to eliminate rubella and prevent CRS as the TAG recommended in 2014, a regional plan of action for rubella elimination and CRS prevention in the Western Pacific should be prepared just as the Western Pacific Regional Plan of Action for Measles Elimination was developed in 2003. Since several countries in the Region are approaching the interruption of indigenous rubella virus transmission, guidelines for verification of rubella elimination should be also developed, similar to what was developed for measles elimination.

Recommendations

1. TAG recommends that countries achieve and maintain high coverage with the timely administration of two doses of measles- and-rubella-containing vaccine in accordance with the national immunization schedule. Countries in the Region that have not yet introduced the second routine dose of measles- and-rubella-containing vaccine (MRCV) should take steps to improve coverage of MRCV1 and introduce MRCV2. School enrolment for all ages (primary, secondary and post-secondary) should be used as an opportunity to check full vaccination status and administer missed doses.

2. Countries experiencing endemic measles virus transmission or measles outbreaks following importation(s) should recommit to implement actions recommended by TAG in its 23rd meeting in June 2014, specifically to:

    - conduct detailed analyses of the coverage data and the epidemiology of measles cases and outbreaks including genotyping data on chains of transmission;
    - update their national measles-rubella elimination plans and strategies;
    - develop or update subnational plans and strategies (endemic countries with large population);
    - update and actively implement their measles outbreak response plans including the early notification of nearby countries and areas about measles virus transmission;
    - enhance surveillance activities with aggressive case detection and thorough outbreak investigations as well as appropriate case management and vaccination of susceptible contacts;
    - identify immunity gaps by geographic area, birth cohort and risk group;
    - fill immunity gaps (e.g. selective immunization activities or smaller-scale, such as regional or province-wide, supplemental immunization activities [SIAs] targeting appropriate age groups; or more frequent follow-up SIAs targeting birth cohorts born after the last SIA in specific regions or provinces), based on country-level data; in outbreak settings, children 6 months of age and older

should be vaccinated. Children who receive a dose of measles-rubella vaccine before the recommended age specified in the national immunization schedule should receive two doses according to the national schedule with at least 30 days between doses. Measles-rubella combination vaccines should be used for all routine and supplementary immunizations activities rather than using single antigen measles or single antigen rubella vaccines;

- conduct high-quality SIAs with >95% coverage based on thorough analysis of and lessons learnt from the past SIAs; analysis should include identification of the susceptible population(s), the geographic areas to be covered and specific high-risk groups; post-campaign coverage surveys should be conducted;

- implement infection control measures and health-care facility practices to prevent nosocomial transmission of measles and rubella including vaccination of health workers; and

- encourage full vaccination prior to international travel for all travelers and especially for those who travel to and from measles-endemic or measles-infected countries and areas.

3. WHO should continue to work with other international partners in supporting countries to plan and conduct these actions.

4. WHO should update the current *Western Pacific Regional Plan of Action for Measles Elimination* (2003) with inclusion of the following components:

   - guidance on conducting risk assessments and outbreak response immunization activities followed by implementation of targeted strategies for preventing and interrupting measles virus transmission among young infants, adolescents and adults by identifying risk factors/characteristics of affected people (e.g. health-care workers, university students, military personnel, migrants); and

   - strategies for rubella elimination.

5. TAG endorses the report and recommendations of the Fourth Annual Meeting of the Regional Verification Commission (RVC) for Measles Elimination in the Western Pacific held in March 2015. TAG encourages expanding the terms of reference of the RVC to include rubella elimination. WHO should update the current *Guidelines on Verification of Measles Elimination* (2013) with inclusion of components for verification of rubella elimination.

6. Now that all countries and areas have introduced (or will introduce during 2015–2016) rubella-containing vaccine into their routine immunization programmes and the Western Pacific Region has committed to eliminate rubella, TAG recommends:
   - establishment of a regional rubella elimination target date of 2020; and
   - that the sixty-seventh session of the Regional Committee for the Western Pacific in 2016 consider setting a target year for rubella elimination as an agenda item.
7. WHO should continue to work with other international partners in supporting countries to strengthen rubella and CRS surveillance, including virological investigation.

C. Hepatitis B accelerated control

Conclusions

TAG is pleased with the tremendous progress towards the 2017 goal of <1% HBsAg prevalence among 5-year-old children. The progress is due to the commitment and actions of Member States and is a true public health success story. TAG recognizes, however, that in several countries additional efforts to increase hepatitis B birth-dose coverage are needed in order to achieve the goal. TAG notes with concern the persistent low birth-dose coverage in high-population countries, including the Philippines and Viet Nam.

TAG notes the increased interest of countries in the Region in using hepatitis B vaccine outside the traditional 2–8° C range. TAG recognizes that this strategy is important for achieving the regional

hepatitis B control goal. The main obstacle to widespread adoption of this strategy is the lack of a hepatitis B vaccine that is labelled for use outside the traditional 2–8° C range. Despite a large body of evidence documenting the safety and effectiveness of many hepatitis B vaccines when used for up to one month at ambient temperatures, without a product label for use in this manner, it is difficult for countries to adopt this strategy.

Recommendations

1. TAG endorses the proposed hepatitis B health worker vaccination target in the *Regional Action Plan for Viral Hepatitis in the Western Pacific*: adoption of a health worker hepatitis B vaccination policy in all Western Pacific Region countries and areas by 2020.

2. TAG recommends that a decision on including a new target on further reducing mother-to-child transmission of hepatitis B in the *Regional Action Plan for Viral Hepatitis in the Western Pacific* be deferred until global guidance on the strategies and a means for measuring progress in reducing mother-to-child hepatitis B transmission, such as the addition of antivirals in late pregnancy, is provided.

3. TAG reiterates its support for the time-limited (up to 30 days) use of hepatitis B vaccine outside of the traditional 2–8° C range for health facilities without a working refrigerator. TAG calls on hepatitis B vaccine manufacturers to initiate the necessary steps to seek a label variation of their hepatitis B vaccine for use at temperatures outside the traditional 2–8° C range in a controlled temperature chain.

4. TAG recommends that countries with hepatitis B vaccine hesitancy problems undertake activities to regain health worker and public confidence in hepatitis B birth-dose vaccination.

5. TAG endorses the 2015 Expert Resource Panel (ERP) recommendations.

6. TAG recommends that countries and areas strengthen collaboration between immunization and maternal and child health programmes to utilize opportunities to improve birth-dose vaccination.

C. Polio eradication and polio endgame strategy

Conclusions

1. TAG acknowledges the tremendous progress towards global polio eradication, noting that in 2015 wild poliovirus Type 1 (WPV1) has been identified in only two countries (Pakistan with 24 cases and Afghanistan with two cases), which is markedly lower than during the same period in 2014. No cases have been reported from Africa in 2015. Furthermore, no wild poliovirus Type 2 (WPV2) has been reported in the world since 1999 and no wild poliovirus Type 3 (WPV3) since 2012. The Western Pacific Region has retained its polio-free status since 2000.
2. TAG notes the presence of countries and subnational areas that have been identified as being at increased risk for poliovirus importation or ongoing transmission following an imported virus.
3. TAG acknowledges the plan for the Global Polio Laboratory Network to expand the number of laboratories in the Region with the capacity to perform intratypic differentiation and to introduce an enhanced intratypic differentiation method to increase the sensitivity for detecting and identifying polioviruses quickly.
4. TAG notes that four countries in the Region are performing environmental surveillance to complement acute flaccid paralysis (AFP) surveillance, and that the Region will need to start preparing for the expansion of environmental surveillance to monitor the effectiveness of Type 2 containment in essential facilities.

5. TAG acknowledges progress at the country and regional levels in implementation of the global *Polio Eradication and Endgame Strategic Plan 2013–2018* with all 17 countries and areas that use only OPV committing to introduce at least one dose of IPV by end 2015.

6. TAG notes that delays in IPV introduction may occur in some countries and areas due to lack of global supply.

7. TAG notes the recent WHA resolution calling on Member States to accelerate preparation and planning for the globally synchronized replacement of tOPV with bOPV in April 2016 (i.e. the switch) including the need for countries to register bOPV before April 2016 for use in routine immunization programmes and to develop costed national switch plans by September 2015.

8. TAG notes the need to support implementation of appropriate containment of WPV2 in essential facilities by the end of 2015 and of Type 2 Sabin poliovirus within three months of global withdrawal in April 2016 of the Type 2 component in OPV as articulated in the *WHO Global Action Plan to Minimize Poliovirus Facility-associated Risk* (GAP III).

Recommendations

1. TAG recommends that countries and areas in the Region achieve and maintain international standards for AFP surveillance performance supported by WHO-accredited laboratories. High-risk areas should be identified by conducting annual subnational risk assessments. Special emphasis to strengthen immunization and surveillance programmes should be given to underperforming and high-risk areas.

2. Countries should finalize their national polio endgame plans addressing all four objectives included in the *Polio Eradication and Endgame Strategic Plan 2013–2018*.

3. TAG recommends that countries and areas adhere to timelines for the 2015 introduction of IPV, recognizing that vaccine supply may force some countries or areas to delay introduction to early 2016.

4. All countries that will continue using OPV in their routine immunization programmes after January 2016 should:

    a. expedite the registration of bOPV for use in the routine immunization programmes and, if required in the interim, authorize its use on the basis of its prequalification granted by WHO;

    b. complete other requirements, such as adding bOPV to the national drug formulary, that may be required for use of bOPV in the routine immunization programme;

    c. in preparation for the April 2016 switch, develop a plan to switch from tOPV to bOPV by September 2015, with plans to include activity timelines, bOPV requirements, a tOPV disposal strategy and costing; and

    d. to increase population immunity, to decrease the risk of vaccine-derived polioviruses (VDPVs) and to reduce vaccine wastage, countries should utilize excess stocks of tOPV in SIAs during the first quarter of 2016.

5. TAG recommends that countries and areas comply with the requirements of GAP III and also:

    a. update national inventories of polio viruses (wild-type, vaccine-derived or OPV/Sabin-like) and prepare for destruction or containment of WPV2 by end of 2015 (Phase I);

    b. nominate a national/subregional poliovirus containment coordinator;

    c. identify a national regulatory authority for containment that shall certify proposed essential facilities as compliant with GAP III in preparation for the commencement of Phase II; and

d. implement appropriate containment of WPV2 in essential facilities by the end of 2015 and of Type 2 Sabin poliovirus within three months of global withdrawal of the Type 2 component in OPV in April 2016 (Phase II) in accordance with GAP III.

D. Maternal and neonatal tetanus elimination

Conclusion

TAG acknowledges progress in the Region towards maternal and neonatal tetanus elimination with the validation of Viet Nam (2005), China (2012) and the Lao People's Democratic Republic (2013).

The TAG congratulates the Philippines for conducting a lot quality assurance-cluster sampling (LQA-CS) survey in 2015 in which 16 of 17 subnational regions were validated as having achieved MNT elimination and notes that additional tetanus toxoid supplementary immunization activities (TT-SIAs) were recommended for the one remaining region, the Autonomous Region of Muslim Mindanao and looks forward to national validation of MNT elimination.

TAG notes that Cambodia is planning to conduct an LQA-CS survey immediately following the TAG meeting in June 2015.

Recommendations

1. TAG recommends that the three remaining countries implement required actions to achieve the validation of MNT elimination as soon as possible:

    - the Philippines should complete the recommended TT-SIAs in the Autonomous Region of Muslim Mindanao by the end of 2016 in order to achieve national validation of MNT elimination;

    - Cambodia should conduct the planned LQA-CS survey in 2015; and

    - Papua New Guinea should complete the planned data review and if supported by data review conduct a pre-validation assessment in 2016.

2. Countries and areas should maintain MNT elimination by implementing the following actions:

    - Review, and if necessary modify, the national immunization schedule to provide protection against tetanus from infancy through adulthood for both males and females;

    - annually review the WHO/UNICEF district data spreadsheet and take appropriate corrective actions;

    - achieve and maintain a sensitive neonatal tetanus surveillance system; and

    - closely collaborate with maternal and child health programmes to promote administration of tetanus-toxoid-containing vaccine (TTCV) during antenatal care visits, as well as clean delivery and clean cord-care practices.

3. In accordance with the 2006 Tetanus vaccine WHO position paper, TAG recommends, as a rule, that vaccine combinations containing diphtheria toxoid and tetanus toxoid, rather than tetanus toxoid alone, should be used when immunization against tetanus is indicated.

E. Evidence-based introduction of new vaccines

Conclusion

TAG notes that low- and middle-income countries in the Western Pacific Region have made significant progress in introducing new and underutilized vaccines, especially PCV, in the past year, yet an equity gap persists as they still lag far behind high-income countries in including new or underutilized vaccines in their national immunization programmes. Achievement of the *Global Vaccine Action Plan* goal for introduction of new and underutilized vaccines, as adopted in the *Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific*, requires that countries evaluate evidence on the epidemiology and burden of disease, cost and cost-effectiveness of vaccination, the role of other disease prevention and control measures, vaccine characteristics, vaccine supply, and immunization programme and health system requirements for introducing the vaccines. It is noted that the introduction of new vaccines increases immunization programme costs for both vaccines and related service delivery.

An increasing number of Member States are collecting and evaluating such evidence to develop and sustain vaccine introduction policies, and some Member States have used the evidence to formulate national plans. Disease-burden evidence from other countries in the Region and official disease-burden estimates are relevant and appropriate to use in assessing the need for a vaccine. WHO plays an important role in providing technical support and capacity strengthening for the generation of required evidence. Surveillance with laboratory confirmation is a key source of evidence, and the quality of surveillance requires consistent attention. Implementation of the recent WHO recommendations for seasonal influenza vaccination requires consideration of regulatory issues and vaccine selection for tropical countries.

Recommendations

1. TAG reiterates its advice that each Member State develops a national plan for evidence-based introduction of new vaccines in consultation with national immunization technical advisory groups (NITAGs) or similar groups. Countries are urged particularly to consider the new and underutilized vaccines recommended for inclusion in all national infant immunization programmes, namely *Haemophilus influenzae* Type b, hepatitis B, inactivated polio, pneumococcal conjugate, rotavirus and rubella vaccines. Japanese encephalitis (JE) vaccine should be considered in endemic areas and human papillomavirus (HPV) vaccine where cervical cancer is a public health priority. TAG suggests that the plan for new vaccine introduction be part of the comprehensive multi-year plan for immunization or other health plans.TAG reiterates its advice that each Member State develops a national plan for evidence-based introduction of new vaccines in consultation with national immunization technical advisory groups (NITAGs) or similar groups. Countries are urged particularly to consider the new and underutilized vaccines recommended for inclusion in all national infant immunization programmes, namely *Haemophilus influenzae* Type b, hepatitis B, inactivated polio, pneumococcal conjugate, rotavirus and rubella vaccines. Japanese encephalitis (JE) vaccine should be considered in endemic areas and human papillomavirus (HPV) vaccine where cervical cancer is a public health priority. TAG suggests that the plan for new vaccine introduction be part of the comprehensive multi-year plan for immunization or other health plans.

2. TAG again urges countries to strengthen surveillance, including laboratory confirmation, for diseases targeted by new vaccines to monitor and improve the quality of surveillance implementation.

3. TAG requests WHO to provide technical support and capacity strengthening for the development of national plans for the evidence-based introduction of new vaccines and to assess and improve the quality of surveillance.

4. TAG encourages countries introducing new vaccines to utilize the opportunities to establish synergistic approaches, as outlined in the *Global Action Plan for Pneumonia and Diarrhoea* and the *Comprehensive Cervical Cancer Prevention and Control* guidance note, and to strengthen immunization systems.

F. Japanese encephalitis accelerated control

Conclusions

TAG notes several important advances in JE control during the past year. In October 2014, the Regional Committee for the Western Pacific endorsed a regional goal for accelerated control of JE. In

addition, advances in the development, licensure and availability of vaccines, as well as global guidance and programmatic steps by Member States, are moving the Region towards achievement of this new regional goal. These advances include the prequalification by WHO of a third JE vaccine, improvement in the choice and availability of vaccines for introduction by countries that rely on Gavi support or UNICEF procurement; publication of a new WHO position paper on JE vaccines; the provision of guidance on vaccine selection and vaccination strategies; and the expansion of JE vaccination programme coverage by the Lao People's Democratic Republic and Viet Nam. In addition, Cambodia and the Philippines established target dates for national JE vaccine introduction, and the Philippines became the first country to use a new tool to assess the quality of JE surveillance.

Although some progress has been made, weaknesses in surveillance continue to limit efforts to define JE epidemiology and disease burden and to measure the impact of vaccination in some countries. Strengthening of surveillance in countries that have not yet achieved a high degree of JE control is critical for providing disease-burden data and evidence of vaccine impact. The quality of testing in the Western Pacific Region JE laboratory network has improved but needs continued strengthening.

Recommendations

1. TAG requests the WHO Regional Office for the Western Pacific develop operational definitions and targets, timelines and strategies to achieve a JE accelerated control goal through consultation with experts and Member States during the coming year.
2. The TAG reiterates the recommendation of the 22nd and 23rd TAGs that JE surveillance with laboratory confirmation should be further strengthened in endemic areas of the Western Pacific Region, and sentinel surveillance should be systematized to facilitate reporting at the regional level.
3. TAG suggests that the WHO Regional Office for the Western Pacific expand use of the JE surveillance structured tool to assess the quality of surveillance in countries that have not yet achieved a high degree of JE control.

G. Strengthening Immunization Systems – Routine Immunization

Conclusions

1. TAG acknowledges the sustained high immunization coverage at the regional level and commends countries' efforts to develop and implement strategies to improve coverage including the Reaching Every Community and Reaching Every Child strategies.
2. TAG notes, especially in priority countries, the uneven progress in vaccination coverage at subnational levels that may be related to inequitable access.
3. TAG notes the heterogeneous (variable and insufficient) progress in vaccination coverage in middle-income countries and welcomes the initiative by WHO and other partners to support middle-income countries without external support to improve vaccination coverage levels and the uptake of new vaccines.
4. Further improvements in immunization coverage will require tailored solutions based on country-specific analysis to access underserved and hard-to-reach children. Among these solutions are two approaches that offer opportunities to reach unvaccinated and under-vaccinated children beyond the first year of life with recommended vaccines to ensure they are fully vaccinated against vaccine-preventable diseases. The strategies are:

    - establishing an immunization visit platform in the second year of life to deliver scheduled vaccines such as DTP4 and MCV2, as well as providing catch-up vaccination for those vaccine doses missed during the first year of life; and
    - establishing routine school immunization record checks and follow-up vaccinations with missed doses of measles, rubella and other vaccines so all children can enter school fully protected from vaccine-preventable diseases.

5. TAG notes the need for continued efforts by Member States to improve the quality of immunization data, including financing-related data.

6. TAG acknowledges increased country ownership of immunization programmes as reflected by the overall trend of increasing domestic expenditures for routine immunization in the Region when compared to the 2010 baseline, but recognizes that countries will continue to be significantly challenged in securing financial sustainability given growing programme costs.

Recommendations

1. TAG recommends countries with insufficient levels of vaccination coverage or prolonged vaccine-preventable disease outbreaks consider conducting comprehensive programme reviews to identify characteristics of children who are unvaccinated or under-vaccinated and define approaches to address them.

2. TAG encourages countries to establish and maintain a platform to provide immunizations in the second year of life as an opportunity to reach all children, including hard-to-reach children, with scheduled vaccines and for catch-up immunizations as needed. The WHO Regional Office for the Western Pacific should inventory which countries and areas have programme policy restrictions that limit vaccinations offered after 12 months of age and should work with countries and areas to remove these barriers to vaccination.

3. TAG encourages all countries to implement school immunization record-checking programmes to maximize immunization coverage through catch-up immunization as needed. The recently published experience of China in the use of school immunization record checking should be distributed to all countries by the Regional Office for the Western Pacific as an example of what can be achieved.

4. TAG reiterates its recommendation from the 23rd TAG to countries to share subnational coverage data with the WHO Regional Office for the Western Pacific.

5. TAG urges Member States to develop costed multi-year immunization plans as a tool to advocate for and enable the development of financial sustainability strategies.

6. Member States are urged to sustain and improve the consistency of annual reporting of government immunization expenditures including vaccine price and procurement information in the WHO–UNICEF Joint reporting form or V3P platform to strengthen programme management and to facilitate monitoring of progress on the *Global Vaccine Action Plan* goal for Strategic Objective 1.

7. TAG continues to endorse the implementation of Immunization Week annually in April and encourages all Member States in the Region to participate in this important event as one mechanism to increase population demand for vaccination.

8. TAG reiterates its request to WHO to explore interest among Member States in the Region to establish a regional pooled procurement mechanism, such as the Vaccine Independence Initiative or VII, to increase vaccine security and to facilitate access to new vaccines.

H. Vaccine/Immunization safety, quality supply and immunization supply chain/logistics

Conclusions

1. TAG reiterates that ensuring immunization safety and effectively responding to AEFIs is critical for building public trust in national EPI programmes. This includes timely and effective communication with the public.

2. TAG appreciates Member States' timely and effective responses to immunization safety incidents.

3. TAG notes that Member States have made strenuous efforts to improve vaccine safety including analysing the capacity gap, developing regional and national guidelines on causality assessment and communications, and conducting national and subnational vaccine safety training.

4. TAG notes the fragility of the immunization supply chain, including the cold chain, logistics and effective supply chain management. TAG notes that Member States and international partners have made considerable efforts to improve cold-chain capacity and logistics through periodic effective vaccine management assessments and updating cold chain and logistics improvement plans.

5. TAG congratulates Viet Nam's Ministry of Health for establishing a fully functional national regulatory authority aligned to WHO's assessment criteria for vaccine-producing countries.

6. TAG notes that NRA systems and functions for vaccines require strengthening in many countries and areas, especially non-producing countries and areas of the Region.

7. TAG appreciates that the WHO Regional Office for the Western Pacific and Member States made progress in establishing a regional alliance to coordinate and support countries in vaccine safety.

Recommendations

TAG urges all Member States:

1. to further strengthen the immunization safety surveillance systems, including AEFI surveillance and NRA adverse drug reactions surveillance, considering the importance of immunization safety practices to maintain high-quality immunization services;

2. to make continuous efforts to analyse the capacity gap, develop and update national guidelines on vaccine safety surveillance, provide national and subnational training, and establish and ensure functionality of national immunization safety causality committees;

3. to provide timely and appropriate responses to immunization safety incidents including effective and timely communication with media and the public, and to share the information rapidly through regional and global vaccine safety surveillance networks;

4. to continue strengthening immunization supply chain performance through periodic effective vaccine management assessments and actively implement and monitor the improvement plans, and ensure that they are incorporated within the overall comprehensive multi-year plan;

5. to invest in human resources for the immunization supply chain, recognizing that they serve as the backbone of immunization programmes;

6. to regularly analyze immunization safety surveillance data and use it to guide capacity-building for immunization safety practices, particularly in areas where programme errors are often observed;

7. to implement appropriate waste-management policies, including recommended systems for disposing sharps;

8. to strengthen vaccine regulatory systems and implement World Health Assembly resolution WHA67.20 on regulatory system strengthening for vaccines as appropriate; and

9. to engage in and strengthen the regional alliance of national regulatory authorities, recognizing the importance of collaboration to pool regulatory capacities to promote greater access to quality, safe, efficacious and affordable vaccines.

The TAG advises WHO:

1. to continue to support Member States to improve vaccine/immunization surveillance systems in low- and middle-income countries in the Region;
2. to accelerate the process of formulating subregional AEFI causality assessment committees for Pacific Island countries and areas;

3. to provide capacity-gap assessment and capacity-building support to low- and middle-income countries for continued improvement of vaccine regulatory systems and implementation of institutional development plans;
4. to promote the greater participation of Member States in existing international and regional initiatives for collaboration and cooperation for regulatory harmonization of norms and standards and procedures in accordance with WHO principles and guidelines; and
5. to develop regional plans for NRA strengthening following global guidance and in consultation with the Regional Alliance for National Regulatory Authorities for Vaccines in the Western Pacific.

* Full report and annexes can be found on the SAGE website *

Hepatitis B Control Through Immunization: A Reference Guide

CONTENTS

FOREWORD

Hepatitis B prevention and control is a high priority for me as the World Health Organization Regional Director for the Western Pacific — the Region which has historically had the highest hepatitis B burden.

Hepatitis B infection causes deadly cirrhosis and cancer of the liver. The best protection from this deadly virus is three doses of vaccine in infancy, with the first dose administered within 24 hours of birth. Extremely safe and effective, the vaccine is the best tool we have for protecting children.

Member States have prioritized hepatitis B vaccination. Now millions of infants receive the complete series every year, and hepatitis B infection among infants and children has fallen dramatically, and continues to decline.

Indeed, the success of the Western Pacific Region has been remarkable. Since 2003, 10 million chronic hepatitis B infections have been prevented in the Region, saving an estimated 2.5 million people from hepatitis B-related deaths.

This milestone is the result of national actions to control hepatitis B. By 2012, 30 countries and areas in the Region had reduced prevalence among children to less than 2% — compared to prevalence rates higher than 6% in the pre-vaccine era.

In October 2013, the Regional Committee for the Western Pacific passed a resolution to further reduce hepatitis B — to less than 1% chronic infection prevalence among children by 2017.

This latest goal will save millions more in the Region from the devastating effects of hepatitis B.

To support Member State efforts to reach this goal, I am pleased to introduce *Hepatitis B Control Through Immunization: A Reference Guide*, which provides guidance and targets for hepatitis B control.

The Western Pacific Region was the first to establish a hepatitis B control goal. With close cooperation and strong government leadership, the Region can also become the first to reduce the disease's deadly toll to historic lows.

As always, I welcome the opportunity to work with each Member State towards the achievement of our shared goal.

Shin Young-soo, MD, Ph.D.
Regional Director for the Western Pacific
World Health Organization

SUMMARY

Hepatitis B Control Through Immunization: A Reference Guide is intended to provide a handy compilation of available guidance for hepatitis B vaccination programs in countries and areas of the Western Pacific Region. The Western Pacific Region, despite being home to approximately 28% of the global population, bears a disproportionate burden of hepatitis B virus (HBV)-related mortality and morbidity, accounting for almost half of all chronic hepatitis B infections worldwide.[1] With an estimated 160 million chronic HBV carriers living in the Region, hepatitis B is responsible for nearly 900 deaths per day, a mortality rate comparable to that of tuberculosis.[1] Most countries had a chronic HBV infection rate of more than 10% before the introduction of vaccination.[2] Of the 325 000 estimated annual deaths caused by HBV infection in the Region, nearly all are consequences of chronic infection, mostly decades after the initial infection at birth or in early childhood. Hepatitis B, therefore, is an important regional public health priority.

Universal childhood immunization with three doses of hepatitis B vaccine in the first year of life has been proven to be the most effective strategy for the prevention and control of hepatitis B. In 2005, the Western Pacific Region achieved the distinction of being the first WHO region to incorporate infant hepatitis B immunization in the national immunization programmes of all its Member States.

Universal childhood immunization with three doses of hepatitis B vaccine in the first year of life has been proven to be the most effective strategy for the prevention and control of hepatitis B.

In 2003, the fifty-fourth session of the WHO Regional Committee for the Western Pacific set a goal to reduce the prevalence of chronic hepatitis B infection among 5-year-old children to less than 1% (WPR/RC54.R3) in 2005 an interim milestone of reducing chronic HBV infection among children to less than 2% by 2012 was established (WPR/RC64.R5). By 2012, the Region as a whole and 30 countries and areas were estimated to have met the milestone. Striving to build upon these gains, in 2013, the sixty-fourth session of the WHO Regional Committee for the Western Pacific has now resolved to meet the goal of reducing chronic HBV infection to less than 1% among 5-year-old children by 2017 (WPR/RC64.R5). Achievement of this goal will translate to an additional 60 000 hepatitis B-related deaths averted per birth cohort in the Region.

There are five key strategic areas for hepatitis B prevention through vaccination.

1. Vaccination of infants

- Strengthening of routine immunization services to achieve and sustain at least 95% coverage with three doses of hepatitis B vaccine by 1 year of age in each birth cohort at the national level, and at least 85% coverage in each district.
- Delivery of a timely birth dose (within 24 hours of birth), with a target of reaching at least 95% of births at the national level and at least 85% coverage in each district.
- Coordination with maternal and child health programmes to improve access to immunization and other neonatal care interventions for births outside of health facilities.

1 Goldstein ST, Zhou F, Hadler SC, Bell BP, Mast EE, Margolis HS. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. Int J Epidemiol. 2005;34:1329–39.
2 Rani M, Yang B, Nesbit R. Hepatitis B control by 2012 in the WHO Western Pacific Region: rationale and implications. Bull World Health Organ. 2009;87:707–13.

2. Vaccination of priority adult population groups

- Immunization of high-risk population groups including health workers, men who have sex with men, sex workers, people who inject drugs, frequent recipients of blood/plasma transfusions, and any other population groups coming in regular contact with blood and blood products.
- Advocacy of national policies requiring free and universal hepatitis B vaccination of health-care workers.

3. Vaccine supply and quality

- Elimination of vaccine stock-outs at the national and district levels through improved training in vaccine management.
- Prevention of vaccine freezing through improved training in temperature monitoring.
- Promotion of use of controlled temperature chain for delivery of hepatitis B birth dose.

4. Advocacy and social mobilization

- Increasing awareness among decision-makers, health workers and caretakers of the risks and consequences of HBV infection and the need for hepatitis B vaccination through:
  - community and civil society engagement,
  - use of media outlets,
  - education materials, and
  - mass awareness campaigns such as World Hepatitis Day and World Immunization Week.

5. Measurement of programme performance and impact

- Measurement of programme performance through monitoring of immunization coverage rates, including establishment of systems to monitor hepatitis B birth dose coverage at the district level.
- Impact measurement through hepatitis B surface antigen (HBsAg) seroprevalence surveys.
- Verification.

Ebola Vaccines and Vaccination

Report of the SAGE Working Group on Ebola Vaccines and Vaccination with provisional recommendations for vaccination

September 30, 2015

SECTION A: INTRODUCTION, EPIDEMIOLOGY AND RISK FACTORS

Table of Contents

Background

In response to the ongoing widespread outbreak of Ebola Virus Disease (EVD) in west Africa, the World Health Organization (WHO) coordinated an effort to accelerate the development of vaccines against EVD for use in the current outbreak, as well as in response to future outbreaks.

In October 2014, the WHO Director General requested the Strategic Advisory Group of Experts (SAGE)[1] on Immunization to advise WHO on the use of the vaccine(s) for the control of EVD. In response to this request, the WHO SAGE secretariat established a Working Group with an urgent program of work to facilitate a SAGE review of the available and emerging evidence to inform the development of the recommendations for the use of Ebola vaccines.

The urgency of the task required that the SAGE Working Group process to review the available evidence and draft recommendations should proceed in parallel with the ongoing phase 1, phase 2 and phase 3 trials of candidate vaccines. Progress with the development and evaluation of vaccines has proceeded with an unprecedented speed. However, while there are several vaccine candidates undergoing clinical evaluation, none of them has as yet received regulatory authorization for use outside a study setting.

This report summarizes the available information on the epidemiology, risk factors and transmission patterns of EVD, with particular reference to the current epidemic in west Africa; the status of vaccine development, along with preliminary results from the evaluation of the most advanced vaccine candidates and the preparations for deployment of these vaccines; projections of the impact of vaccination under different epidemiological scenarios; and proposes provisional recommendations for the consideration of SAGE.

Epidemiology of Ebola Virus Disease

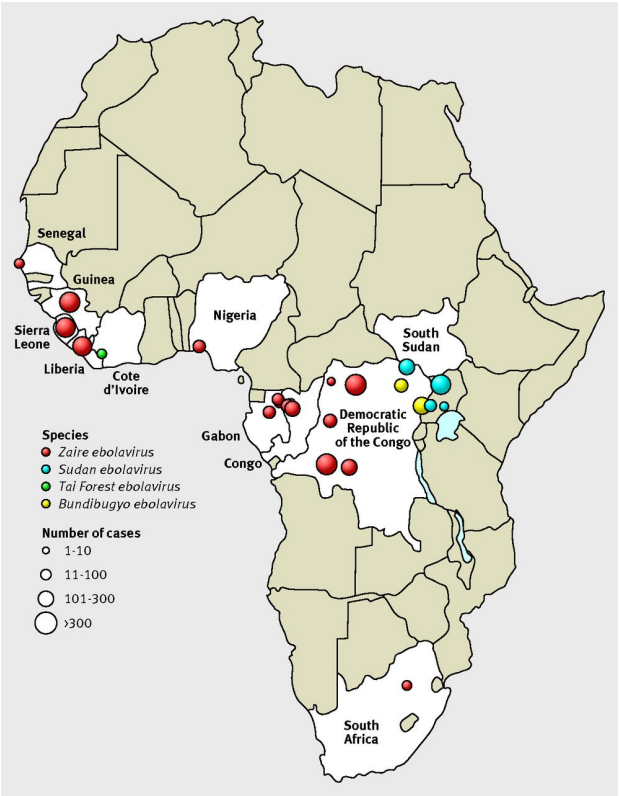
Ebola viruses and disease in humans: review of the published literature

Ebola viruses are members of the Filovirus family. Five species of *Ebolavirus* have been identified (*Zaire ebolavirus*, *Sudan ebolavirus*, *Bundibugyo ebolavirus*, *Tai Forest ebolavirus*, and *Reston ebolavirus*), of which the former three species have each caused multiple outbreaks of EVD; case fatality in these outbreaks has ranged from 40%-90%. Of note, while the current outbreak in West Africa is due to *Zaire ebolavirus*, approximately half of all previous outbreaks have been due to other species (*Sudan ebolavirus* or *Bundibugyo ebolavirus*). The geographic distribution of zoonotic spill-over events in previous EVD outbreaks roughly splits the continent of Africa, with all outbreaks due to *Zaire ebolavirus* occurring west of central Democratic Republic of Congo (DRC) and outbreaks due to *Sudan ebolavirus* and *Bundibugyo ebolavirus* occurring east of central DRC. Importantly, most of the current advanced vaccine prospects in clinical trials are monovalent vaccines containing the

[1] Strategic Advisory Group of Experts (SAGE) on Immunization- http://www.who.int/immunization/policy/sage/en/

Zaire ebolavirus glycoprotein and may have limited protection against other viral species. There is currently no efficacy data indicating cross-protection of *Zaire ebolavirus* glycoprotein in humans.

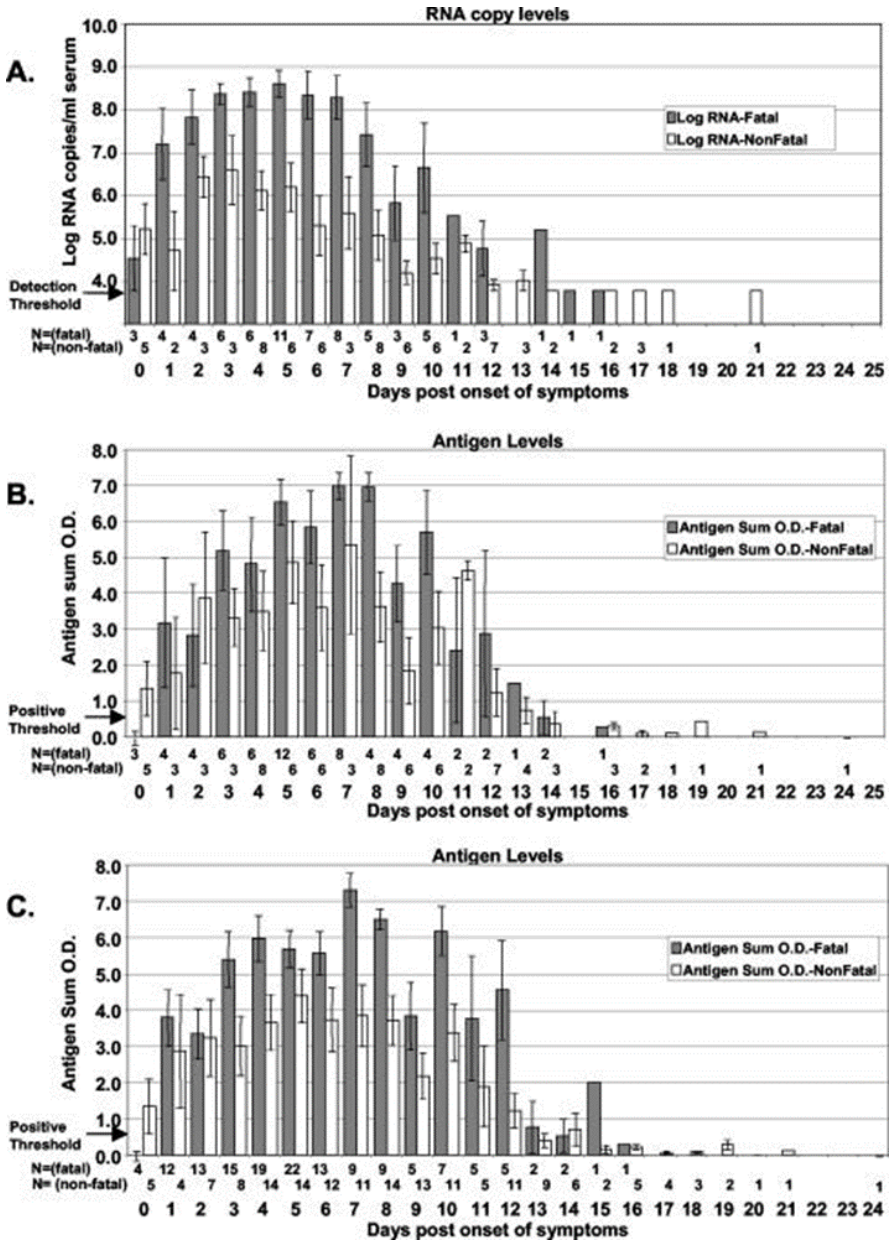
Figure 1: Geographic distribution of human EVD outbreaks (*Beeching et al., 2014*)



Ebola virus disease and transmission dynamics

The multiple species of the *Ebolavirus* genera are believed to be maintained in zoonotic reservoirs, however, once animal-human spill-over events occur, outbreaks are driven by person-to-person transmission. Ebola virus typically enters the body through penetration of the skin or by percutaneous exposure. The virus causes a disseminated infection, replicating in multiple organs, including the lymph nodes, liver, and kidneys, and eventually the endothelium (*Messaoudi et al, 2015*). Viraemia typically corresponds with the severity of the disease stage, with low titres early in disease, and increasingly higher titres during later, disseminated stages of disease, leading to eventual death or a decrease in titres corresponding with recovery and onset of adaptive immune response (*Ksiazek et al., 1999; Spengler et al., 2015; Towner et al., 2004*).

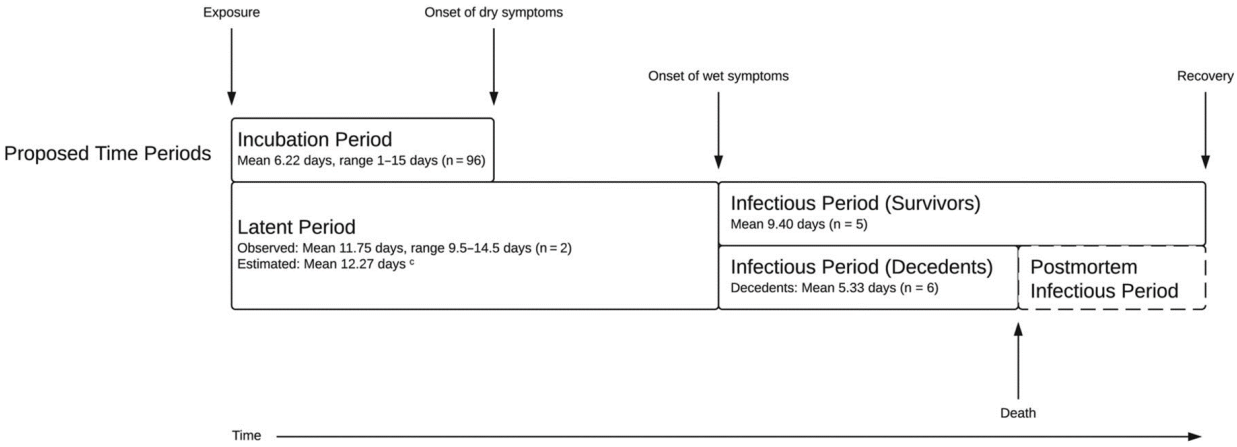
Figure 2: Kinetics of viraemia, relative to date of symptom onset, Gulu, Uganda (*Towner et al. 2004*)



The incubation period of Ebola virus in humans has been typically reported to be in the range of 2-21 days, with a mean of approximately a week. Early, non-specific signs and symptoms, including fever, chills, malaise, and myalgia mark the onset of disease. These are followed by late signs and symptoms, including general systemic signs and symptoms such as prostration, and organ system specific signs and symptoms involving the gastrointestinal (anorexia, nausea, vomiting, abdominal pain, diarrhoea), respiratory (chest pain, shortness of breath, cough, nasal discharge), vascular (conjunctival injection, postural hypotension, oedema), and neurological (headache, confusion, coma) systems. A subset of patients develops additional haemorrhagic symptoms including petechiae, ecchymosis, oozing from venepuncture sites, and mucosal haemorrhages (*Feldman and Geisbert, 2011*). In terms of risk of transmission, signs and symptoms can be classified as 'dry' (fever,

chills, myalgia, malaise etc.) and 'wet' (vomiting, diarrhoea, cough, petechiae, ecchymosis, oozing from venepuncture sites, and mucosal haemorrhages etc.). Wet symptoms and signs increase the risk of exposure to infectious body fluids and, therefore, the risk of transmission (*Velásquez et al. 2015*). A recent paper reviewed data from all known instances of EVD, associated with a known 1-day exposure, to characterize the disease development and risk of transmission on the basis of clinical signs and symptoms. Importantly, this review indicated the presence of distinct incubation and latent periods of disease, occuring a mean of 7 and 12 days post-exposure, respectively (*Velásquez et al. 2015*).

Figure 3 : Time line of Ebola virus disease (*adapted from Velásquez et al. 2015*)



Due to the high viral titres found in blood during viraemia, contact with blood of an actively infected patient represents a high-risk exposure for infection. In addition to blood, Ebola virus has been detected from a number of other clinical specimens from infected patients, including saliva, stool, semen, breast milk, tears, nasal blood, and skin swabs. However, there is limited ability to detect virus from environment samples of patient wards, suggesting a much higher risk of transmission from direct contact with bodily fluids than from contaminated surfaces (*Bausch et al., 2007*).

Consistent with the biological evidence that transmission is likely to be associated with contact with bodily fluids; studies from multiple outbreaks have provided similarly evidence. For instance, Dowell et al. (1999) evaluated risk factors for transmission in 27 households, in Kikwit, DRC, in 1995, which led to 28 secondary cases of EVD. In this investigation, all secondary cases had direct physical contact with a primary case and contact with bodily fluids conferred a high risk of transmission (RR=3.6; 1.9-6.8). Touching cadaver and exposure during the hospital phase were additionally noted as risk factors (*Dowell et al., 1999*). In a study by Francesconi et al., among 26 cases and 65 contacts in Gulu, Uganda, in 2001, contact with patient body fluid was the strongest risk factor for transmission (PRR=4.61; 1.73-12.29) (*Francesconi et al., 2003*).

Risk groups for transmission and infection with Ebolavirus and outcomes of disease

Based on epidemiologic data from multiple previous outbreaks, there are 3 risk groups that consistently have been at a high risk for acquiring EVD: household/close contacts of Ebola cases, healthcare workers, and individuals who attend funerals (*World Health Organization, 1978; Baron et*

al. 1983; Khan et al. 1999; Wamala et al., 2010; Borchert et al., 2011; Maganga et al., 2014). Importantly these risk groups are consistent with high risk of direct exposure to infected individuals or their bodily fluids.

Among household/close contacts, the primary risk factor identified for transmission of Ebola virus is direct contact with the infected patient. Osterholm et al. recently reviewed data involving household contact and Ebola virus transmission (*Osterholm et al., 2015*) and noted the strong association between direct physical contact and transmission, although they also noted that a small proportion of cases may be due to indirect or fomite spread (*Dowell et al., 1999; Baron et al., 1983; Francesconi P et al., 2003*).

Table 1: Summary data from Osterholm et al (*Osterholm et al., 2015*)

Study and contact status	Development of EVD		
	No. (%) who became ill	No. (%) who were not ill	Total
Dowell et al			
Direct contact	28 (100)	67 (46)	95
No direct contact	0 (0)	78 (54)	78
Total	28	145	173
Baron et al			
Direct contact	27 (93)	59 (57)	86
No direct contact	2* (7)	44 (43)	46
Total	29	103	132
Francesconi et al			
Direct contact	26 (96)	47 (80)	73
No direct contact	1** (4)	12 (20)	13
Total	27	59	86
Summation			
Direct contact	81 (96)	173 (56)	254
No direct contact	3 (4)	134 (44)	137
Total	84	307	391

* Contact status unknown

** The patient had probably fomite exposure, i.e. used a blanket that the primary case had used before death

The transmission of Ebola virus to healthcare workers has consistently been noted in numerous outbreaks, with healthcare workers sometimes accounting for a high proportion of the total number of cases in the outbreak. In general, nurses and physicians have had the highest incidence of disease among healthcare workers, however, transmission to other occupations, including laboratory workers and cleaners has been noted (*World Health Organization, 1978; Tomori O et al 1999; Muyembe-Tamfum et al, 1999; Centers for Disease Control 1995; Kerstiens et al. 1999; Borchert et al, 2011; Centers for Disease Control 2001; Wamala et al 2010; Bah et al, 2015; Kilmarx et al, 2014; Matanock et al, 2014*).

Across multiple outbreaks, the one consistent risk factor for fatal EVD is age, with the elderly tending to have higher risk of death. In contrast, gender typically has little impact in disease outcome. Higher viral loads have been reported among individuals with fatal outcomes, consistent with more severe infectious burden. While some studies have reported certain clinical signs and symptoms that are associated with fatal outcomes, there are no definitive high risk signs or symptoms and interpretation of data across multiple outbreaks, with varying degrees of clinical information

collected or coded, represents a significant challenge to interpretation of clinical data (*World Health Organization, 1978; Anonymous, 1978; Khan et al.; Ksiazek et al., 1999; Sadek et al., 1999; Rowe et al, 1999; Towner et al., 2004, ;MacNeil et al. 2010; Yan et al., 2015*) .

Potential for sexual transmission of Ebola virus

There are a number of lines of evidence that suggest potential for sexual transmission of Ebola virus from recovered individuals for a significant time period during convalescence. The potential for sexual transmission has been hypothesized for a number of years as a result of multiple studies identifying virus in semen of males, for months following recovery (*Rowe et al., 1999; Bausch et al., 2007*). A recent report has indicated the presumptive sexual transmission of Ebola virus, and re-introduction of the disease in Liberia, from a male patient who had recovered approximately 4 months prior to sexual contact with a partner who developed EVD (*Christie et al., 2015*). A presumptive explanation for the long-term presence of Ebola virus in semen is the persistence of virus within immune-privileged tissue sites within the body. Consistent with this hypothesis, recently, viable virus was detected in aqueous humor 9 weeks after clearance of viraemia from an EVD survivor with uveitis (*Varkey et al., 2015*).

Summary points

- Multiple species of Ebola virus are known to cause EVD, however, most currently advanced vaccine candidates contain only *Zaire ebolavirus* antigen
- Ebola virus infection results in a disseminated acute infection. Viraemia is highest at the severe stage of disease and the virus can be detected in numerous bodily fluids, indicating risk of infection is highest through direct contact with patients or their bodily fluids
- Common risk groups for infection in outbreaks include household/close contacts of cases, healthcare workers, and individuals attending funerals
- There is presumptive potential for sexual transmission of virus, from surviving patients, a number of months following recovery

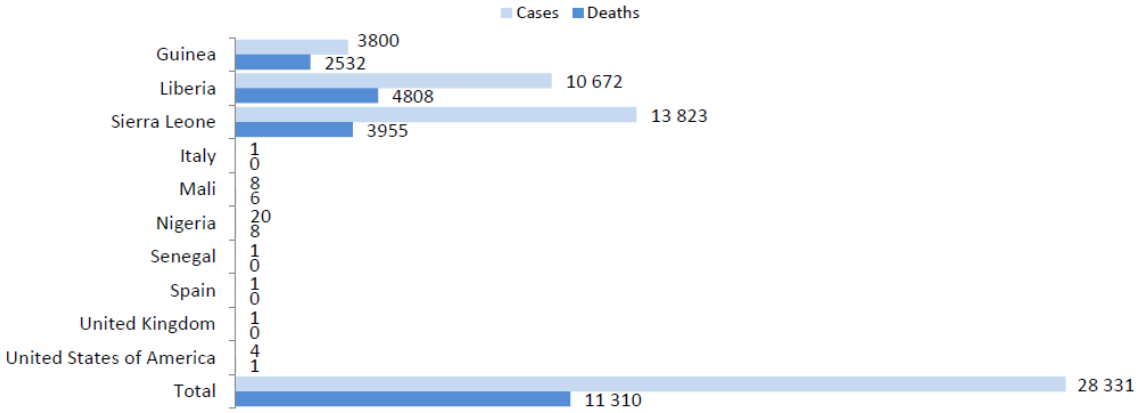
Epidemiology of the current epidemic of EVD in West Africa: analysis of reported data in the WHO viral haemorrhagic fever (VHF) database

Status of the current epidemic

(From the September 23 Ebola Situation Report. Latest situation report available at: http://apps.who.int/ebola/ebola-situation-reports)

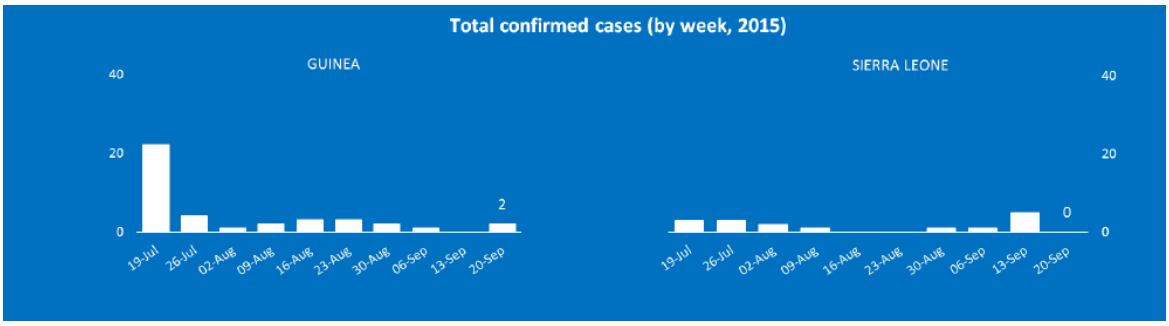
As of September 20, 2015, there were 28 331 cases of confirmed, probable and suspected cases of EVD related to the current outbreak in west Africa and 11 310 deaths (Figure 4).

Figure 4: Confirmed, probable and suspected EVD cases worldwide (data up to 20 September 2015)



There were 2 confirmed cases of EVD reported in the week of September 20, both of which were in Guinea. The number of cases has remained below 10 per week since the last week of July (Figure 5).

Figure 5: Total confirmed cases (by week), 2015



Over the same period of time, transmission of virus has been geographically confined to several small areas in western Guinea and Sierra Leone, marking a transition to a distinct third phase of the epidemic. Improvements to rapid and accurate case investigation and contact tracing, rapid isolation and treatment, and effective engagement with affected communities have all played a crucial role in reducing case incidence to its current low level. A refined phase 3 response[2] coordinated by the Interagency Collaboration on Ebola[3] will build on these existing measures to drive case incidence to zero and ensure a sustained end to Ebola virus transmission.

After recording 14 consecutive days with zero confirmed cases, two new confirmed cases were reported from Guinea during the week ending 20 September: a 10-year-old girl who died after moving from the Ratoma area of Conakry to Forecariah, and a 24-year-old woman who was identified as Ebola virus-positive in the Dixinn area of Conakry. Neither case was a registered contact, although both cases have a strong epidemiological link to a probable case thought to have died from EVD at the end of August. Investigations incorporating genetic sequencing of Ebola virus from both

[2] Ebola response phase 3: framework for achieving and sustaining a resilient zero: http://www.who.int/csr/resources/publications/ebola/ebola-response-phase3/en/
[3] Interagency Collaboration on Ebola: http://www.who.int/csr/resources/publications/ebola/ebola-response-phase3/en/

confirmed cases suggest they are part of the Ratoma chain of transmission—the only chain of transmission known to be currently active (past 21 days) in Guinea.

No new confirmed cases were reported from Sierra Leone in the week of 20 September. Over 700 contacts have been identified in association with the previous week's reported case from Bombali: a 16 year-old girl identified as EVD-positive after post-mortem testing. Investigations into the origin of her infection have not yet concluded, but preliminary findings suggest that a survivor may have been the source.

Robust surveillance measures are essential to ensure the rapid detection of any reintroduction or re-emergence of EVD in currently unaffected areas. Surveillance in the three countries will be enhanced in line with the phase-3 response framework.

Risk factors for Ebola Virus Disease in the general population

The analysis of data for the assessment of risk factors was limited to data from the current epidemic in Guinea, Liberia and Sierra Leone.

1. Risk of infection

The risk of infection in the general population was assessed by comparing the cumulative cases, attack rates and relative risk of EVD by age group and sex. The data are those presented to the WG as of August 12, 2015. While the number of cases has increased slightly since then, the general patterns and trends remain the same.

Table 2 shows the total numbers of cases reported to the VHF database, stratified by country, sex and age group as of 12 August, 2015.

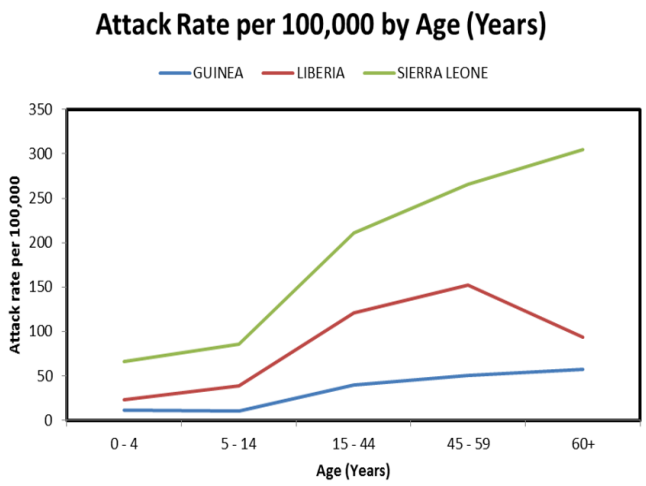
Table 2: Total Numbers of Cases by Age and Sex (12 August 2015)

	Number of cases				
	Cumulative				
	Confirmed				
	Male	Female	Both sexes		
Country	All ages (total)	All ages (total)	0-14	15-44	45+
Guinea	1589	1735	529	1894	857
Liberia	1911[i]	1838[i]	561[i]	2060[i]	703[i]
Sierra Leone	4792	5081	1978	5592	2129
All countries	8292[i]	8654[i]	3068[i]	9546[i]	3689[i]

The numbers of cases were similar in males and females in all three countries. The highest numbers of cases in each country, and in all three countries overall, was in the 15-44 year age group.

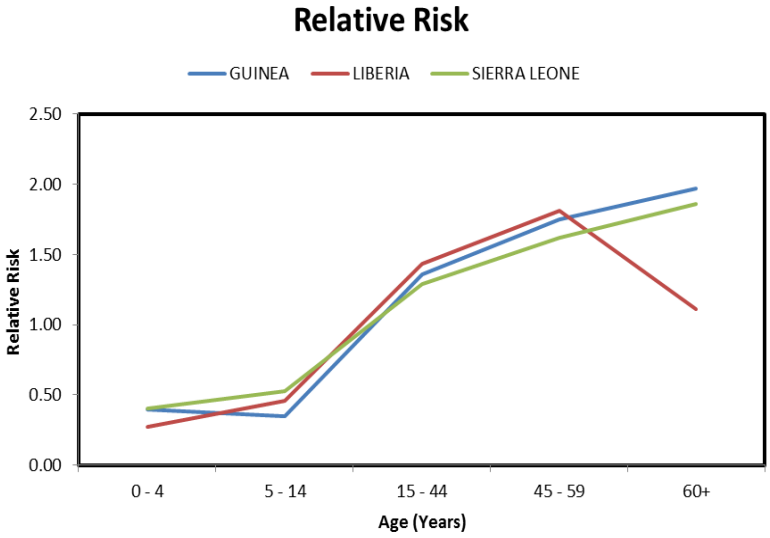
The attack rates and relative risk by age in each country are shown in Figures 6 and 7. Regardless of age, attack rate is highest in Sierra Leone followed by Liberia and Guinea. In general, the attack rates increase as age rises, the exception being a decrease in attack rates in those 60+ in Liberia, compared to those 45-59 of years.

Figure 6: Attack rates per 100,000 by age (years



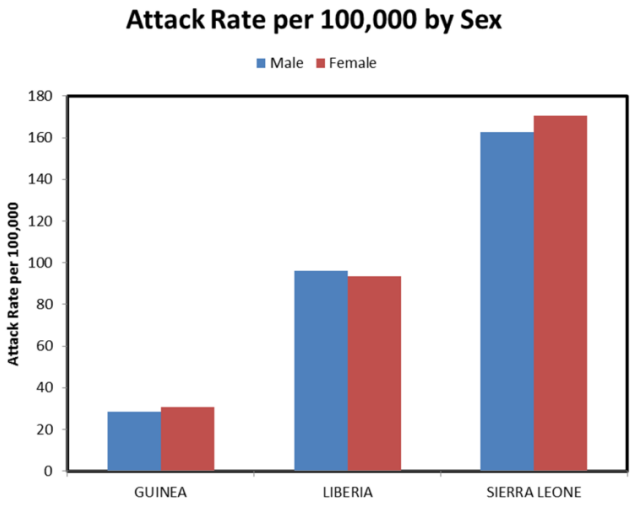
Source: VHF database; United Nations, Department of Economic and Social Affairs, Population Division (2013). World Population Prospects: The 2012 Revision.

Figure 7: Relative risk of disease by age



Source: VHF database; United Nations, Department of Economic and Social Affairs, Population Division (2013). World Population Prospects: The 2012 Revision.

Figure 8: Attack rates per 100,000 by sex



The calculations of the relative risks are based on the incidence of disease in the particular age group in reference to the overall incidence rate in the entire population in each of the three countries during the current epidemic, till the time of analysis.

Figure 8 shows the attack rates by sex in each of the three most affected countries. As stated earlier, the attack rate is highest in Sierra Leone, followed by Liberia and Guinea. However, there is no significant difference in attack rate between sexes in all the three countries.

2. Risk of death

Case Fatality Ratio (CFR) stratified by age and sex was used to evaluate the risk of death in the general population.

Figure 9: Case fatality ratio by age

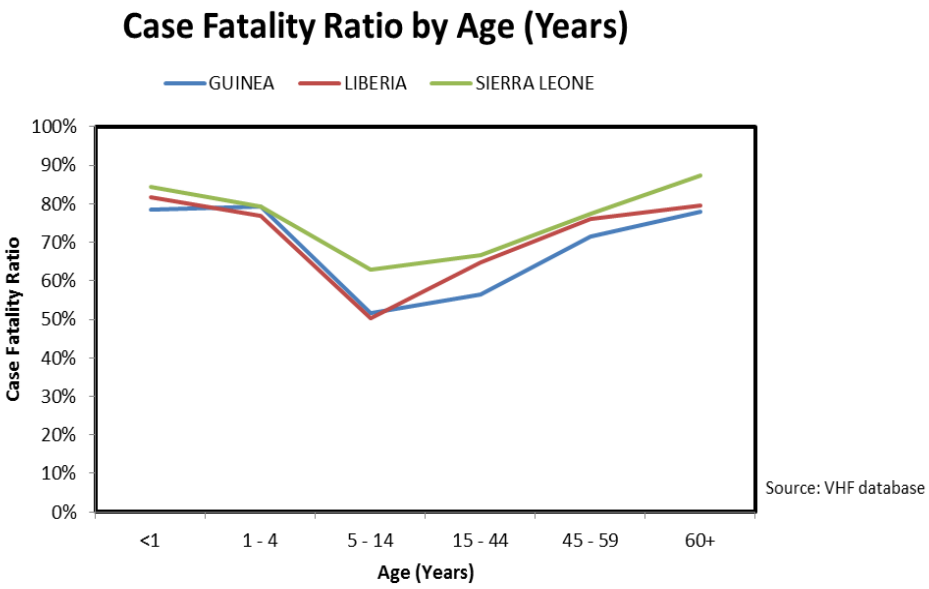
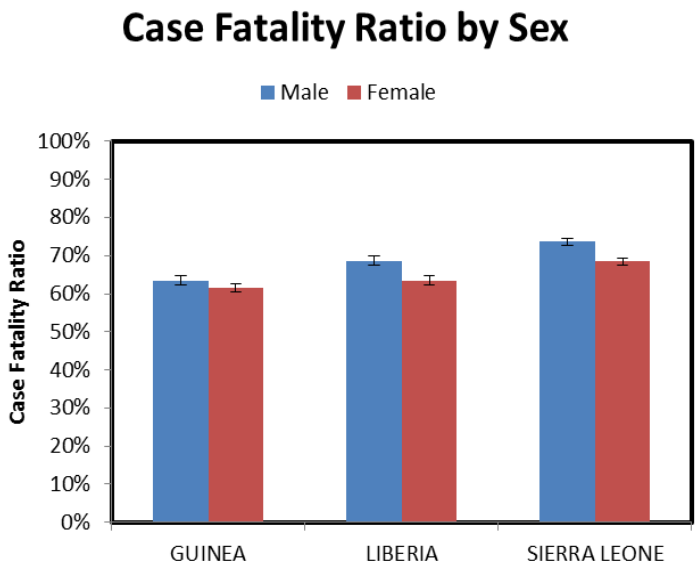


Figure 10: Case fatality ratio by sex



Figures 9 and 10 show the CFR by age and by sex, respectively. The curve lines for CFR by age in each of the countries were U-shaped, with highest CFR at the extremes of age and lower CFR in the 5 to 14 and 15- 44 year age groups.

The CFR was similar between males and females in all three countries.

Exposure patterns driving Ebola virus transmission in west Africa

Abstract from unpublished manuscript reviewed by the WG titled "Exposure patterns driving Ebola transmission in West Africa" from the WHO Ebola Response Team (corresponding authors: Christopher Dye (WHO, Geneva), Neil Ferguson, and Christophe Fraser (both Imperial College, UK))

To understand the drivers of the Ebola epidemic in west Africa, we investigated a unique dataset of nearly 10,000 exposures to potential source cases reported by more than 19,000 Ebola cases. We find transmission is highly variable, with evidence of super-spreading. Exposures have been concentrated within households and families, with exposure around death and at funerals playing a key role. Ebola Treatment Units provided more effective infection control than other health care facilities, and protection of health care workers improved over the course of the epidemic. We find that prompt hospitalization and reduced exposure from funerals predicts district-level epidemic intensity, suggesting that these measures contributed to epidemic control. Our findings contribute to the evidence-base for the control of Ebola.

Risk of disease and death in special populations

Most of the available data on risk of EVD are from health care and other front line workers. There are limited data on the risk of death and fetal and neonatal outcomes in pregnant women that indicate very high CFR among pregnant women and almost universal fetal loss or early neonatal death. A more detailed analysis of the available data from the current outbreak is being conducted by MSF, but was not available at the time of the WG review.

Health workers infections in Guinea, Liberia and Sierra Leone

Based on excerpts from "A preliminary report: Health worker Ebola infections in Guinea, Liberia and Sierra Leone" and additional analyses as requested.

See full "Preliminary report": **http://www.who.int/csr/resources/publications/ebola/health-worker-infections/en/**

Methods

- The Viral Haemorrhagic Fever (VHF) database, which was made available for these analyses by WHO headquarters, is comprised of the national VHF databases from Guinea, Liberia, and Sierra Leone. Ongoing efforts are underway to update and triangulate case information about cases from multiple sources. For these reasons, the number of health workers in this report is preliminary and may differ from the MOH Situation Reports
- The analyses in this study only include confirmed and probable EVD cases (suspected cases were excluded).
- Cumulative incidence was calculated using confirmed and probable cases from the beginning of the outbreak to March 31, 2015. The denominator data used to calculate the cumulative incidence rate is based on the most recent health workforce data obtained from the three

countries (Guinea: 2014[4], Sierra Leone: 2014[5], Liberia: 2015[6]). Workforce data from Liberia and Guinea were disaggregated by sex and age. Population figures for the cumulative incidence amongst the non-health worker population ≥ 15 years of age are based on estimates from the United Nations Department of Economic and Social Affairs, Population Division[7].

- Since the Human Resource databases of the countries are in the process of being updated, cumulative incidence rates were calculated only for selected registered professions where data were more complete.
- At the request of SAGE, analyses on additional types of health workers were performed with all associated limitations as described below.

Limitations

- First, under-reporting of health worker cases and conversely case duplications have been observed through special health workers studies. Therefore, it should be noted that these are preliminary data since the VHF databases of Liberia and Sierra Leone are currently being revised and updated. For this reason, our data might differ from those available in the countries. In addition, some health worker categories, particularly non-clinical health staff, such as hospital cleaners, ambulance drivers, burial team members, might not have been recorded as health workers. Finally, there is a significant number of suspected health worker infections for whom the final infection status remains unknown.
- Second, data were incomplete for some important variables for our analysis, such as health worker position.
- Third, the risk calculation is based on health workforce denominators which had its own limitations. Cumulative incidence rates were determined for selected health worker types where denominator data were likely to be most complete. Health worker denominators did not include the private sector and efforts are underway to improve the completeness and reliability of the Human Resource Information Systems. Future risk calculations will be able to utilize updated health worker denominator information for an expanded number of health worker types.

Results:

Health worker infection risk (**directly from Report**)

- The cumulative incidence was analyzed for "selected" health professions (medical doctors, registered nurses and laboratory technicians) for which the Human Resource databases may be more accurate and complete in the 3 countries. Depending on the health profession studied, the risk was between 21 to 32 times higher in health workers compared with non-health workers ≥ 15 years of age. While the risk of infection among those selected health workers is very high, it is however, much lower than the risk previously reported (Table 3).

[4] Guinea: Recensement biométrique des personnels de santé du Ministère de la Santé, République de Guinée, December 2014
[5] Sierra Leone: MOHS Human Resources for Health database, November 2014 (public sector only)
[6] Liberia: MOH Personnel Unit and MOH Office of Financial Management, February 2015 (public sector only)
[7] United Nations Department of Economic and Social Affairs, Population Division

Table 3: Cumulative EVD incidence rate for selected health worker types for the 3 countries combined, 1 Jan 2014 to 31 March 2015

	Cumulative incidence rate per 1000 (95% CI)	Rate ratio (95% CI)	p-value
Non-health workers ≥ 15 years	1.4 (1.4-1.4)	Reference	
Medical doctors	29.5 (22.6-36.4)	21.4 (17.0-27.1)	<0.01
Registered nurses	43.7 (37.5-49.9)	31.7 (27.5-36.6)	<0.01
Laboratory technicians	40.4 (26.2-54.6)	29.3 (20.7-41.7)	<0.01

Sources of health worker denominator data:

- *Guinea: Recensement biométrique des personnels de santé du Ministère de la Santé, République de Guinée, 2014*
- *Sierra Leone: MOH Human Resources for Health database, November 2014 (public sector only)*
- *Liberia: MOH Personnel Unit and MOH Office of Financial Management, February 2015 (public sector only)*
- *General population over 15 years of age are based on estimates from the Population Division, United Nations Department of Economic and Social Affairs.*

Additional analyses for SAGE-including all broad health worker categories:

Table 4: Cumulative EVD incidence rate and risk ratio by health worker categories for the 3 countries combined, 1 Jan 2014 to 31 March 2015

Health worker categories	Numerators	Denominators	Cumulative incidence rate per 1000	Risk Ratio (reference used: adult non-health workers)
Medical workers	**83**	**2854**	**29**	**21**
Registered nurses[1]	**183**	**4187**	**44**	**31**
Other nursing workers (include nurse assistants, aides and ATS but exclude MCHA[#])[1]	**163**	**9752**	**17**	**12**
Lab workers (includes lab techn and assistants)	**48**	**989**	**49**	**35**
Midwifery workers (registered midwife, midwife assistant, TBA**)+ MCHA (**maternal and child health aides)[#]	**50**	**3988**	**13**	**9**
Community health workers	**24**	**NA**	**NA**	**NA**
Pharmacy workers	**21**	**1335**		
Ambulance workers	**22**	**NA**	**NA**	**NA**
Trade and elementary workers (maintenance, cleaners, laundry, etc.)	**47**	**4110**	**11**	**8**
All others (surveillance, hygienists, counsellors, X-Ray, etc.**)** [2, 3]	**68**[3]	**1571**[3]	**43**	**31**
Health service management and admin	**9**	**3618**	**2.5**	**1.8**
Unknown positions	**97**	**NA**	**NA**	**NA**
All health workers (includes unknown positions)–upper level estimate	**815**	**32404**	**25**	**18**
All health workers excluding unknown positions-lower level estimate	**718**	**32404**	**22**	**16**
NON-HEALTH workers 15 years and older	**16231**	**11786439**	**1.4**	**reference**

1. Nursing workers were split in 2 categories since registered nurses had higher risk than other nursing workers which include nurse assistants, aides and ATS-agents techniques de santé (Guinea)
2. Include 1 burial team, 1 burial team/sprayer and 2 sprayers
3. Includes all other types of health workers for which the number of health care workers affected was less than 20 (except for Health service management and Admin used here to illustrate lowest risk among health workers). Includes also all types of health workers which could not be attributed to the other better defined categories because of limited info- therefore some of them may have been misclassified. Finally, denominator may not be accurate, hence, overestimating the risk.

Note: This differs from data reported in "A preliminary report" since MCHA were included under Nursing workers in the Report and are here included in Midwifery workers. In fact, their work is a blend of primary health and midwifery care (could likely be included in either one).

Based on the available data, with its limitations, three categories of risk were proposed to the WG, as shown in Table 5.

Table 5: Health worker categories by proposed level of risk among health workers

Higher risk level (direct contact with EVD patients or with infectious specimens)	Medium risk level (more limited or indirect contact with EVD patients)	Lower risk level among health workers (in principle, no contact with EVD patients)
Medical workers	All other health workers (excluding Health service management and admin)	Health service management and admin
Nursing workers (particularly registered nurses)		
Laboratory workers		

Note: unfortunately, the risk for burial workers, contact tracers, and community health workers could not be determined:

- first of all, because we do not have denominator data for these categories of health workers
- second, because there may have been under-reporting of, at least, burial workers and contact tracers as "health workers" since those positions were created in the context of the Ebola epidemic and may not have been considered and recorded as health workers.

Social Risk Factors for Ebola virus Transmission

The following draws together qualitative reports of the Ebola outbreak, and outlines some of the socio-cultural dimensions of Ebola virus transmission that should be taken account in prioritizing immunization efforts.

In general, anthropologists stress that behaviours in a situation of crisis are **highly dynamic** and many observations from the 2014-15 outbreak will be **context and time-specifi**c. There are, however, some general insights that are potentially relevant for prioritizing target groups for vaccination; or at the very least, in considering how best to approach deployment for future epidemics.

General Notes on population characteristics relevant for EVD risk

Ethnicity

- The affective region is home to a number of highly diverse cultural groups (e.g. Mende, Kissi, Kono, Krio, Temne, Fula, Mandingo/Malinké, and Toma/Loma) but share important commonalities of history and culture, and longstanding traditions of movement and mixing across national borders.

- The region has many religions, Christian, Muslim and 'traditional' beliefs, elements of which are often integrated into health and ritual practices. Depending on the locality, different community members will play a significant role in the care of the sick and preparation of the dead.

Social Geography

- National borders and identities will typically be of less relevance than local variations in practices—particularly true in rural areas, where many villages are highly self-reliant and there is a noticeable distrust of persons born outside the local community.
- Rural and 'interior' areas should not be considered to be separate or remote from urban areas, as people move frequently from village to town (and across national borders) for a wide array of social and economic reasons, including the search for health care.
- In crisis situations, people tend to return to family villages and avoid major conurbations.

Economy

- A long history of violence and resources extraction has entrenched population vulnerability and government distrust, exacerbated in rapidly expanding peri-urban settlements and isolated rural areas.

Gender

- Many people in the region belong to gender-specific initiation—or 'secret'—societies, which are central to the politics in the region and whose power has been reinforced by recent wars. These groups tend to be involved in funerary practices.
- Peripheral Health Units (PHUs) that offer primary care at the community level are often perceived as gendered facilities providing primarily maternal and child health care— a reflection of the substantial donor, government and NGO funds which have been channeled towards maternal and child health targets (most visible in the Free Health Care Initiative which offers free health care to pregnant women, nursing mothers and children under five).
- Since the outbreak, increasing gender-based violence has been reported and failure to observe safe-sex practices following recovery. Reports have focused on women; however, it is clear that men who have sex with men (MSM) are also at risk.

Key Points

1. Ethnic/religious differences are unlikely to map directly onto EVD risk.
2. Economic indicators are more relevant factors for EVD risk than cultural differences. Areas where there is limited access to basic infrastructure should be prioritized.
3. Engaging 'secret societies' can provide a critical foundation for community acceptance of a vaccine, it is equally important to approach these collectives with an appropriate local introduction to avoid suspicion and backlash.
4. The movement of populations across rural/urban areas and borders advises against prioritization of any one specific area and/or community over another.
5. As transmission rates drop, the likelihood of unpredictable flare-ups suggests that some special consideration should be given to local health providers in areas where services are scarce.

High Risk Socio-Cultural Domains

Reservoir Contact

- Bush meat consumption and trade are generally believed to precipitate EVD spill-over. A great deal of national and international policy attention and intervention has focused on bush meat sensitization and bans to varying success.
- Hunting of animals, which has continued fairly unabated in rural areas despite the ban, is generally carried out with dogs and machetes or traps designed and set by children. These varied practices, often occurring near the home rather than the 'bush', have raised some critical questions about other species as possible EVD vectors and other points and routes of spill-over.

Therapeutic Care

- In protecting 'Health Workers', attention should be given to the cohort of informal care-givers—traditional birth attendants, spiritual and private healers—who are usually the first to have contact with suspected cases.
- Where public services are weak and/or inaccessible, people tend to place trust in unofficial health providers for both everyday health needs and emergency care. These preferences often reflect a pragmatic response to a history of poor quality care rather than a deep-seated distrust of biomedicine.
- Belief in spiritual causes does not correlate to levels of education. People with secondary and tertiary education make sense of unfortunate events and circumstances in terms of spiritual causes.
- In times of panic, populations often tend to rely on more familiar styles of healthcare, traveling long distances to visit a traditional health practitioner with a good reputation.

Burials:

- Burials have been identified as key occasions for disease spread and amplification.
- Mortuary practices are generally orchestrated to enable the dead person to accede to the 'village of the ancestors,' where they might be reunited with their already-dead relatives and friends. A proper burial, performed in the deceased community of origin, is a key aspect of west African social life.
- There are several aspects of mortuary practices that may involving touching the bodies – e.g. the corpses is usually washed, oiled (often twice), wrapped in a fie cloth and re-clothed for burial.
- In general, men will prepare men and women, women. Corpse preparation and burial of leading members of the Secret Societies are matters for those societies and the procedures are secret.

Stigma/Marginalization

- Survivors face a number of challenges, from physical complications from the disease to social ostracisation and financial ruin. They face uncertainties about their risk of transmitting to others and also about potentially contracting the disease again.
- The risk of sexual transmission is a central concern for sex workers, both female and male.
- Drug users will also be at risk.

Key points

a. Children, who engage with animals in the context of play, may be the first points of contact but are often neglected in these campaigns.
b. Traditional or private healers, herbalists and birth attendants are often among the first to whom many infected with Ebola virus will turn. Health worker or frontline worker category must be expanded to include the diverse range of informal care providers
c. Burial practices are not standardized, have changed in response to the outbreak, and therefore, need to be discussed on a locality-by-locality basis. However, while practices differ, corpse preparation is often carried out by elders.
d. Pregnant women are at high risk and should be considered, also for program acceptability. If they must be excluded for safety reasons, alternatives and outreach programs should be devised.
e. Community members should be approached to ensure program acceptance.

Annex 1. Health worker categorization

Health workers categories	ISCO codes*	Examples of health worker positions entered in VHF database (English and French) – may include positions not usually included in the ISCO categories.
Medical workers	2211, 2212,	Doctor, MD, physician assistant, medical student, médecin, stagiaire en médicine
Nursing workers	2221, 3221	Nurse, nurse aide, nurse assistant, Maternal and Child Health (MCH) Aide, vaccinator, infirmier, Assistant Technique en santé (ATS, equivalent to nurse aide)
Midwifery workers	2222, 3222	Midwife, traditional birth attendant (TBA) , matronne, sage-femme
Ambulance Workers	3258	Ambulance worker, ambulancier, brancardier Note> ambulance drivers were included in this category but not the other drivers.
Laboratory workers	2312, 3141	Laboratory technician, laboratory aide
Pharmacy workers	2262, 3213	Pharmacist, dispenser, pharmacy technician, pharmacien,
Community Health care workers	3253	Community health worker, community health volunteer, community health assistant, CHO-community health officer, agent communautaire
Social work and counselling	2635	Social worker, mental health, HIV counsellor
Radiology workers	3211	Radiologist, X-ray technician, radiologie
Hygiene workers	No code	Burial team, sprayer, hygienist, hygiéniste, morgue
Trade and Elementary workers	No code	Maintenance, cleaner, janitor, housekeeper, laundry, driver, garcon de salle, agent d'entretien
Surveillance workers	No code	Surveillance officer, public health worker, contact tracer,
Health service management and administration	1342	Manager, hospital matron, Public health officer(PHO) Administrative, accountant, registrar, data clerk
Other	----	Security, volunteer, gardien, volontaire, etc.

*Codes from on the International Standard Classification of Occupations (ISCO, 2008 revision) used for broad categorization purpose only.

Annex 2: Background references for section on epidemiology (published literature)

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Ebola Vaccines and Vaccination

Report of the SAGE Working Group on Ebola Vaccines and Vaccination with provisional recommendations for vaccination

September 30, 2015

SECTION B: VACCINES AND VACCINATION

Introduction

On 8 August 2014, the World Health Organization declared a public health emergency of international concern related to the ebola virus disease outbreak originating in Guinea and causing ongoing transmission in Sierra Leone and Liberia[1]. For Ebola vaccine development what followed was a chain of events leading to accelerated timelines for vaccine development.

During the several years before the crisis, scientists and, governments had generated promising preclinical data on several Ebola vaccine candidates.

However development stalled in part because public sector investment mechanisms were not in place to support pre-emptive clinical evaluation of these candidates, and there was a perception that regulatory pathways were limited for Ebola vaccines.

Efforts need to be coordinated amongst scientists, international organizations, national governments, industry and major non-governmental organizations.

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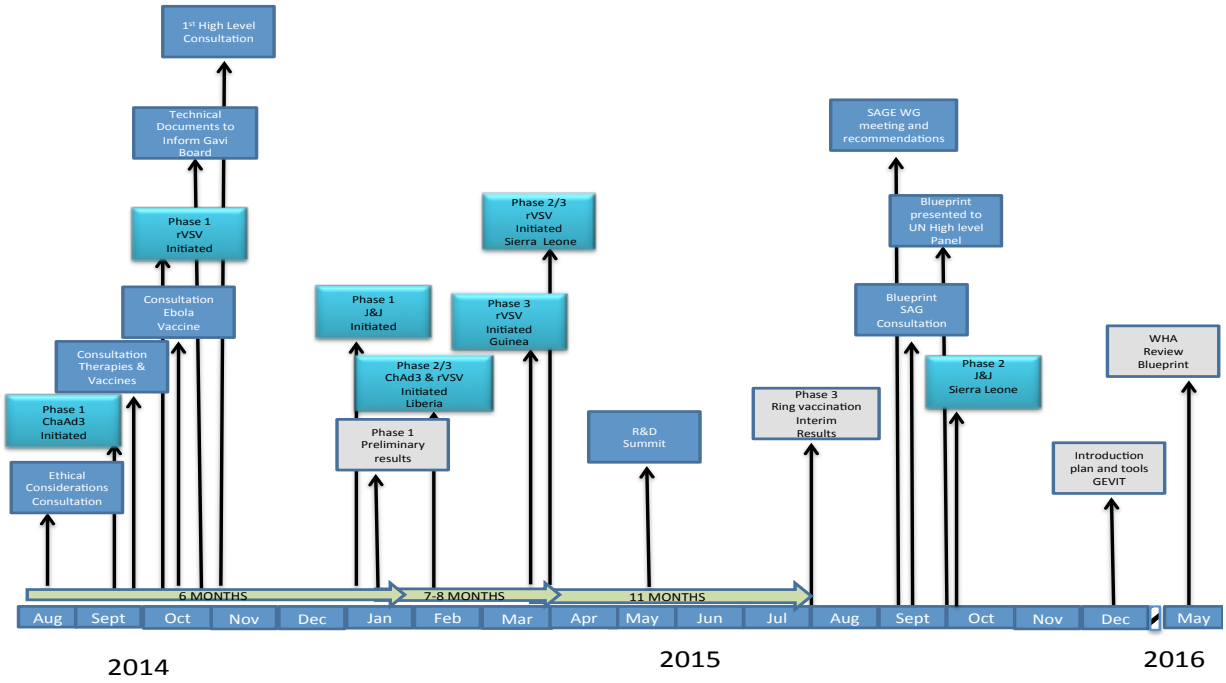
Figure 1. Overview of selected milestones



[1] http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/

A. OVERVIEW OF MAJOR ACTIVITIES

The Ebola R&D effort has mobilised people, institutions and resources globally in ways never seen before. This is one positive outcome in an otherwise terrible human calamity. New tools have been developed with unprecedented speed, though the window of opportunity for testing some is closing.

This is a contribution to scientific knowledge, but it is also a contribution to better preparedness. Thanks to the work of the entire scientific community, the world will be far better equipped to respond when the next Ebola outbreak inevitably occurs. What we see emerging, over a very short time, is a new model for the accelerated development, testing, and approval of new medical products during emergencies caused by any emerging or re-emerging infectious disease.

The collaborative efforts prove that the traditional R&D model can be adapted, timeframes can be compressed, and partnerships that are otherwise unlikely can be formed.

The task now is to harness the lessons from Ebola to create a new R&D framework that can be used for any epidemic-prone disease, in any infectious disease emergency. In this sense, the R&D response to Ebola marks an historical, ground-breaking event. Public research institutes, private funders, civil society, countries, and industry have collaborated, in unprecedented ways, to defend the world against a deadly and deeply dreaded disease.

This document provides an overview of some major activities and achievements recognizing that many more efforts took place and should also be catalogued and documented in the future.

1. Construction of ad-hoc international forums for global coordination and scientific deliberations

When the emergency was declared WHO consulted widely, and immediately and fostered interactions with the international scientific, ethics, regulatory and funders' communities on key activities to undertake on an emergency basis. The consensus was that even in the emergency setting, clinical trial data would be required on novel vaccine candidates to determine how best they could complement the public health response.

Notably, WHO convened meetings from August 2014 of high-level government representatives and these were from development partners as well as from Ebola-affected countries. In addition, there were scientists, vaccine manufacturers, regulatory authorities, international organizations, funding agencies and civil society.

The purpose was to discuss and agree on how to fast-track the testing and the deployment of promising vaccines in sufficient numbers to use in the field in 2015 to try and impact the Ebola epidemic curve. Three important consensus commitments came from this meeting.

First, that phase 1 clinical trials of the two most advanced vaccines had started. Without waiting for the results of the phase 1 all was to be put in place, by all partners, to start efficacy trials in affected countries as early as December 2014.

Second, the pharmaceutical companies developing vaccines committed to ramping up the production capacity to millions of doses in 2015, with hundreds of thousands ready in the first half of 2015.

Third, community engagement would be key and work should be scaled up urgently in partnership between local communities, national governments, and other stakeholders to have this happen.

All parties called upon WHO to coordinate efforts and ensure effective communication between the various actors.

Table 1. Overview of selected consultations to coordinate vaccine R&D

Meeting title	Internet link
Ethical considerations for use of unregistered interventions for Ebola virus disease, 15 August 2014	http://who.int/entity/csr/resources/publications/ebola/ethical-considerations/en/index.html
WHO Consultation on potential Ebola therapies and vaccines, 4–5 September 2014	http://www.who.int/entity/csr/resources/publications/ebola/ebola-therapies/en/index.html
WHO Consultation on Ebola vaccines 29-30 September 2014	http://www.who.int/entity/immunization/diseases/ebola/WHO_consultation_ebola_sep2014/en/index.html
First WHO High-level meeting on Ebola vaccines access and financing, 23 Oct 2014	http://www.who.int/mediacentre/news/ebola/23-october-2014/en/ http://apps.who.int/iris/bitstream/10665/137184/1/WHO_EVD_Meet_EMP_14.2_eng.pdf?ua=1
Development of technical document on Ebola vaccines to inform Gavi Alliance Board decision to commit to purchasing Ebola vaccine for affected countries, Oct 2014	http://www.gavi.org/Library/News/Press-releases/2014/Gavi-commits-to-purchasing-Ebola-vaccine-for-affected-countries/
WHO Meeting of the Scientific and Technical Advisory Committee on Ebola Experimental Interventions, 13 Nov 2014	http://www.who.int/medicines/ebola-treatment/scientific_tech_meeting/en/
First meeting of WHO Ebola Science Committee, 13-14 Nov 2014	http://www.who.int/medicines/ebola-treatment/meetings/ebola_science_committee/en/
WHO Technical Consultation: Heterologous Prime-Boost Immunization in Ebola vaccine development and testing, licensure and use, 21 Nov 2014	http://www.who.int/immunization/research/meetings_workshops/ebola_primeboost_21nov14/en/
The VSV Ebola Consortium (VEBCON)	http://www.ncbi.nlm.nih.gov/pubmed/25289888?dopt=Abstract
Second WHO High-level meeting on Ebola vaccines access and financing, January 8, 2015	http://apps.who.int/iris/bitstream/10665/149045/1/WHO_EVD_Meet_HIS_15.1_eng.pdf
WHO Ebola Science Committee, 3-4 March 2015	http://www.who.int/medicines/ebola-treatment/meetings/science-committee-march/en/
WHO Ebola R&D summit , 11-12 May 2015	http://www.who.int/entity/medicines/ebola-treatment/meetings/Executive-summary-WHO-Ebola-RandD-summit.pdf?ua=1
Developing Global Norms for Sharing Data and Results during Public Health Emergencies , 1-2 September 2015	http://www.who.int/entity/medicines/ebola-treatment/data-sharing_phe/en/index.html
Draft framework for formulating recommendations for the deployment of Ebola vaccines. SAGE Working Group on Ebola Vaccines and Vaccination	http://www.who.int/entity/immunization/sage/meetings/2015/april/Ebola_vaccine_Draft_framework_final.pdf

2. Laying out the regulatory support to guide clinical trials oversight in the context of this emergency

A series of consultations on regulatory approaches for expediting development and availability of Ebola vaccines were held. Overall the regulatory experts debated around the following objectives:

- to review the critical regulatory paths for the lead candidate Ebola vaccines and identify the main regulatory challenges;
- to clarify the timelines for availability of these vaccines for both clinical trials and potential future large-scale deployment;
- to discuss and map out possible avenues to address the regulatory challenges while keeping safety as a main concern.

Table 2. Overview of selected consultations to discuss regulatory pathways and oversight of planned Ebola vaccines trials

Meeting title	Internet link
First teleconference on regulatory approaches for expediting development and availability of Ebola vaccines 30 October 2014	http://www.who.int/medicines/ebola-treatment/meetings/2014-1030_1stT_RegEbola_vaccines_summary.pdf?ua=1
African Vaccine Regulatory Forum (AVAREF), 3-7 November 2014	http://www.who.int/immunization_standards/vaccine_regulation/africa_network/en/
Report of the joint review facilitated by WHO for the GSK ChAd3 Ebola Vaccine clinical trials application, 17 December, 2014	http://www.who.int/immunization_standards/vaccine_regulation/2014-1217_BriefingAfricanNRA_EC.pdf?ua=1
Second teleconference on regulatory approaches for expediting development and availability of Ebola vaccines, 27 January 2015	http://www.who.int/entity/medicines/ebola-treatment/meetings/2015-0127_2ndTC_RegEbola.pdf?ua=1
WHO hosts joint review of Phase II clinical trial application for GSK Ebola vaccine, 15-16 December 2014	http://www.who.int/entity/medicines/ebola-treatment/meetings/phaseII_clinical_trial_meeting/en/index.html
Phase II clinical trial application for ChAd3 Ebola vaccine reviewed by national regulators, 18 December 2014	http://www.who.int/entity/medicines/ebola-treatment/meetings/phaseII_clinical_trial_meeting_outcomes/en/index.html
WHO Informal Consultation on regulatory considerations for evaluation of Ebola Vaccines intended for emergency use, WHO/HQ Geneva, Switzerland , 18-19 March 2015	http://www.who.int/immunization/GIN_March_2015.pdf
The AVAREF joint review process of Ebola clinical trial applications. WHO, Jan 8, 2015	http://www.who.int/mediacentre/events/2015/S3.3_Stahl_AVAREF_joint_review_process.pdf

Regulatory support was provided through AVAREF meetings, whereby regulators from high-income authorities, attended consultations in support of African regulators (North-South collaboration). In addition AVAREF enabled African authorities with experience of pre-licensure vaccine trials to support those in the most affected countries with less experience of clinical trials (South-South collaboration).

3. Promoting scientific debate on trial designs and enabling parallel Phase 1,2 and 3 clinical trials of Ebola vaccines

On 8 August and subsequent days, WHO rapidly assembled consortia linking regulatory authorities, ethics committees, health research funders, the two prioritized manufacturers (GSK, and Newlink later Merck) and clinical and laboratory investigators together with appropriate independent oversight mechanisms including DSMB and GCP monitoring (Figure 1).

Information sharing throughout all of the above required activities was facilitated by regular convenings, and conference calls, including some hosted by WHO DG Margaret Chan. WHO played a critical role in sharing information between all stakeholders in the accelerated vaccine R&D effort.

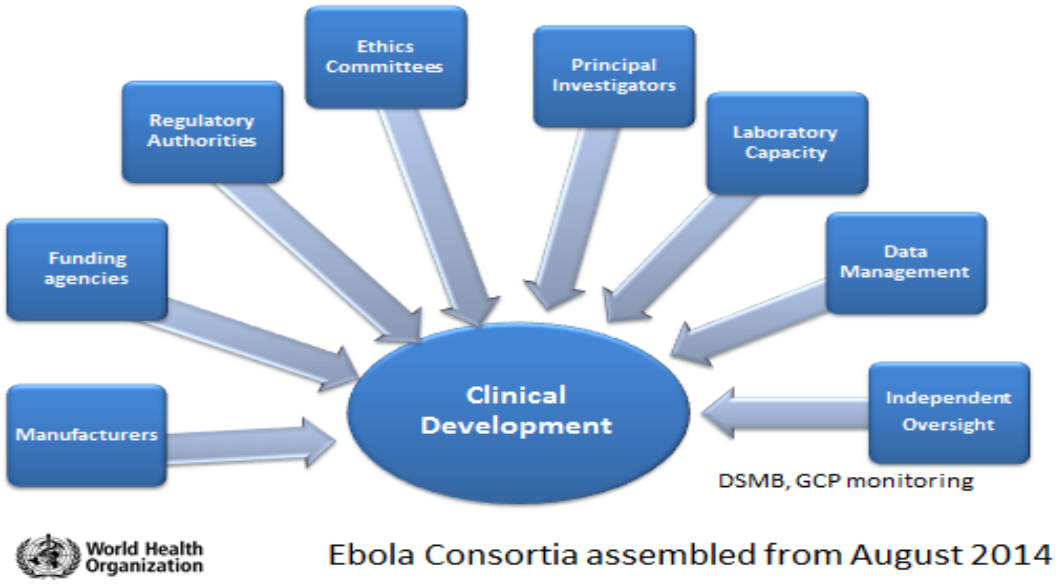


Figure 2: Key elements of the consortia assembled from August 2014

WHO used a set of criteria to objectively assess which vaccine candidates would be proactively fast-tracked for clinical evaluation. The criteria included availability of Good Manufacturing Practice grade vials after lot release for clinical trials, and that 100% efficacy had been documented in non-human primates with acceptable pre-clinical safety.

Both GSK (ChAd3) and Newlink (rVSV) were the two commercial entities with candidate vaccines that met those criteria as of August 2014. J&J (Ad26/MVA) and Novavax (recombinant protein) met the criteria later in the epidemic.

In addition, WHO hosted a series of scientific meetings to discuss trial design options, locations of the studies and timetables towards the initiation and completion of the trials.

Table 3. Overview of selected consultations hosted by WHO to discuss clinical trial design and progress with the conduct of the Ebola vaccines trials

Meeting title	Internet link
WHO consultation on potential Ebola therapies and vaccines, September 2014	http://apps.who.int/iris/bitstream/10665/136103/1/WHO_EVD_Meet_EMP_14.1_eng.pdf
WHO consultation on Ebola Vaccines September 29-30, 2014	http://www.who.int/immunization/diseases/ebola/WHO_consultation_ebola_sep2014/en/
First teleconference on vaccine clinical trial designs in Guinea, Liberia, and Sierra Leone 28 October 2014	http://www.who.int/medicines/ebola-treatment/2014-1028_Minutes-1stTC_on_vaccine_clinical_trials.pdf
Second teleconference on vaccine clinical trials design for Guinea, Liberia, and Sierra Leone , 25 November 2014	http://www.who.int/medicines/ebola-treatment/2014-1125_Minutes-2ndTC_on_vaccine_clinical_trials.pdf?ua=1
Third teleconference on vaccine clinical trials design for Guinea, Liberia, and Sierra Leone. 18 December 2014	http://www.who.int/medicines/ebola-treatment/3rd-teleconference-vaccines.pdf
The rVSV vaccine was selected for the Guinea trial according to a framework developed by the WHO Scientific and Technical Advisory Committee on Ebola Experimental interventions (STAC-EE).	http://www.who.int/medicines/ebola/treatment/guinea_ebola_trial/en/
Fourth teleconference on Ebola vaccine clinical trials in Guinea, Liberia, and Sierra Leone., 30 March 2015	http://www.who.int/medicines/ebola-treatment/4th_teleconference_vaccine_clinical_trials.pdf?ua=1
Fifth Teleconference on Vaccine Clinical Trials Design in Guinea, Liberia and Sierra Leone. 21 July 2015	http://www.who.int/medicines/ebola-treatment/meetings/fifth_tel-conf_clinictrials/en/
Report on the 2nd WHO Consultation on Biobanking: Focus on West Africa, 6-7 August 2015	http://www.who.int/entity/medicines/ebola-treatment/meetings/2nd_who_biobaking-consultation/en/index.html
Developing Global Norms for Sharing Data and Results during Public Health Emergencies 1-2 September 2015	http://www.who.int/entity/medicines/ebola-treatment/data-sharing_phe/en/index.html

The following set of activities were deemed important and were initiated by the international community:

- Use of Parallel Phase 1-2 trials had to be launched in sites with optimal first-in-human clinical management facilities, followed as quickly as possible by Phase 1-2 in Africa. These trials were to be conducted on highly expedited timelines. The trials were to be larger than usual Phase 1 trials, to allow for simultaneous safety, immunogenicity and dose finding evaluations.
- Given the lack of a standardised assay, centralised laboratory facilities were chosen to allow for head-to-head comparability evaluations between all clinical trial sites, and different vaccines.
- Data management by investigator-initiated trials were to be promoted, with data transfer to the entities responsible for licensure submission. Independent oversight including Data Safety Monitoring Boards (DSMB) and Good Clinical Practice (GCP)

monitoring needed to be established. All regulatory and ethics oversight steps would need to occur to the same high standards but in greatly compressed timelines

- The trial protocols were adapted to take into consideration safety and immunogenicity results of the phase 1 trial as they became available and the evolution of the epidemic.

4. Preparing for the deployment of vaccines

To rapidly implement campaigns in the affected countries once vaccine becomes available, public health officials needed to be planning the most optimal vaccination strategies for vaccine deployment as soon as feasible.

The essential objective of the collaborative deployment planning has been to finalize development of a framework to enable roll out of a vaccine in public health Ebola emergencies, as soon as vaccines are regulatory approved and recommended for use. This overarching framework could subsequently be included in the country preparedness plans for Ebola response activities.

Vaccination strategies may require triage of vaccine to those at highest risk of exposure, depending on availability of vaccine doses, with expansion to additional populations over time as more doses arrive. If triage of vaccination is necessary, early engagement of in-country community leaders in shaping the strategy or strategies will be critical to the success of any vaccination campaign.

In the last quarter of 2014, while phase 1/2 clinical trials yielded promising results and the most advanced vaccine candidates prepared to enter Phase 3 trials, it was deemed essential, to start considering preparations for public health deployment, if and as soon as appropriate as part of the measures to control the outbreak and to support future Ebola prevention and control activities.

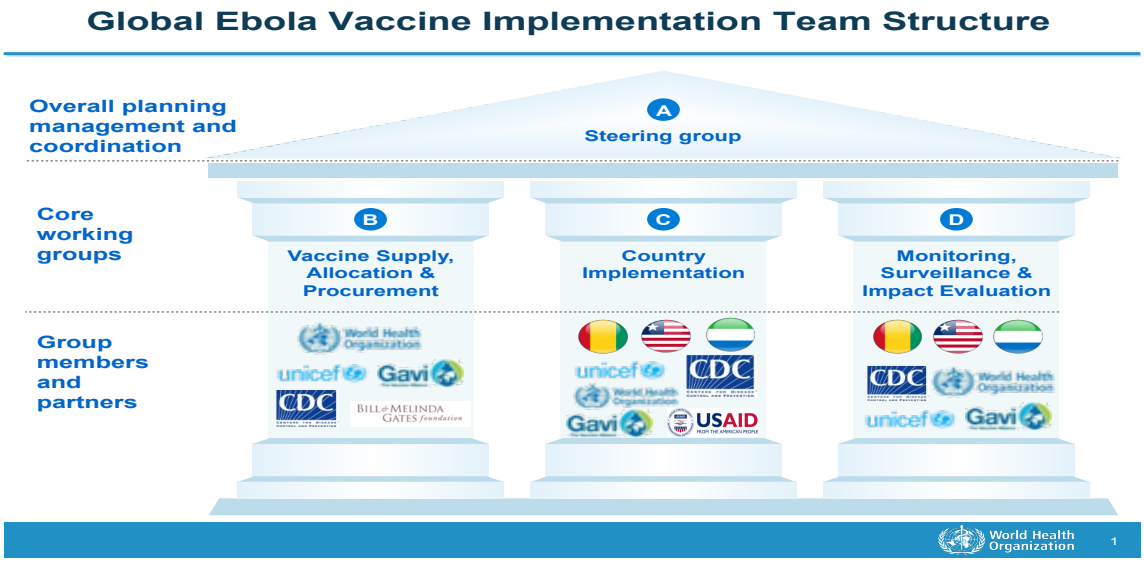


Figure 3: Global Ebola Vaccine Implementation Team (GEVIT) structure

Early in the process, it was clear that in order to be successful such effort would have to be highly collaborative and a Global Ebola Vaccine Implementation Team (GEVIT) was created with WHO leadership in order to facilitate the collaborative planning for the potential introduction of Ebola vaccines[2].

GEVIT associated countries most affected by the ongoing Ebola Virus Disease (EVD) outbreak and key partners, who would be closely involved in procuring and introducing an Ebola vaccine (Figure2).

A Steering Group was established to provide leadership and coordination to a global team organized in three Working Groups:

(1) Vaccine Supply, Allocation and Procurement;

(2) Country Implementation; and

(3) Monitoring, Surveillance and Impact Evaluation.

The scope of work of GEVIT is to support affected countries in their efforts to plan for the potential deployment of Ebola vaccines, in accordance with WHO recommendations and with the following two main objectives:

(i) to support development and dissemination of tools and guidelines, synthesis of evidence to inform strategies and policies, and community engagement strategies;
(ii) to provide capacity and work with Ministries of Health and partners to develop and implement their country plans, enabling and facilitating in-country planning, management, and coordination mechanisms, as and when relevant.

The plans and tools are near finalization and are intended for use during the ongoing outbreak or as a framework for deployment in public health Ebola emergencies, particularly in resource-limited settings.

B. SUMMARY OF KEY ACHIEVEMENYS TO DATE

C.

The timelines achieved for the two most advanced candidate vaccines were absolutely unprecedented in vaccine evaluation, and all those involved have thereby learnt that the previously accepted norms for expedited evaluation can be greatly accelerated by international partnerships, emergency funding and leadership by WHO.

Each regulator, ethics committee, scientist, partner and funding agency deserves to be commended for responsiveness to the crisis. Notably both GSK and Newlink/Merck responded in exceptional timeframes to their responsibilities as part of the vaccine development matrix.

[2] First workshop of the partners group on Ebola vaccines deployment. Summary report, 24-26 February 2015. http://www.who.int/healthsystems/publications/vaccines-deployment-workshop/en/)

1.Unprecedented and diligent design, review and implementation of clinical trials

Regulatory and ethics timelines were faster than ever before achieved in many cases. In one example a first-in-human Phase 1 was authorized in 4 working days by regulators in the UK, including initial assessment, and time to review responses by the applicant. Surging human resources into the assessment process achieved this; the rigour of the assessment process was maintained with the emphasis on product quality and participant safety.

Protocol development occurred within a few weeks thanks to the involvement of many of the leading scientists and methodologists globally.

Clinical trial investigators in Africa requested that Phase 1 data was available from Europe or North America before trial start in Africa; in practice an interval of about 4-6 weeks was achieved between clinical trial start dates in high income countries, and in Africa.

Five Phase 1 trials of ChAd3 and eight Phase 1 rVSV trials were initiated between September and December 2014 in North America, Europe and Africa. Centralised laboratory testing occurred at several laboratories.

Safety and immunogenicity data was available by February 2015 from most of these trials. The first publication was a preliminary report of the first ChAd3 trial, which was published in a journal at the end of November 2014. The information available by February allowed for dose selection data-informed decisions to be made for the three Phase 2-3 trials

Phase 2 and 3 trials were planned and initiated in record time in each of the three worst affected countries (Liberia and Sierra Leone and Guinea)

The first trial initiated was in Liberia (PREVAIL) in February, 2015 only 6 months after the global public health emergency was declared, followed by the STRIVE trial in Sierra Leone and the "Ring Vaccination trial" in Guinea which started in March 2015.

These trials are an example of international partnerships with researchers and authorities from the Ebola affected countries at the core of the same.

2. Encouraging results on safety, immunogenicity and preliminary results on efficacy and effectiveness

The safety and immunogenicity of the ChAd3-EBO-Z and the rVSV-ZEBOV have been evaluated in multiple Phase 1 clinical trials in the United States, Europe and West Africa.

Initial results indicate that these vaccines are immunogenic and do not present safety concerns that would prevent their evaluation in larger Phase 2 and Phase 3 clinical trials.

In addition, while unpublished, multiple promising two-dose schedules have been evaluated in the clinic, and these may be of relevance where long term protection is required. These two dose schedules include Ad26/MVA, ChAd3/MVA and a two-dose recombinant protein vaccine.

No further details on two-dose schedules are given as results are not yet published.

Global Advisory Committee on Vaccine safety (GACVS)

Safety of two candidate Ebola virus vaccines[1]

Phase 1 studies of the ChAd3 vaccine began in September 2014 with limited data already published. A total number of 271 healthy adults were vaccinated with ChAd3-EBO-Z in Phase 1 studies in the United States, the United Kingdom, Mali and Switzerland, with doses ranging from 1010 to 1011 viral particles. An additional Phase 1 study including 2 arms testing monovalent ChAd3-EBO-Z (n=34) was undertaken in Uganda. Based on safety and immunogenicity data from Phase 1 studies, the viral particle dose was selected for further clinical testing. Phase 2 studies in healthy adults and in children are planned in West African countries adjacent to the current outbreak zone. A Phase 2/3 study, in collaboration with the U.S. National Institutes of Health, was begun in Liberia in February 2015 but safety data were not available at the time of the GACVS meeting. In the Phase 1 studies, dose-related reactogenicity was observed, with injection-site pain and fever mainly occurring within the first 24 hours after vaccination. In most recipients, fever resolved within 24 hours. Transient clinically non-significant reductions in lymphocyte and platelet counts were observed, as is seen with many live virus vaccines. No serious adverse events ascribed to the vaccine or other unexpected serious adverse reactions were found.

Phase 1 studies of the rVSV-ZEBOV-GP vaccine began in October 2014 with limited data already published.11, 12 In total, 248 volunteers were vaccinated across 7 studies in the United States, Switzerland, Germany, Gabon, Kenya and Canada; enrollment for all studies was completed by May 2015. Collection of long-term safety and immunogenicity data from these studies is ongoing. A Phase 1b dose-ranging study, with 256 volunteers receiving doses of rVSV-ZEBOV ranging from 3 x 103 to 3 x 106 or placebo (n=74) was initiated in the United States in December 2014.

In those studies, pain at the injection site was common as were systemic symptoms including fever, malaise, and "flu-like symptoms" (chills, myalgia, headaches and fatigue) were common after vaccination and generally lasted 1 to 3 days. Administration of rVSV vaccine results in viraemia that is detectable by polymerase chain reaction (PCR) during the first and sometimes second week after vaccination, with a peak found on day 2. Vaccine virus was detected by PCR in urine and saliva in <10% of subjects. No vaccine-related serious adverse reactions have been reported to date from Phase 1 or 1b studies. Arthralgia, arthritis, dermatitis, rash and cutaneous vasculitis were reported, with varying frequency between study sites, in the 2nd week following vaccination; these reactions are associated with vaccine virus replication in the joints and the skin as demonstrated by PCR testing of specimens collected from those sites and evidence of local viral gene expression documented by immunohistochemistry. In subjects with arthritis, pain generally lasted 2–3 weeks, but occasionally more than 3 months. Joint reactions did not occur more frequently with higher doses of vaccine, but were more common among older subjects. A small number of skin vesicles and mouth ulcers were also observed and limited data did not indicate that virus had been detected by PCR. Transient, non-clinically significant reductions in neutrophil and lymphocyte counts were found in some recipients in the first few days following vaccination.

The rVSV vaccine is currently being tested in Phase 2/3 studies in Liberia, Guinea, and Sierra Leone; safety data are not yet available from those studies. Additional assessment of joint and skin events is planned in upcoming clinical studies. Safety data from Phase 1 studies of both ChAd3 and rVSV vaccines indicate an acceptable safety profile in healthy adults. Ongoing studies will provide additional experience in adults, and will allow more extensive assessment of safety. No data are currently available regarding the safety of these vaccines in subjects with underlying disease or medical conditions. There are also no data regarding the safety of these products in paediatric and pregnant subjects.

Phase 1 trials

ChAd3

Phase 1 trials confirmed a dose response in terms of both reactogenicity and immunogenicity from 1x10(10) vp to 1x10(11) vp (Table 1). Given that toxicity was not limiting at higher doses, and immunogenicity at 1x10(11) was approaching the range where non-human primates were reliably protected from challenge, this higher dose of 1x10(11) vp was chosen for further Phase 2/3 evaluation.

Unlike rVSV several hundred humans have received the identical ChAd3 backbone in Hepatitis C and RSV Phase 1 trials, with no SAE causally related to vaccination, and no unexpected safety signal.

Table 4. Overview of ChAd3 Phase 1 trials to evaluate safety and immunogenicity in healthy adults

Phase of Trial	Site	ChAd3 EBO Z dose level	Subjects Enrolled as of 22 Sep 2015	Preliminary results published
Phase 1 adults	VRC – USA (bivalent)	$2x10^{10}$ $2x\ 10^{11}$	20	N Engl J Med. 2014 Nov 26.
	Oxford – UK	$1\ x10^{10}$ $2.5\ x10^{10}$ $5\ x10^{10}$	76	N Engl J Med. 2015 Jan 28
	CVD – Mali	$1\ x10^{10}$ $2.5\ x10^{10}$ $5\ x10^{10}$ $1\ x10^{11}$	91	In press
	Lausanne – Switzerland	$2.5\ x10^{10}$ $5\ x10^{10}$	100	In press
	University of Maryland – USA	$1\ x10^{10}$ $1\ x10^{11}$	20	
	MUWRP - Uganda	$1\ x10^{10}$ $1\ x10^{11}$	34	
	2^{nd} Oxford study - UK	$2.5\ x10^{10}$	32	
	CHUD Dakar - Senegal	$2.5\ x10^{10}$ $3.7\ x10^{10}$	40	
Phase 2 adults	Senegal, Mali, Nigeria, Cameroon	$1\ x10^{11}$	722 enrolled /3000 planned	
Phase 2 paediatric	Senegal, Mali, Nigeria, Cameroon, Ghana	$1\ x10^{11}$	Not started	

rVSV Vaccine

For rVSV reactogenicity was dose related, but the dose response from 3x10(5) pfu to 5x10(7) pfu was rather flat in terms of IgG binding antibodies as measured by ELISA (Table 2). There was a dose response seen in terms of neutralising activity, with the highest response seen at 2x10(7). Unlike for ChAd3, an unexpected safety signal was detected in the rVSV trials, namely mild to moderate and generally short lived arthritis or arthralgia of onset during the second week after vaccination, in a small minority of individuals (20% in one site and less than 5% in other sites). This was confirmed to be related to dissemination of non-mutated rVSV-ZEBOV vaccine virus to joints, and is most likely caused by the known tropism of ebola virus for joints. Thus the chimeric virus shares tropism from the VSV backbone and the Ebola glycoprotein. The arthritis/arthralgia is not dose related as it was seen at a similar frequency in vaccinees that received 3x10(5) as for those receiving 5 x10(7) pfu. The decision was therefore taken to modify protocols to include solicited data collection for this adverse event, and to continue Phase 2/3 at 2x10(7) pfu.

Table 5. Overview of rVSV Phase 1 trials to evaluate safety and immunogenicity in healthy adults

Phase of Trial	Site	rVSV dose level	Subjects Enrolled as of Sep 2015	Preliminary results (D28 from partial enrolment)
Phase 1	WRAIR – USA	$3x10^6$ $2x10^7$ $1x10^8$	30	December 2014 N Engl J Med. 2015 Apr 1
	NIAID - USA	$3x10^6$ $2x10^7$ $1x10^8$	30	December 2014 N Engl J Med. 2015 Apr 1
	Geneva - Switzerland	$3x10^5$ $1x10^7$ $5x10^7$	100	January 2015 N Engl J Med. 2015 Apr 1 Lancet Infect Dis. 2015 Aug 3
	Germany	$3x10^5$ $3x10^6$ $2x10^7$	30	January 2015 N Engl J Med. 2015 Apr 1
	Gabon	$3x10^3$ $3x10^4$ $3x10^5$ $3x10^6$	115 (40 paediatric)	January 2015 N Engl J Med. 2015 Apr 1

Phase of Trial	Site	rVSV dose level	Subjects Enrolled as of Sep 2015	Preliminary results (D28 from partial enrolment)
		$2x10^7$		
	Kenya	$3x10^6$ $1x10^7$	40	February 2015 N Engl J Med. 2015 Apr 1
	Canada	$1x10^5$ $5x10^5$ $3x10^6$	30	
	NewLink-1b multiple sites - USA	$3x10^3$ $3x10^4$ $3x10^5$ $3x10^6$ $9x10^6$ $2x10^7$ $1x10^8$	442	

Phase 2/3 trials

The NIAID, the Liberia College of Physicians and Surgeons and the Liberian Institute for Biomedical Research are conducting a study in Liberia that started early February 2015. The study is called Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) and is a Phase 2/3 clinical trial designed to evaluate the safety and efficacy of two investigational vaccines intended to prevent Ebola virus infection: the ChAd3 and the rVSV vaccines.

The US Centers for Disease Control and Prevention (CDC), the Sierra Leone College of Medicine and Allied Health Sciences (COMAHS), and the Sierra Leone Ministry of Health and Sanitation (MoHS) are conducting a study in Sierra Leone that started in April 2015. This phase 3 study is called the Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE). It is an event-driven, unblinded, randomized, phased introduction vaccine trial to assess the safety and efficacy of the rVSV Ebola vaccine among health care and other frontline workers.

The STRIVE and PREVAIL studies are designed to assess vaccine efficacy based on clinical disease endpoints, and serum samples will be collected for immunogenicity analysis. In addition to the 2 large Phase 3 trials sponsored by the US government,

The Guinea Consortium, a large international partnership including the Government of Guinea and the World Health Organization (WHO) is implementing a cluster randomised trial (*Ebola ça suffit* ring vaccination trial) in Guinea using the rVSV-ZEBOV vaccine.

In this novel adaptive trial design, rings are randomised 1:1 to (a) immediate vaccination of individuals at raised risk of infection due to their connection to a case or (b) vaccination delayed by 21 days.

Vaccine efficacy against disease is assessed in participants over equivalent periods from the day of randomisation. In addition a prospective cohort study among frontline workers is being conducted to obtain additional evidence on the safety and immunogenicity of rVSV.

Table 6. Overview of Phase 3 Ebola vaccine trials (1)

Study	Design	Schedule / Vaccine(s)	Sample Size (Target)	Target popn	Age inclusion criteria	Primary end points	Follow up period
Liberia PREVAIL	Double blinded, individually randomized controlled	One dose rVSV ChAd3 (Placebo)	Phase 2: 500 rVSV 500 ChAd3 (Phase 3: 27,570)	Individuals at risk for EVD	≥ 18 years	Safety, Immuno-genicity (lab confirmed EVD)	Monthly follow-up through event driven closing date
Sierra Leone STRIVE	Individually randomized,(unblinded) to immediate vs delayed arm (6 months)	One dose rVSV	Phase 3: 9000	Health Care Workers	≥ 18 years	Safety, Sub-group immu-nogenicity (lab confirmed EVD)	One year
Sierra Leone EBOVAC MoH/LSHTM/J&J	Cluster randomized in 3 stages and 2 arms to immediate vs delayed arm (6 months)	Prime + Boost Ad26 + MVA	Stage 1: (40) Stage 2: (400) Stage 3: (3160) (Phase 3: 800,000, clusters of approx. 5,000 people)	General population	Stage 1: ≥ 18 years (Stage2 & Stage 3: >12 months)	Safety, Immuno-genicity (lab confirmed EVD)	Stage 1 & Stage 2: 1year Stage 3: 5 months, with 1 year in sentinel groups
Guinée Ebola ÇA SUFFIT -essai Clinique*	Cluster randomized in areas with EVD - to immediate vs delayed arm (21 days) Cohort study among FLWs	One dose rVSV (ChAd3)	(190 rings Approx. 10,000 people) 1200	Eligible individuals who are contacts and contacts of contacts of lab conf. EVD cases	≥ 18 years & since August 2015: 13-17 yrs. 6-12 yrs.	(lab confirmed EVD) Safety, Immuno-genicity	84 days after vaccination

* Sierra Leone trial extension since September 2015

Table 6. Overview of Phase 3 Ebola vaccine trials (2)

Study	Exclusion criteria	Number of subjects enrolled to date	Status
Liberia PREVAIL	Fever (38.0 Celsius) History of EVD Pregnancy (negative urine pregnancy test required)	Phase 2: Started January 2015, Enrolment completed: 600 volunteers (Phase 3: not initiated)	Closed, Analysis ongoing (Searching new location)
Sierra Leone STRIVE	History of EVD or HIV Fever (algorithm for evaluation) *Pregnancy*	Started April 2015 Enrolment completed: 9000 volunteers, 4500 vaccinated in immediate arm, vaccinations in delayed arm on-going	Ongoing
Sierra Leone EBOVAC MoH/LSHTM/J&J	Pregnancy, individuals, medically unfit for vaccination through chronic illness	To start in September 2015	Not recruiting yet
Guinée Ebola ÇA SUFFIT -essai clinique*	Fever Pregnancy History of EVD or HIV History of immunosuppression Disease requiring hospitalization at the time of vaccination	Ring- Started March 2015 Enrolments and vaccinations completed in randomized rings in July 2015, non-randomized immediate rings continuing FLWs – started March 2015, Enrolment completed: 1200 volunteers Trial extension with safety only for new enrolments	Ongoing Interim results published Lancet. 2015 Aug 29

* Sierra Leone trial extension since September 2015

From the declaration of the public health emergency to the publication of interim results of efficacy from the Guinea ring vaccination trial the interval was less than 12 months, even though not a single person had been enrolled in a clinical trial when the emergency was declared.Between April 1, 2015, and July 20, 2015, 90 clusters, with a total population of 7651 people were included in the planned interim analysis. 48 of these clusters (4123 people) were randomly assigned to immediate vaccination with rVSV-ZEBOV, and 42 clusters (3528 people) were randomly assigned to delayed vaccination with rVSV-ZEBOV.

In the immediate vaccination group, there were no cases of Ebola virus disease with symptom onset at least 10 days after randomisation, whereas in the delayed vaccination group there were 16 cases of Ebola virus disease from seven clusters, showing a vaccine efficacy of 100% (95% CI 74·7–100·0; p=0·0036). No new cases of Ebola virus disease were diagnosed in vaccinees from the immediate or delayed groups from 6 days post-vaccination.

At the cluster level, with the inclusion of all eligible adults, vaccine effectiveness was 75·1% (95% CI −7·1 to 94·2; p=0·1791), and 76·3% (95% CI −15·5 to 95·1; p=0·3351) with the inclusion of everyone (eligible or not eligible for vaccination).

	All vaccinated in immediate versus all eligible in delayed (primary analysis)	All eligible and consented	All eligible (eligible adults, contacts and contacts of contacts)	All (all contacts and contacts of contacts)
Number of individuals (clusters)				
Immediate	2014 (48)	2048 (48)	3035 (48)	4123 (48)
Delayed	2380 (42)	1930 (42)	2380 (42)	3528 (42)
Number of cases at <10 days (affected clusters)				
Immediate	9 (4)	10 (5)	18 (9)	21 (9)
Delayed	16 (12)	6 (5)	16 (12)	25 (13)
Number of cases at ≥10 days (affected clusters)				
Immediate	0 (0)	0 (0)	6* (3)	8* (4)
Delayed	16† (7)	11† (5)	16† (7)	21† (7)
Vaccine efficacy/ effectiveness‡ (%; 95% CI)	100% (74·7 to 100)	100% (70·8 to 100)	75·1% (–7·1 to 94·2)	76·3% (–15·5 to 95·1)
p value§	0·0036	0·0194	0·1791	0·3351

*All cases occurred in unvaccinated individuals. †Four cases were vaccinated and developed symptoms on day 0, 2, 6, or 6 after vaccination. ‡From fitting a β-binomial distribution to the cluster-level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine efficacy (first two columns); from Cox proportional hazards model to estimate vaccine effectiveness (last two columns). §From Fisher's exact test (two-sided).

Table 7. Calculations of vaccine efficacy and effectiveness based on different study populations 9preliminary results), Ring vaccination trial, Guinea.

According to Fisher's exact test comparing the proportions of clusters with one or more eligible case, the p value for the efficacy estimate was 0 ·0036 and did not cross the interim analysis threshold of p=0 ·0027. The estimated vaccine efficacy in all members of the 90 clusters is 76 ·3% (95% CI –15 ·5 to 95 ·1, p=0 ·3351.

The full data on the secondary outcomes for efficacy and effectiveness and safety will be part of a future report once follow-up is completed for all participants and analyses have been done and follow-up is completed for all participants and analyses have been done.

The continued enrolment, immediate vaccination, and follow-up of clusters will generate additional data about the effectiveness of ring vaccination to protect communities through herd immunity.

This trial is thought to serve as a proof of concept for a novel ring vaccination cluster-randomised trial design. This trial design is logistically feasible, even in resource-poor settings and in a crisis situation.

3. Plans and tools in preparation for vaccine deployment

Significant progress has been made in the three areas of work.

First, in terms of vaccine supply, allocation and procurement:

(i) models of supply capacity and timing of availability have been developed, closely engaging with manufacturers of advanced vaccine candidates, to be refined as new information arise;
(ii) potential demand scenarios based on a range of vaccination strategies are being considered in close collaboration with mathematical modelers;
(iii) an International Coordinating Group (ICG) for Ebola vaccine has been established, its terms of reference and processes are being defined based on the experience with ICGs for vaccines against other epidemic diseases such as meningitis or cholera; and
(iv) vaccine procurement modalities are being developed.

Second, in terms of country implementation: a guidance document has been drafted based on experience with vaccination activities during outbreak response for other infectious diseases. The guidance is organized around four main areas:

(i) vaccines and vaccination strategies;
(ii) overall planning for deployment including infection control measures;
(iii) cold chain and logistics, including provision for ultra-cold temperature equipment and related power supply, with particular attention to sustainability, flexibility and alignment with the health system needs;
(iv) shaping community engagement and risk communication strategies building on experience from both the Ebola response and the vaccine trials, including key messages and addressing possible responses to questions, concerns and perceptions.

Third and last, in terms of monitoring and evaluation, guidance documents have been drafted to address the following three areas: (i) monitoring and evaluation of the Ebola vaccination delivery strategy; (ii) evaluation of the impact of the vaccine use and potentially efficacy, with attention to elements and definitions to be adapted or added to the surveillance system; and (iii) vaccine safety surveillance including the development of case definitions for Adverse Events Following Immunization (AEFI) and guidelines to strengthen AEFI Monitoring and Evaluation.

GEVIT will now seek to reach consensus on the documents and tools, so that the blueprint be completed by December 2015.

A regional workshop will be a significant milestone to advance and integrate plans together with countries, using case studies and simulation exercises. It will be held in Brazzaville just after the October 2015 meeting of the WHO's Strategic Advisory Group of Experts on Immunization (SAGE) to benefit from their draft recommendations on Ebola vaccines and vaccination.

C. PREPARING FOR THE INEVITABLE – BUILDING AN R&D LINE OF DEFENCE FOR GLOBAL HEALTH THREATS

WHO R&D blueprint for epidemics

Objectives:

- To develop and implement a roadmap for R&D preparedness,
- To enable roll-out of an emergency R&D plan as early as possible during future public health emergencies due to highly infectious pathogens

Five Work-streams:

1. Mechanism to prioritize pathogens for research and product development

- Identification of the top priority infectious diseases for which R&D should be conducted urgently for better preparedness. This work will build on prioritization exercises conducted by various organizations.
- Development of a methodology, based on explicit criteria, for revising these R&D priorities annually or when needed, in order to take into consideration new emerging pathogens.

2. R&D preparedness: gap analysis and identification of research priorities

- Production of a template for a fully developed roadmap for R&D preparedness for priority infectious pathogens, including priority research as well as product R&D. One of the identified priority pathogens (MERS-CoV) will be used as an example to articulate the main elements of this roadmap.

3. Organization, coordination of stakeholders and gap analysis of capacities

- Investigation of a stakeholder engagement plan and governance structure that efficiently allows for National and International actors to work in concert in support of a global effort.
- Mapping of capacities, platforms, tools and templates needed to enable conduct of an efficient research response during a public emergency. This will facilitate the last steps of R&D for identified priority diseases, as well initiation of R&D for previously unknown pathogens

4. Assessment of preparedness level and (Impact assessment) of interventions

- Development of a mechanism for monitoring and evaluation of the effectiveness of the outputs over the near- and longer-terms will be developed

5. Funding options for preparedness and emergency response

- Exploration of options for complementary funding models from centrally pooled resources in R&D funds, to joint planning with individual implementation by different entities in line with the agreed blueprint activities, and agreed roles and responsibilities for different agencies.

Ebola Vaccines and Vaccination

Report of the SAGE Working Group on Ebola Vaccines and Vaccination with provisional recommendations for vaccination

September 30, 2015

SECTION C: CONCLUSIONS AND RECOMMENDATIONS

Conclusions of the Working Group and draft recommendations for consideration by SAGE

Conclusions:

General

- Based on the available data on the safety and immunogenicity of the leading vaccine candidates[1] and the preliminary data on the efficacy and effectiveness of the recombinant, replication-competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of *Zaire ebolavirus* (rVSV-ΔG-ZEBOV), the Working Group (WG) concluded **that vaccination is likely to provide added value in controlling outbreaks of Ebola Virus Disease (EVD) caused by the *Zaire ebolavirus* (ZEBOV) species**.

- Previous outbreaks had been curtailed using public health measures other than vaccination and transmission was interrupted in the recent outbreak in Liberia without the use of vaccines. Vaccination should be part of an integrated strategy and complement other public health measures in order to effectively interrupt transmission.

- Currently, there are no data to make any recommendations on vaccines against species of *Ebolavirus* other than ZEBOV. However, the WG took note that one of the leading candidate vaccines has a multivalent "boost" component (MVA) and that a bivalent ChAd3-vectored *Zaire-Sudan ebolavirus* vaccine is under development.

- The accelerated development of several candidate vaccines is unprecedented. Parallel processes to define the regulatory pathways, establish policy recommendations and prepare for introduction in the affected countries is a testament to the value of partnership, participatory approaches and co-ordination.

Vaccine safety

Adults

- Safety data from Phase 1 studies of both ChAd3-ZEBOV and rVSV-ΔG-ZEBOV vaccines indicate an acceptable safety profile in healthy adults. Ongoing studies will provide additional experience in adults, and will allow more extensive assessment of safety. At the time of this recommendation, follow-up of human vaccine recipients did not exceed one year. The total number of recipients

[1] The four leading vaccine candidates reviewed by the SAGE WG are: (1) a chimeric, replication-competent vesicular stomatitis virus-based vaccine expressing surface glycoprotein of *Zaire ebolavirus* (rVSV-ΔG-ZEBOV); (2) a recombinant non-replicating chimpanzee adenovirus type 3-based vaccine expressing surface glycoprotein of *Zaire ebolavirus* (ChAd3-ZEBOV); (3) a heterologous prime boost approach based on 2 components, namely a non-replicating type 26 human adenoviral vector expressing *Zaire ebolavirus* surface glycoprotein (Ad26-ZEBOV) and a non-replicating modified vaccinia Ankara (MVA) vector expressing the *Zaire ebolavirus*, *Sudan ebolavirus* and Marburg virus glycoproteins and the *Tai Forest ebolavirus* nucleoprotein; and (4) A recombinant protein vaccine based *Zaire ebolavirus* glycoprotein adjuvanted with Matrix M

of any Ebola virus vaccine is not sufficient to detect potential adverse events that would occur in less than one in a few thousand vaccine doses.

- Arthritis and skin vesicular lesions have been reported in phase 1 studies with rVSV-ΔG-ZEBOV. High rates (24/102 recipients) were noted in one study, which might be associated with the higher median age of volunteers (41 years); while the symptoms subsided in most, 8 reported persistent joint stiffness, whereas 5 reported transient recurrence of joint pain and/or swelling. Vaccine RNA was detected in joint and vesicular fluid. In studies in African countries, reported rates of arthritis or arthralgia were low. Additional assessment of joint and skin events is planned in upcoming clinical studies.

Children

- Data on the safety of the rVSV-ΔG-ZEBOV vaccine are currently insufficient to make definitive recommendations for vaccination. Additional data on the safety of the rVSV-ΔG-ZEBOV in children over 6 years are expected from a trial in Gabon and from children (6-12 years of age) and adolescents (13-18 years of age) who are now eligible for vaccination in the Guinea ring vaccination trial. In addition, Phase 2 trials of the ChAd3-ZEBOV and the Ad26-ZEBOV/MVA vaccines in children are planned.

Special populations

- No data are currently available regarding the safety of the four leading candidate vaccines in subjects with underlying disease or medical conditions.

- There are currently no publicly available data on the safety of the available vaccine candidates in pregnant women. Pregnant women were inadvertently vaccinated in the ongoing phase 2/3 trials with rVSV-ΔG-ZEBOV and ChAd3-ZEBOV. Analysis of data from these individuals will provide preliminary data on safety and immunogenicity in this group.

- There are no publicly available data on the safety of the candidate vaccines among HIV infected individuals to permit recommendations for vaccination. Volunteers in the Liberia PREVAIL trial, which was a Phase 2/3 trial evaluating rVSV-ΔG-ZEBOV and ChAd3-ZEBOV vaccines, were screened for HIV but not excluded if positive. Analysis of data from the HIV-infected individuals in this trial will provide preliminary data on safety and immunogenicity in this group.

Immunogenicity, efficacy and effectiveness

- Both rVSV-ΔG-ZEBOV and ChAd3-ZEBOV vaccines are immunogenic when provided in a single dose (by both binding ELISA and neutralizing assay) at the chosen dose levels of $2x10^7$ *pfu* and 1 x 10^{11} *vp,* respectively. Three different two-dose schedules have also been evaluated in clinical trials for Ebola vaccines. Two of these are using two different vaccines for the two doses known as heterologous prime-boost approach. These are: (1) recombinant Ad26 and recombinant MVA used in either order; and (2) ChAd3 followed by MVA. There is also a more traditional two-dose schedule using a recombinant protein based approach. In all 3 cases there is good

immunogenicity after the two doses. While it is difficult to compare these with the one dose ChAd3-ZEBOV and rVSV-ΔG-ZEBOV vaccine schedules because of differences in assays, immunogenicity after two doses (Ad26/MVA, ChAd3/MVA or protein/protein) appears similar or higher to that seen after one dose of ChAd3-ZEBOV or rVSV-ΔG-ZEBOV alone.

- An important question is comparability of immune responses between vaccine candidates. Unfortunately, there is limited information testing different vaccines using the same assay methodology and the same vaccine antigen vs test antigen matching, though an international partnership led by WHO made major efforts to allow for comparability. From data made available to WHO, the magnitude of the humoral immune response is similar for ChAd3-ZEBOV and rVSV-ΔG-ZEBOV vaccines at 1 x 10^{11} and 2 x 10^{7}dose levels, respectively, 28 days following vaccination.

- There are efficacy and effectiveness data from an interim analysis of a phase 3 trial of the rVSV-ΔG-ZEBOV vaccine in Guinea. The results of this interim analysis suggest that rVSV-ΔG-ZEBOV is efficacious (efficacy= 100%, 95% CL 74.7-100, p=0.0036), safe, and likely to be effective at the population level (effectiveness=75.1%, 95% CL -15.5 to 95, p=0.1791) when delivered during an EVD outbreak using a ring vaccination strategy.

- The WG takes note of the fact that the rVSV-ΔG-ZEBOV vaccine ring vaccination trial has been expanded from the Guinée Maritime to Sierra Leone. Randomization was stopped on 26 July, 2015 and all new rings, around newly confirmed index cases, are allocated to immediate vaccination aiming to collect additional safety and effectiveness data. In addition, given the preliminary efficacy results, it is anticipated that the ring vaccination strategy may contribute to preventing the spread of disease.

Vaccine development and registration

- Although data on the available candidate vaccines, including efficacy data for the rVSV-ΔG-ZEBOV, is accruing, current regulatory approvals are limited to the use of vaccine in a clinical trial setting.

Service delivery

- In a trial setting, it was possible to deliver vaccine at the community level while maintaining the stringent cold chain requirements (i.e. - 80◦ C). Studies are ongoing to evaluate the thermostability of different vaccines at temperatures more suitable for delivery of vaccine at the community level.

Draft Recommendations:

- Based on the review of current data on disease epidemiology, risk factors for infection and death from EVD, disease transmission patterns and projected impact of vaccination using different delivery strategies under different epidemiological scenarios, the WG proposes the following **provisional** recommendations for consideration by SAGE. These recommendations may need to be reviewed and revised in light of the emerging data on the different vaccines.

- The currently available evidence only allow for recommendations for reactive vaccination (i.e. in response to an outbreak). The evidence is insufficient to formulate recommendations for preventive vaccination (i.e. in the absence of any cases).

- While the rVSV-ΔG-ZEBOV vaccine and other candidate vaccines are currently being used in the context of a clinical trial, recommendations for use outside a trial setting will depend on the vaccines receiving regulatory approval (i.e. full licensure, conditional licensure or emergency use authorization outside a clinical trial setting).

- These draft recommendations are prepared on the basis of interim trial results suggesting high efficacy of the rVSV-ΔG-ZEBOV vaccine and immunogenicity data for the ChAd3-ZEBOV that suggest that it is comparable to rVSV-ΔG-ZEBOV. However, it is important to note that the recommendations do not apply to any specific vaccine. Vaccine-specific recommendations will be made once a vaccine is registered for use outside a trial setting. Meanwhile, it is important that the development and evaluation of other candidate Ebola vaccines continue, as there may be a need for alternative vaccines with different characteristics more suited for certain conditions or in specific target populations.

Recommendations for use of vaccine, provisional to regulatory authorization for use outside a trial setting

Objectives of vaccination: The main objectives for vaccination are interruption of transmission and individual protection for those at high risk for infection.

Target populations: While all eligible individuals should be vaccinated as per the chosen vaccination strategy, certain high-risk groups merit special consideration. Individuals who come into direct contact with patients or infectious body fluids from patients with EVD are at highest risk of infection. The data from the three worst affected countries in the current outbreak in West Africa indicates that among the frontline workers, health care workers (doctors, registered nurses, and laboratory workers) are at highest risk for infection. Limited data suggest that other categories of health workers (mid-wives, surveillance staff, radiographers, cleaners and laundry workers) may also be at high risk. While hard evidence is not available, certain other categories of individuals have a greater likelihood of exposure to infectious body fluids. They include informal health care providers (e.g. traditional healers, herbalists etc.), and those involved in funeral rites (elders, religious leaders, senior members of secret societies, and traditional washers). The categories of front-line workers and other risk groups may vary from one community to the other and may need to be defined locally.

These high-risk categories, including first responders, should be given priority consideration in any vaccination strategy.

Vaccination delivery strategy: The vaccination delivery strategy of choice will depend on the extent of the spread of disease, the number of cases being confirmed per week at the time when vaccination is initiated, the status of implementation of other public health measures, the effectiveness of contact tracing and the available supply of vaccine. Regular reviews of the epidemiological data should be used to inform adjustments to the delivery strategies throughout the outbreak. Potential strategies include ring vaccination, geographic targeting of an area (mass vaccination) and front line worker vaccination. When more data are available, it may be possible to provide more precise recommendations on the choice of vaccination strategy.

Other considerations for improving acceptability or impact of vaccination

- The absolute and per capita case incidence of EVD among children younger than 16 years of age has been significantly and consistently much lower than the incidence among adults in all three countries. This pattern is similar to that observed in past EVD outbreaks. The case fatality rate (CFR) was lowest among children between 10 and 15 years of age. Pregnant women and infants have very high CFR. They may be protected by indirect protection if others in the community are vaccinated. Inclusion of pregnant women as a means to indirectly protect their infants and young children might need consideration in the future.

- A communication strategy tailored for the affected communities should be considered, including:
    - Public vaccination of community leaders (e.g. religious leaders, members of Parliament, chiefs, etc.).
    - Information provided on an anticipatory, iterative and responsive basis to address rumors, anxieties and resistance. Appropriate media including m-Health messaging, should be utilized in in the affected communities if pertinent.
    - Engaging survivor networks for advocacy to enhance the acceptability of vaccination.

- Introduction of Ebola vaccination will require specific preparation and will need to be closely integrated as part of EVD outbreak control measures. Therefore, careful planning should be promoted to ensure readiness for introduction as soon as feasible. The work of the Global Ebola Vaccine Implementation Team (GEVIT) to develop tools and generic deployment plans is critical to ensure the timely and successful deployment of any vaccine(s) and should be completed as soon as possible.

Recommendations on further research

- The WG requests researchers to share data from pregnant women and immunocompromised subjects vaccinated during the ongoing trials once they become available. All future trials should consider collecting data on the safety and immunogenicity of the respective vaccine candidates in children and adolescents, pregnant and lactating women, and immunocompromised individuals.

- Noting that relatively large outbreaks have occurred with Sudan, Bundibugyo and Marburg viruses, the WG recommends continued efforts to develop and evaluate vaccines against filoviruses other than ZEBOV, such as Sudan, Bundibugyo and Marburg. Multi-valent filo virus vaccines are desirable. The WG is encouraged by efforts to develop a bivalent *Zaire-Sudan ebolavirus* vaccine.

- Should the data on safety, immunogenicity or efficacy result in pregnant women being precluded from vaccination, then alternate strategies should be evaluated, recognizing the high case fatality. Alternative or complementary approaches might include the effect of cocoon vaccination approach (i.e. vaccination of possible contacts of pregnant women).

- All trials should carefully document adverse events using standard definitions, including duration, severity and sequelae. In particular, for rVSV-ΔG-ZEBOV vaccine, safety monitoring should document and clearly distinguish arthritis from arthralgia.

- Future studies should evaluate the feasibility and effectiveness of the delivery approaches, duration of protection, and measures that ensure high levels of community acceptance.

- Future research should implement community-based participatory approaches to engage participants in all stages of clinical trials, including design, monitoring and evaluations.

- The WG acknowledges the ongoing work to improve the thermostability of the candidate vaccines and encourages optimization of thermostability to meet the WHO criteria for programmatic suitability for prequalification.

- Pre-approved and pre-positioned protocols and local research capacity strengthening in countries at risk for future outbreaks should be put in place now to facilitate rapid implementation of relevant studies including assessment of newer vaccine products, in the event of future outbreaks. Such protocols are included in the blueprint for conducting research during public health emergencies, which is currently being developed under the leadership of WHO.

- The ongoing efforts to model the impact of different Ebola vaccination strategies on preventing disease and transmission should be pursued and expanded to further inform the understanding of their respective value in controlling an outbreak.

Summary of the June 2015 Gavi Alliance Board Meeting

Gavi Partner Engagement Framework (PEF): The Gavi Alliance Board approved changes to the new modus operandi of the Alliance with targeted and innovative investments across the Alliance partnership through the new Partners Engagement Framework (PEF). A lot of emphasis was made by the Board on the high expectations in achieving the Alliance's coverage and equity objectives, with increased accountability and in ensuring successful transition of countries. The supporting decisions include:

- **Approved** commitments in an annual amount of US$ 31.2 million for the Foundational Support for partners (UNICEF, CDC, World Bank, CSO constituency and WHO) in the years 2016 and 2017 and, subject to satisfactory performance, in the annual amount of US$ 31.2 million for the Foundational Support for partners in the years 2018-2020.

- **Approved** annual commitments in an annual amount of US$ 5.2 million for the Foundational Support for IPV introduction in the years 2016 and 2017 for WHO and UNICEF. The Board commended the huge amount of work by partners to facilitate over 100 IPV introductions in 2015.

Transition Support to Countries: The Board approved new policies allowing graduated Gavi countries to be included in UNICEF tenders for specific vaccines, with the aim of continuing to provide them with access to Gavi prices for a five year period. This is within the scope of the WHO lead strategy for supporting Middle Income Countries endorsed by the SAGE in April and aims at ensuring access to affordable vaccines for all Gavi supported countries. The supporting decisions include:

- **Approved c**hanges to the current co-financing and transition support policies providing a time-limited opportunity to access exceptional catalytic support for the introduction of HPV, MR and/or JE vaccines for those Phase 2 countries that did not have the possibility to apply for these vaccines, due to the timing of the vaccines' availability.

- **Approved** the Alliance's approach to ensuring access to appropriate pricing for Phase 3 [graduated] Gavi countries by continuing to seek appropriate and sustainable prices through market shaping activities consistent with Gavi's Vaccine Supply and Procurement Strategy. Furthermore, allowing Phase 3 [graduated] Gavi countries to be included in UNICEF tenders on behalf of Gavi-eligible and Phase 2 [graduating] countries for specific vaccines with the aim of continuing to provide them with access to Gavi prices for a five year period (provided a country commits to key terms to be defined by UNICEF and Gavi).

- **Approved** providing a catalytic investment if US$ 5 million towards the capitalisation of UNICEF's Vaccine Independence Initiative (VII), a revolving fund which supports timely availability of financing for countries to meeting payment terms. The use of this investment will be prioritised towards Gavi countries, subject to UNICEF approval of each country application to participate in VII.

Innovative Cold Chain Platform: the Board approved the creation of an innovative mechanism to strengthen country cold chain systems and advance the Alliance's Supply Chain Strategy and, ultimately, its coverage and equity goals (the "CCE platform) with an initial allocation of US$ 50 million for 2016-2020.

Gavi Support to Ebola: Board members were informed that a lot of work had already taken place in relation to vaccine deployment and of the strategy being developed for SAGE to consider. The Board highlighted that one of the main priorities now in the affected countries will be to work on restoring routine immunisation services.

Sustainable Development Goal Indicators: The Board raised concerns regarding the latest IAEG SDG indicator meeting report with no mention of vaccines and immunisation and committed to continue advocacy efforts to ensure critical inclusion of GVAP coverage indicator.

SAGE Polio Working Group

Monday 8th June 2015

Conference Call Notes

INTRODUCTION

A SAGE Polio Working Group (WG) teleconference was held on 8th June 2015 to discuss the epidemiology of persistent cVPDV2 transmission; the preparations for OPV2 withdrawal, including the IPV supply strategy and monitoring framework for tOPV withdrawal. The call was attended by the following WG members: Peter Figueroa (Chair), Walter Orenstein, Walter Dowdle, T Jacob John, Elizabeth Miller, Kimberly Thompson, Hyam Bashour, Yagob Al-Mazrou, Nick Grassly, Antoine Kabore, Francis Nkrumah. Zulfiqar Bhutta was unable to attend. This note presents a summary of the presentations, key discussion points, decisions and recommendations from the call.

OBJECTIVES

The objectives of the meeting were to:

1. Review the current status of persistent cVDPV2 transmission in Nigeria and Pakistan and the updated global SIA calendar. (**Information**)
2. Review the preparations for OPV2 withdrawal (**Information**), including
    a. Global IPV introduction schedule for OPV-only using countries, including IPV supply situation for 2015 and 2016
    b. bOPV licensure
    c. mOPV2 stockpile
    d. Monitoring system for tOPV withdrawal
    e. Containment
    f. Verification and certification of wild poliovirus type 2

PRESENTATIONS, DISCUSSIONS AND CONCLUSIONS

TOPIC 1 **Epidemiological status of persistent cVDPV2 transmission in Nigeria and Pakistan (Information)**
WG reviewed the epidemiology of persistent cVDPV2 in Nigeria and Pakistan. To date in 2015, the program made considerable progress in eliminating persistent cVDPV2 cases, but the virus continued to be detected in environmental samples collected from certain sites in Nigeria and Pakistan. In Nigeria, no cVDPV2 cases have been reported in 2015, with only one isolate of persistent cVDPV2 detected from one environmental surveillance site in Kaduna, in March 2015. Nigeria conducted two successive tOPV rounds in March and April 2015; both were NIDs. IPV was co-administered with tOPV in the affected LGAs of Kaduna during the April NID. All subsequent environmental samples from Kaduna for the months of April and May 2015 have been confirmed as negative. Further rounds are planned for July (SNID) and September (SNID) 2015. Nigeria is currently on track to stop persistent cVDPV2 circulation within the first half of 2015 with its aggressive use of tOPV SIAs and the addition of IPV in selected high-risk areas. Also, in Pakistan, there have been no persistent cVDPV2 cases reported in 2015. A new persistent cVDPV2 emerged in July 2014, and continued to be detected in environmental surveillance in Gaddap, Karachi until March 2015, with all subsequent environmental surveillance samples from Gaddap for the months of April and May 2015 confirmed as negative. A single positive environmental sample was also detected in Quetta, Balochistan in March 2015, with all subsequent samples collected from Quetta during April and May confirmed as negative. Pakistan conducted 4 tOPV campaigns during the first half of 2015 in areas affected by persistent cVDPV2 in 2014, 1 in March (NID), and 2 in May (SNIDs), with IPV added in selected highest-risk areas, such as in Quetta.

In Gaddap, specific activities targeting missed children were initiated last month, with female community volunteers vaccinating children <5 years of age twice a month. More tOPV rounds are planned for June (local SIA in Karachi) and September (SNID) 2015. Thereafter, the epidemiology of cVDPV2 will be reviewed and further tOPV rounds will be added after September 2015 as necessary.

Both Nigeria and Pakistan are mopping up in any infected areas. In addition, Nigeria introduced IPV in February 2015, and Pakistan is forecast to introduce IPV in July 2015 in their national routine immunization schedules.

WG comments

The WG acknowledged the significant progress made towards eliminating persistent cVDPV2 in Nigeria and Pakistan. However, it expressed concern over potential ongoing cVDPV2 circulation in Pakistan and requested the program to continue aggressive tOPV rounds especially in infected areas. The WG requested another review of progress of the epidemiology of persistent cVDPV2 status in advance of the face to face meeting in September. Most members of the WG agreed that IPV should be selectively used in addition to OPV in previously inaccessible areas to fully utilize the opportunity to immunize children.

TOPIC 2
Global preparations for OPV2 withdrawal (Decision)

The WG reviewed the different aspects of preparations for the OPV2 withdrawal.

Global IPV supply situation for 2015 and 2016:

Since January 2013, among the 126 tOPV-only using countries, 20 have introduced IPV and the remaining 106 have either formally committed to or have expressed intent to introduce IPV by the end of 2015. There are currently only 2 suppliers of IPV and global IPV supply is extremely tight, due to manufacturing constraints and use in SIAs. The situation is further exacerbated by the request to set aside IPV supply for use in outbreak response campaigns. From a supply perspective, all Tier 1 and 2 countries can introduce IPV in 2015, however given the supply scenario, some Tier 3 and 4 countries will need to postpone IPV introduction to 1Q 2016, but before the anticipated switch date of April 2016. However, should there be additional requests for doses for IPV or problems with production at one of the manufacturers, some Tier 3 and Tier 4 countries may need to postpone introduction to mid-2016.

bOPV licensure for routine immunization:

Out of 149 countries with tOPV in their immunization schedule, 16 have already licensed bOPV, and 102 countries either accept WHO prequalification or have used bOPV in SIAs such that routine use should not represent a major issue. WHO and partners are providing focused support to the remaining 31 countries.

On May 26th 2015, the World Health Assembly (WHA) adopted the resolution that calls on member states to expedite the process of bOPV registration for routine immunization use, and if necessary to authorize bOPV use on the basis of its WHO prequalification while full registration is ongoing. Following the WHA, formal correspondence was sent from WHO to all Ministries of Health. In addition, 3 bOPV manufacturers and fillers (GSK, Sanofi Pasteur, and Panacea) applied for bOPV label change to include routine use, with approval already granted by the Belgian NRA for GSK in June 2015, and approvals expected for Sanofi Pasteur and Panacea, by their respective NRAs, in mid-2015.

mOPV2 stockpile:

The procurement and management of the mOPV2 stockpile has one key objective, which is to have the capacity to rapidly deploy mOPV2 for emergency vaccination in the event of a poliovirus type 2 outbreak. Regarding mOPV2 preparations, two mOPV2 manufacturers have already been contracted to supply 519 million doses in bulk form. This quantity is already available and secured at -40°C. 100 million doses of this bulk is being filled in vials (50 million doses by April 2016, and another 50 million doses before the end of July 2016). The contract with GSK (to fill 50M doses of mOPV2) has already been finalized, and the contract with Sanofi (to fill the additional 50M doses) is currently in progress.

Monitoring strategy for tOPV withdrawal:

The 3 key objectives of monitoring the switch from tOPV to bOPV were outlined: a) to ensure that tOPV is no

longer available for use after the national switch date; b) to assess the performance of the switch; and c) to assess the status of bOPV and IPV introduction at the monitored facilities. Balancing technical rigor with cost/feasibility, the proposed monitoring strategy will focus efforts on visiting all cold chain stores of vaccines down to the district level, where the largest stocks of tOPV are held in-country, and assuring that these stocks have been removed from the cold chain and sent/marked for destruction. At the health facility level (the point of service delivery), a non-random purposive sampling will be conducted (10% of targeted facilities per district), as these facilities typically store stock for about one month. In the event of a finding of opened or unopened vials of tOPV in the cold chain at these visited facilities, an additional 5% of facilities would be visited; if tOPV stocks continue to be found in the cold chain in these additional facilities then the whole district would be swept to identify any remaining tOPV vials.

Containment

In preparation for OPV2 withdrawal in April 2016, all Regions need to update their inventories according to the revised phase I of GAP III, and contain, transfer or destroy WPV2 infectious or potentially infectious material including cVDPV2 by the end of 2015, and all OPV2/Sabin 2 virus by the end of 2016. To facilitate the process, WHO will provide GAP III implementation training to Global Polio Laboratories, vaccine manufacturers, and national oversight bodies. WHO is also finalizing the Containment Certification Scheme (CCS) which provides guidance to stakeholders (facilities, national oversight bodies, RCCs, WHO) on the implementation of containment.

Verification and certification of wild poliovirus type 2 eradication

In March 2015, the six WHO Regional Directors sent communication to all the member states in their respective regions requesting them to present existing data on the last WPV2 detection in country (if any) and requested Ministers to confirm data, or provide additional findings. In September 2015, WHO will organize a meeting of the Global Certification Commission (GCC) to review the evidence submitted to WHO ROs / RCCs, and this will be followed by formal GCC declaration that WPV2 was eradicated > 15 years ago.

WG comments

Overall, the WG is comfortable with the progress with the preparations. It agreed with the proposed approach to manage the tight IPV supply, including prioritizing IPV introduction in Tier 1 and 2 countries, as well as judiciously allocating IPV for SIAs in polio-infected areas and for cVDPV2 outbreak response after type 2 OPV withdrawal.

The WG discussed whether IPV introduction in every country is a pre-requisite for OPV2 withdrawal, and WHO clarified that IPV introduction is one of the criteria to assess readiness for the switch, rather than a pre-requisite per se. The introduction of IPV is a means to reduce the risks associated with VDPVs and other risks of emergence in the medium and longer terms, and it will be important for Tier 1 and 2 (high risk) countries to have introduced IPV by the end of 2015. While the WG agreed that all countries should have introduced IPV by the time of the switch, some members considered that the relatively low risk of cVDPV2 emergence in lower risk countries (Tier 3 and 4 countries) could still be managed adequately if, because of the constraints in IPV supply, a few of them introduced IPV within a short interval after the switch.

The WG endorsed the strategy for monitoring the switch at country level, highlighting the importance of in-country communication to ensure all tOPV vials are collected or destroyed and that health workers understand the importance of not using these vials after the date of the switch. Regarding containment preparations, the WG emphasised that WHO should further strengthen efforts to actively communicate with relevant virological laboratories on GAPIII requirements.

During the face to face meeting in September 2015, the WG requested to review the different aspects of preparation for the OPV type 2 withdrawal in more detail, specifically:

- Epidemiology of persistent cVDPV2 in Nigeria and Pakistan
- IPV introduction status and global IPV supply situation
- Progress report on the implementation of containment plan (including phase I and phase II progress, by Region)
- Revised type 2 outbreak response protocol
- Detailed switch monitoring guidelines

Report of the SAGE Polio Working Group Meeting
7-8 September 2015

The SAGE Polio Working Group met on 7-8 September 2015 in Geneva, Switzerland. This report summarises the group's discussions, conclusions and recommendations.

Background

The Global Polio Eradication Initiative (GPEI) is making strong progress towards polio eradication. In 2015[1], there have been just 39 cases of wild poliovirus (WPV) to date. At this time in 2014, there had been four times as many WPV cases – 169 in total. Since September 2014, WPV has affected only two countries – Pakistan and Afghanistan. The entire African continent has not detected a case of WPV since 11 August 2014. Nigeria, until recently a polio endemic country, has not had a case of WPV since July 2014.

This significant progress has created momentum towards achieving the program's objectives and has increased public and donor confidence in GPEI's ability to fully implement The Polio Eradication and Endgame Strategic Plan 2013-18. To optimize program accountability and ensure success, in June 2015 the Strategy Committee of the GPEI conducted a "midterm review" of the GPEI's progress in implementing the Strategic Plan. The review identified specific priority strategic adjustments that emphasized enhancing surveillance for poliovirus, reaching missed children, preparedness and capacity for outbreak response, and acceleration of activities to implement facility containment of type 2 poliovirus prior to the global withdrawal of type 2 OPV (OPV2). GPEI has taken steps and made investments to implement the strategic adjustments identified by the Mid-term Review.

Context for the withdrawal of type 2 OPV

The last case of type 2 wild poliovirus (WPV2) occurred sixteen years ago, in 1999. Despite this, widespread use of type 2 oral polio vaccine (OPV2) has continued, as a component of trivalent oral polio vaccine (tOPV). Since 1999, this continued use of OPV2 has caused an estimated 100-200 cases of Vaccine Associated Paralytic Poliomyelitis (VAPP) globally per year, accounting for 1600-3200 cases of paralysis between 2000 and 2015[1]. Over the same period OPV2 has also caused 684 known cases of type 2

[1] As of 9 September 2015

circulating vaccine-derived poliovirus (cVDPV2), which occurs when type 2 containing OPV is used in populations with suboptimal coverage, allowing the vaccine virus to be transmitted from one susceptible individual to another, progressively acquiring through mutation the transmissibility and neurovirulence characteristics of wild polioviruses.

A major objective of the Polio Eradication and Endgame Strategic Plan 2013-18 is the globally synchronized withdrawal of OPV2 by switching from trivalent OPV to bivalent OPV (bOPV). Withdrawing OPV2 is a crucial step towards the global eradication of poliovirus. The process of doing so will also provide an opportunity to learn from experience prior to the full withdrawal of all OPVs, which will be possible when wild poliovirus types 1 and 3 have also been certified as eradicated.

Being able to switch from tOPV to bOPV requires extensive preparatory measures to be taken, which have been set out as readiness criteria for the switch[2]. These apply globally, and are:

1) introduction of at least one dose of inactivated poliovirus vaccine into routine immunisation;
2) access to a bivalent oral polio vaccine that is licensed for routine immunization;
3) implementation of surveillance and response protocols for type 2 poliovirus (including constitution of a stockpile of monovalent oral polio vaccine type 2);
4) completion of phase 1 poliovirus containment activities, with appropriate handling of residual type 2 materials; and
5) verification of global eradication of wild poliovirus type 2.

The trigger for setting a definitive date for the withdrawal of OPV2 was set as the absence of all persistent cVDPV2 for at least six months, in addition to attainment of the readiness criteria.

The date for the tOPV-bOPV switch: April 2016

In April 2015, SAGE concluded that progress towards elimination of persistent cVDPV2 was on track, and recommended that all countries and GPEI should plan firmly for April 2016 as the designated date for withdrawal of OPV2. SAGE specified that it would consider delaying OPV2

[2] Sixty-Seventh World Health Assembly (2014); Report by the Secretariat on Poliomyelitis: intensification of the global eradication initiative: http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_38-en.pdf

withdrawal only if the Working Group reports in October 2015 that the assessed risk of persistent cVDPV2 transmission is high[3].

In May 2015, the World Health Assembly commended the progress across Africa and the success of the program in halting three large multi-country outbreaks in the Middle East, Horn of Africa and Central Africa. Member States expressed their full support for the program, adopted a resolution to stop polio, and committed to meeting preparedness criteria for the phased withdrawal of oral polio vaccines starting with the withdrawal of OPV2 in April 2016[4].

The SAGE and the SAGE Polio Working Group (WG) have provided extensive input into the planning of the tOPV-bOPV switch, and have regularly monitored its preparations through teleconferences and meetings.

At its meeting of 7-8 September 2015, the WG reviewed the current epidemiology of cVDPV2 and assessed all readiness criteria. As is set out below, the WG unanimously concluded that the withdrawal of OPV2 with the switch from tOPV to bOPV should go ahead as planned in April 2016, and makes this recommendation to the SAGE.

Current Epidemiology of Type 2 vaccine-derived poliovirus (VDPV2)

VDPV2 circulation: summary table

Virus type	Definition	Status
VDPV2	OPV type 2 virus strains with >= 6 NT changes	In 2014-15, 15 countries have detected 46 emergences; only 4 became cVDPV
cVDPV2	VDPV2 isolates for which there is evidence of person-to-person transmission in the community	12 events in 2010-15 2 events in 2014-15 (South Sudan and Guinea).
Persistent	cVDPV2 strains	Pakistan:

[3] World Health Organization (2015). Meeting of the Strategic Advisory Group of Experts on immunization, April 2015: conclusions and recommendations. World Epidemiological Record. No. 22, 2015, 90, 261–280

[4] Sixty-Eighth World Health Assembly Resolution (2015); Agenda item 15.2 on Poliomyelitis: http://apps.who.int/gb/ebwha/pdf_files/WHA65/A65_R5-en.pdf

VDPV2	that continue to circulate for >= six months following detection	- Eliminated two longstanding lineages that circulated until June 2014 - New emergence of cVDPV2 in July 2014, last detected in March 2015 Nigeria: - Eliminated two longstanding lineages that circulated until March 2015 - New emergence of cVDPV2 in August 2014, last detected in May 2015

Persistent cVDPV2: The longstanding and highly mutated persistent cVDPV2 strains that circulated widely in northern Nigeria and in parts of Pakistan for multiple years have not been detected in AFP cases or environmental samples since March 2015 in Nigeria and since June 2014 in Pakistan. Both countries appear to have successfully eliminated these multiple lineages of persistent cVDPV2 strains which had established longstanding circulation.

There have been, however, two new instances of cVDPV2 emergence that became persistent within the last year – one in Nigeria and one in Pakistan. These new strains emerged in specific pockets with remaining program gaps (Zaria LGA in Kaduna, Nigeria and Gadap Town in Karachi, Pakistan).The first detection of the strain in Pakistan was in an environmental sample in July 2014. A full outbreak response was mounted, and this strain has not been detected since March 2015 in in AFP cases or environmental samples. Although VDPV2 has been detected in three children with AFP in 2015 in Pakistan, these have not shown evidence of circulation and no cVDPV2 case has been detected in Pakistan in 2015. The Nigeria emergence was first detected in an environmental sample in August 2014 and the only case to date was reported in May 2015 from the Federal Capital Territory. A full outbreak response was mounted and the cVDPV2 strain has not been detected since.

VDPV2: In 2014-15, 15 countries have detected 46 separate emergences of VDPV2 in AFP and environmental surveillance[5]. Most of these

[5] As of 9 September 2015

emergences did not become circulating VDPVs (cVDPV2). Only two emergences (in South Sudan and Guinea) evolved into cVDPV2, and two emergences (one in Pakistan and one in Nigeria, as noted above) became persistent cVPDV2.

cVDPV2: Between 2010 and 2015, there were 12 outbreaks of cVDPV2[6] in countries other than Nigeria and Pakistan. Of these, 92% (11/12) were stopped after four SIAs, in less than six months.

The GPEI is currently managing two outbreaks of cVDPV2, one in South Sudan and another in Guinea. In South Sudan, VDPV2 strains linked to isolates from cases detected in September 2014 have not been detected since then and their circulation has likely stopped following the outbreak response. However, a new VDPV2 strain was isolated from a case with onset in June 2015. Given the extent of nucleotide changes and the setting of conflict in South Sudan, a full cVDPV2 outbreak response is being implemented.

The outbreak in Guinea was confirmed this month (September 2015) with the detection of cVDPV2 in a case investigated in Mali. The isolate is genetically linked to a case in Guinea, with onset on 30 August 2014. The GPEI is implementing a full outbreak response in Guinea and adjoining Mali. Surveillance in Guinea had been diminished as a result of the Ebola outbreak – most notably, stool samples could not be shipped out of the country for testing. Testing of samples from Guinea has commenced in June 2015. The infrastructure established to deal with the Ebola outbreak is now being used to support the response to this cVDPV2 outbreak.

Strategies to mitigate the risk of emergence and stop the circulation of Type 2 vaccine-derived poliovirus (VDPV2)

Updated definition for VDPV and program guidelines for responding to VDPV2

VDPV2 are considered in three categories:

- Vaccine-derived poliovirus (VDPV) is defined as an "OPV virus strain that is > 1% divergent (or >= 10 nt changes) for types 1 and 3 or >= 0.6% divergent (>= 6 NT changes) for type 2 from the corresponding OPV strain in the VP1 genomic region".

[6] Excluding two emergences in Nigeria and Pakistan which became persistent cVDPV

- Circulating VDPVs (cVDPVs) are broadly defined as "VDPV isolates for which there is evidence of person-to-person transmission in the community", and are more precisely defined below.
- Persistent cVDPVs are defined as "cVDPVs that continue to circulate for more than six months following detection"[7]. Persistent cVDPVs therefore represent failures in the program to contain the cVDPV outbreak within 6 months of detection.

In July 2015, GPEI revised the definition of cVDPVs, enhancing the sensitivity of the definition of cVDPV. Under the new guidelines cVDPV is defined as:

- Genetically linked VDPVs, isolated:

  i) from at least two individuals – not necessarily acute flaccid paralysis (AFP) cases – who are not household contacts,

  ii) from one individual and one or more environmental surveillance (ES) samples, or

  iii) from two or more ES samples if they were collected at more than one distinct ES collection site (no overlapping of catchment areas), or from one site if collection was more than two months apart[1]

or

- *a single VDPV isolate, with genetic features indicating prolonged circulation (i.e. a number of nucleotide changes from parent Sabin strains suggesting >= 1.5 yrs of circulation or 15 nt changes).*

The program has developed updated guidelines for immediately responding to VDPV2 between August 2015 and OPV2 withdrawal in countries using OPV. In summary, the guidelines emphasize that 1) the response to VDPV2 detection should not wait for classification of the strain as cVDPV2 or iVDPV2; 2) a rapid local response should be implemented to prevent further circulation; 3) immediately 3 mop up rounds with tOPV should be planned and implemented; 4) the first round should commence within 14 days of notification of the VDPV2; 5) the size and geographic scope should be based on risk of spread and estimated duration of circulation; 6) 3 rounds

[7] Global Polio Eradication Initiative (2015). Reporting and classification of vaccine-derived polioviruses: http://www.polioeradication.org/Portals/0/Document/Resources/VDPV_ReportingClassification.pdf

with tOPV should be completed even if the circulation of VDPV is not confirmed.

If the VDPV2 is confirmed as cVDPV, the scope of mopping up SIAs should be further expanded. All areas at risk should be covered in line with the GPEI Standard Operating Procedures for polio outbreak response. A minimum of 2 million children should be covered and tOPV SIAs should continue until 3 rounds have been implemented following the most recent cVDPV2 isolate. The WG also expanded that where 2 million children did not exist within a reasonable radius, all children, or children of 2 million total population could be targeted. The use of IPV should be considered, per existing guidelines.

To mitigate the risk of emergence of new VDPV2 in advance of the OPV2 withdrawal, a further intensified schedule of tOPV SIAs planned between September 2015 and March 2016 was presented to the WG.

WG comments on epidemiology of VDPV2

Persistent cVDPV2: The WG appreciated the strong progress that has been made in both Nigeria and Pakistan, toward improvement of surveillance and quality of immunization campaigns. The overall type 2 population immunity has improved substantially in both countries following increases in quality and frequency of tOPV campaigns supplemented by IPV. The group concluded that both countries appear to have successfully interrupted the transmission of the highly mutated cVDPV2 strains that had established prolonged widespread circulation. The new persistent strains had emerged recently in specific pockets in Kaduna and Karachi with residual gaps in immunization coverage. The group assessed that transmission of these recent persistent cVDPV2 strains has probably been stopped as a result of intensified programme activities.

The WG reviewed the planned Supplementary Immunisation Activity (SIA) schedules of both Nigeria and Pakistan between September 2015 and April 2016. The WG was satisfied that Nigeria's schedule includes sufficient tOPV to appropriately reduce the risk of further cVDPV2 emergence. However, the WG judged that Pakistan's planned schedule was not sufficient in this regard. The WG strongly recommended that Pakistan review its planned tOPV SIA schedule, in close coordination with its TAG, to ensure that the vaccine mix and geographic scope of SIAs will provide sufficient population immunity against emergence of VDPV2 before the switch, as well as for interruption of wild poliovirus transmission. The WG welcomed the

commitment of the Pakistan program to undertake such a review immediately.

VDPV2 emergence: The WG appreciated and endorsed the new definitions for VDPVs and updated guidelines for responding to VDPV2. The group also endorsed the intensified global schedule of SIAs planned to prevent the emergence of new VDPVs around the time of OPV2 withdrawal. Noting the guidelines and plans, the group emphasized the importance of ensuring sufficient supplies of tOPV.

The Working Group noted, however, that the definitive approach to stopping VDPV2 emergences is the coordinated withdrawal of OPV2. Until that time, the risk of VDPV2 emergence and circulation will remain due to insufficient coverage resulting in inadequate population immunity to type 2, particularly in settings of complex emergencies and conflicts where immunization programs are severely disrupted.

Stopping cVDPV2 transmission: The Working Group assessed the risk of continued cVDPV2 transmission at the time of the switch as low because:

- All persistent cVDPV2 transmission has probably been stopped;
- The GPEI has demonstrated its ability to rapidly stop cVDPV2 outbreaks, and has further intensified its approach with new definitions for cVDPV2 and outbreak response guidelines from August 2015.

The Working Group therefore assessed that the remaining risk of cVDPV2 transmission should not stop the tOPV-bOPV switch from proceeding as planned in April 2016.

The Working Group re-emphasised, however, the need for the current cVDPV2 outbreak in Guinea/, and the VDPV2 outbreak in South Sudan to be stopped rapidly, and welcomed the GPEI's work to allocate additional resources to doing so. The group acknowledged that the outbreak response guidelines set a target of stopping such outbreaks within 120 days. It is important that this is achieved. The Working Group also reiterated that, although the intensified tOPV SIA schedule will substantially reduce the probability of VDPV2 emergence, the risk of one or more cVDPV2 outbreaks occurring close to the time of the switch will remain regardless of the date of the switch.

Status of readiness criteria

The WG reviewed the progress of the five readiness criteria:

- **Introduction of at least one dose of inactivated poliovirus vaccine**

  As of September 2015, 105 countries have introduced IPV in their routine immunization program. A global shortage in IPV supply has forced some delays for other countries. However, almost all 126 OPV-using countries (including all Tier 1 and 2 countries) are forecast to introduce IPV prior to the switch. The only exceptions are Indonesia, and 10 other Tier 3 and 4 countries, which intend to introduce IPV after April 2016[8].

- **Access to a bivalent oral polio vaccine that is licensed for routine immunization**

  There are 149 countries and 7 territories currently using OPV (156 total), which need to approve bOPV for use in their routine schedule by the switch date. To date, 55 countries are using bOPV in campaigns and approval for routine use is not anticipated to be an issue. The approval process is on track for completion in time for 93 countries that have not used bOPV yet. The countries in the latter group either accept WHO prequalified products, plan to go to an all-IPV schedule or accept WHO prequalification as a temporary licensure measure while the national licensure/registration process is ongoing. The remaining eight countries do not yet have appropriate regulatory pathways in place for expediting the bOPV licensure. This is particularly an issue in some OPV-producing countries that supply for domestic needs and which request in-country clinical trials for bOPV licensure. For these countries, a transitional contingency involving expedited licensure with WHO support or interim use of imported bOPV is being pursued as part of their switch readiness plan.

  WHO HQ, in collaboration with regional offices and partners, is conducting an intensive program of work with prequalified bOPV manufacturers and national OPV suppliers to coordinate support to

[8] Tier 1: WPV endemic countries OR countries that have reported a cVDPV2 since 2000; Tier 2: Countries who have reported a cVDPV1/cVDPV3 since 2000 OR large/medium sized countries with DTP3 coverage <80% in 2011, 2012, 2013 as per WHO-UNICEF; Tier 3: Large/medium countries adjacent to Tier 1 countries that reported WPV since 2003 OR countries bordering with the current cVDPV2 outbreaks, if not already included in tier 1 and 2, OR countries that have experienced a WPV Importation since 2011; Tier 4: All other OPV only using countries

countries identified at risk and to monitor the approval of bOPV for use in routine immunization before March 2016.

The WG concluded that bOPV approval for use is on track to date. However, the WG emphasised the importance of ensuring that this work is completed in due time as it is absolutely vital that all countries are ready to use bOPV in routine immunisation at the time of the switch.

- **Detection and response protocols for type 2 poliovirus, including constitution of a stockpile of monovalent oral polio vaccine type 2**

  Surveillance: The GPEI has established a surveillance strengthening plan in the high-risk countries of Central and West Africa, including Central African Republic, Gabon, Niger, Mali, Liberia, Guinea, and Sierra Leone. The plan includes capacity building, refresher trainings, strengthening of active surveillance, expansion of environmental surveillance, and programme reviews. In addition, the GPEI has developed specific plans to manage surveillance in difficult-to-access areas (e.g. South Sudan, Somalia, Nigeria, Lake Chad, Afghanistan, Middle East) including engaging NGOs, increasing field presence, conducting contact sampling and stool surveys, focusing on high risk-mobile populations (e.g. internally displaced persons/IDPs, Nomads), and growing the networks of community informants.

- **Outbreak detection and response protocol:** The outbreak detection and response protocol was endorsed by SAGE in October 2014. An update with further refinements to this protocol is now being finalized. The WG reviewed the updates and provided input.

  The updated protocol reflects the change in definition of cVDPV2 described above, and also reflects new scientific evidence on the VDPV2 emergence risk after the switch, on waning mucosal immunity, on the role of IPV, and on the effectiveness of the Short Interval Additional Dose Strategy. The major proposed changes are:

  1) a new definition of VDPV2 outbreaks, aligned with the new VDPV2 definition;
  2) wider use of IPV in outbreak response;
  3) expansion of the scope of the immunization response.

The WG endorsed the updates with the following specific guidance:

1) The definitions and response for confirmed, probable and possible type 2 virus circulation should be segmented between vaccine-derived poliovirus, wild poliovirus, and Sabin viruses.

2) IPV-only response should be considered in selected cases, as below:
    a. Initial response following detection of confirmed cVDPV in zone 3 (areas with low transmission risks) in phase 1 (<1 year after the switch) and for all geographic zones with probable VDPV2 transmission in all phases[9].

    b. Initial response following detection of probable WPV transmission (i.e. detection of WPV in ES) in the absence of evidence of replication in human population (e.g. likely poliovirus release from a facility) for all geographic zones[10] and phases.

    c. Protection of household and immediate community/work contacts for detection of a WPV2 AFP case with known exposure to poliovirus in a facility (e.g. from laboratory exposure) or for detection of new iVDPV2 cases.

The WG recognizes that the development of outbreak response guidelines is an iterative process; it requested the program to review and revise the guidelines after one year of the switch. The WG also suggested highlighting that countries exclusively using IPV prior to the switch will have a different risk pattern than countries that have used tOPV.

The WG also reviewed the results from a regulatory fractional intradermal (ID) IPV study recently conducted among adults in Cuba, comparing immune response rates following a booster dose of ID fractional IPV versus IM full dose IPV. The differences in immune response rates between the study groups met the non-inferiority criteria of <10% at day 7, which was maintained at days 28 and 56

[9] Time since OPV2 cessation: Phase I: within 1yr; Phase 2: 2-3 yrs; Phase 3: 4+yrs
[10] Zone 1 (high risk): Clear history of sustained WPV or reported cVDPV2 since 2000; OR affected community with other risks for low immunity or high mobility links to susceptible communities; Zone 2 (high-medium risk): Consistently low DTP3 coverage <80% in the previous 3 years; OR history of imported WPV or any cVDPV in the previous 3 years; OR with DTP3 coverage <90% and adjacent to affected area; Zone 3 (low risk): DTP3 coverage consistently >80%; affected community with few risk factors for sustained transmission

after booster dose. The WG welcomed the progress of the development of ID IPV as this would mitigate the IPV supply shortage for outbreak response. It also encouraged the GPEI to accelerate the development and introduction of ID IPV devices as ID administration with needle and syringe required highly trained health workers.

mOPV2 stockpile: A global stockpile of mOPV2 is being established and will be maintained after the switch, for potential use in responding to type 2 polio outbreaks following withdrawal of type 2 OPV. The operational framework for the mOPV2 stockpile was approved by the SAGE in October 2014. Since then, the framework has been updated according to the new VDPV2 classification, and the new approach for type 2 outbreak response. A stockpile of 50 million doses of mOPV2 in finished product has been purchased and will be available for deployment by March 2016. An additional 50 million doses to be available by July 2016 are currently under negotiation. GPEI will identify countries that decide to build a national mOPV2 stockpile and ensure the authorities are fully aware of commitments under WHA 68.3 related to storage under appropriate containment and use of mOPV2 only after authorization by the Director General of WHO. The WG welcomed this progress and requested WHO to finalize the stockpile release criteria and establish the expert group that will advise the Director General of WHO on release of mOPV2 in response to type 2 poliovirus detection.

The WG noted that the programme has reserved more than 4 million doses of IPV for use in response to a cVDPV2 detection after the switch.

- **Verification of global eradication of wild poliovirus type 2** After the WG's meeting, on 20-21 September 2015, the Global Certificate Commission (GCC) met to review evidence submitted to WHO and Regional Certification Commissions (RCCs). It concluded that WPV2 has been eradicated globally. Its report will be made available to SAGE at its meeting of 20-22 October 2015. (The recommendation of the SAGE WG – that the tOPV-bOPV switch should go ahead as planned in April 2016 – was based on the assumption that the GCC would declare that indigenous WPV2 has been eradicated).

- **Completion of phase 1 poliovirus containment activities, with appropriate handling of residual type 2 materials**[11]

  To date, inventory of facilities storing or handling WPV has been completed in all countries in AMRO, EURO, SEARO and WPRO, the four regions that have been certified as polio free. However, only 15 of 47 countries in AFRO and 18 of 21 countries in EMRO have completed this inventory. The WG emphasized the importance of these remaining countries urgently completing their inventory. Also, all countries in every region should update national inventories of poliovirus facilities and confirm the number of facilities holding WPV2 and type 2 Sabin material on time for completion of Phase I.

  Poliovirus essential facilities are those which serve essential functions, including IPV and Sabin-IPV production, storage of OPV stockpiles, vaccine quality assurance, diagnostic reagent production, virus diagnostic and reference functions, and/or crucial research. As such, these facilities are nominated and certified by governments[12]. Although the number of designated 'Poliovirus- Essential Facilities' that will hold or handle type 2 poliovirus materials is expected to be less than 50, and in a limited number of countries, the GPEI anticipates challenges in implementation of full containment in phase II[13]. A national regulatory framework for containment needs to be established in countries that decide to host poliovirus-essential facilities; in parallel, national authorities for ensuring facility containment will need to be designated, and international expertise needs to be brought together to help oversee and guide the implementation of containment in essential facilities. Interim risk management measures are therefore being established during this period until full containment is implemented. The SAGE has previously endorsed the principles of the scheme to certify appropriate containment in poliovirus-essential facilities. The scheme will be reviewed and endorsed by the Global Commission for Certification of Polio Eradication in September 2015. The WG stated that the implementation of GAP III must be adequately resourced at all levels from WHO HQ to the regions and countries.

[11] Phase I refers to: Preparation for containment of poliovirus type 2, including national laboratory inventory, destroying un-needed type 2 materials, transferring needed type 2 materials to essential poliovirus facilities, informing governments about upcoming need for poliovirus containment, and certifying designated essential poliovirus facilities for containment

[12] WHO Global Action Plan to minimize poliovirus facility-associated risk (GAPIII): http://www.polioeradication.org/Portals/0/Document/Resources/PostEradication/GAPIII_2014.pdf

[13] Phase II refers to: Poliovirus type 2 containment period, including introduction of at least 1 dose of IPV in routine immunization, implementation of surveillance and response protocol for type 2 poliovirus outbreak, completion of phase I activities and verification of global eradication of WPV2

Rationale for proceeding with tOPV-bOPV switch in April 2016

The SAGE Polio Working Group unanimously recommends to SAGE that the tOPV-bOPV switch proceed, as planned, in April 2016.

Evidence shows that national efforts with support from GPEI have eliminated several persistent cVDVP2 outbreaks in Nigeria and Pakistan, and the more recently identified persistent cVDPV2 outbreaks have probably stopped. GPEI has developed robust strategies and plans to prevent VDPV2 emergence. The program has also demonstrated the ability to rapidly stop cVDPV2 outbreaks.

There has been strong progress towards the achievement of readiness criteria. Although these have not yet all been met in full, the WG assesses that there are no critical gaps, and that the gaps that do exist are clear to the GPEI and are being addressed and/or mitigated.

The WG judges that it is appropriate to proceed despite the readiness criteria not being met in full. The tOPV-bOPV switch can never be risk-free, and determining whether or not to proceed requires a balanced judgement of risk.

One key risk applies regardless of whether the switch proceeds in April 2016 or is delayed:

- VDPV or cVDPV outbreaks: The GPEI may not be able to stop a new outbreak just before the date of the switch, although the tOPV SIAs planned between now and April 2016 should significantly help to prevent outbreaks before and after the switch. The post-switch outbreak response protocol covers the management of any outbreaks that occur. Because VDPV emergence will continue until OPV2 use is stopped, this risk will likely not be reduced by delaying the switch rather than by proceeding with it as planned.

One potential risk of proceeding in April 2016 is:

- Full containment measures are currently behind schedule. Delaying the switch would allow an additional year to make progress. The WG, however, is of the opinion that facility-associated risks of poliovirus transmission can be reduced substantially with full implementation of Phase I of GAP III, including destruction of WPV2 by end 2015 and other residual type 2 materials by July 2016.

The main additional risks of the alternative – delaying the switch to April 2017 – are:

- Historical experience suggests that delaying the switch by a year will result in an additional 100-200 children being paralysed by VAPP, and a smaller additional number of children being paralysed by new cVDPV2 outbreaks. Continuing use of the type 2 component of OPV is hard to justify since there have been no WPV2 cases naturally occurring since 1999.
- The GPEI currently has an unprecedented level of capacity, which will begin to diminish by April 2017. In particular, the current surveillance and outbreak capacity in Africa has been heightened as part of the intensive program to stop WPV transmission, but cannot be maintained indefinitely. Thus the program's ability to detect and stop pre- and post-switch cVDPV2 outbreaks would be reduced.
- The conditions in which the GPEI is currently operating could deteriorate, making stopping pre-switch cVDPV outbreaks more difficult. This is particularly relevant in Nigeria and Pakistan, where a period of relatively stable operating conditions has enabled the GPEI to stop several strains of persistent cVDPV2 recently. Immunization programs continue to be disrupted in several regions, particularly affecting countries in the Middle East, Horn of Africa and Central Africa and in Ukraine, increasing the risk of emergence and circulation of VDPV2.
- Based on the clear advice of SAGE, countries are well-prepared for the April 2016 switch. Preparation has required significant financial and political investment. If the switch was now delayed, the delayed switch date would have less credibility and therefore readiness for it may well be reduced. There is also the risk of program losing credibility with countries, its donors and other stakeholders.

The Working Group assessed that the risks of delaying the switch significantly outweigh the risks of proceeding with it as planned. However, it must be reinforced that:

- The tOPV-bOPV switch can never be risk-free, and the risks outlined above must be carefully managed
- In particular, stopping current cVDPV2 outbreaks, implementing the intensified tOPV SIA schedule and the acceleration of containment measures are vital, as detailed below.

Recommendations for additional risk-reducing measures

In conclusion, the WG recommends proceeding with the tOPV-bOPV switch in April 2016.

Three particular areas of risk have been highlighted in this report, and are repeated here in summary:

Pakistan SIA schedule: The WG was not satisfied that Pakistan's planned Supplementary Immunisation Activity (SIA) schedule between September 2015 and April 2016 includes sufficient tOPV to appropriately reduce the risk of further cVDPV2 emergence. The WG strongly recommends that Pakistan review its planned schedule, in close coordination with its TAG, to ensure that the vaccine mix and geographic scope of SIAs will provide sufficient population immunity against VDPV2 before the switch. The WG welcomed the intention of the Pakistan program to undertake such a review immediately.

Current outbreaks: The WG recommends that the GPEI ensures that a full outbreak response is mounted to interrupt the new cVDPV2 outbreak in Guinea, and the current cVDPV2 outbreak in South Sudan, within the period of 120 days that the Polio Eradication and Endgame Strategic Plan specifies.

Containment: The primary purpose of implementing GAPIII is to reduce the risk of release and subsequent circulation of poliovirus from facilities that store or handle poliovirus. The WG recommended that the GPEI now:

- accelerate the implementation of phase I of GAPIII, including: a) all countries complete phase I, and b) focal points in all regions closely monitor country level activities and ensure that each country completes and updates its inventories of facilities that hold or handle polioviruses, have destroyed or commits to destroying WPV2 by end 2015 and any other type 2 materials including Sabin poliovirus by July 2016;

- develop a targeted advocacy plan to engage countries that have not responded or will be late in completing phase I;

- develop an intensified communications plan to ensure that countries and key stakeholders and actors take necessary actions taking into consideration the recent WHA resolution and the confirmation by SAGE of April 2016 as the date for OPV2 withdrawal – a global landmark. The communication should also guide actions by research

and academic facilities that store clinical samples that may be potentially contaminated with WPV or Sabin 2 poliovirus;

- identify any remaining risk of delay in phase I, and rapidly develop an interim risk management plan to address them; and

- develop a separate advocacy plan for countries that plan to host poliovirus-essential facilities to ensure establishment of national regulations and authorities to assure compliance with regulations on containment.

Given the global impact and reach of the decisions made, as well as the fluidity of the programmatic and epidemiological situation, the WG agreed to meet in January 2016 to review the progress of implementation of the aforementioned recommendations.

Poliomyelitis

The Sixty-eighth World Health Assembly,

Having considered the report on poliomyelitis[1] and the course of action decided by the Executive Board at its 136th session;[2]

Recalling resolution WHA65.5 on poliomyelitis: intensification of the global eradication initiative, and that the Sixty-sixth World Health Assembly noted the Polio Eradication and Endgame Strategic Plan 2013–2018 and reviewed progress towards its implementation subsequently;[3]

Recalling that on 5 May 2014, the Director-General declared the international spread of wild poliovirus a public health emergency of international concern and issued temporary recommendations under the International Health Regulations (2005);[4]

Noting that more than 85% of all new cases in 2014 and 2015 have occurred in Pakistan, and commending the heroic efforts of the front-line health workers, Government, people and civil and religious leaders of Pakistan for their strengthened commitment to polio eradication, as evidenced by efforts to implement the low-transmission season plan for the first half of 2015, while faced with unique challenges;

Recalling United Nations General Assembly resolution 69/132 on global health and foreign policy, which "urges full respect for the rules and principles of international humanitarian law … [and] stresses the obligation … to respect and protect medical personnel and humanitarian personnel … and urges States to develop effective measures to prevent and address violence against such personnel";

Recognizing the conclusions of the meeting of the Strategic Advisory Group of Experts on immunization (Geneva, 21–23 October 2014) that preparations are on track for the global withdrawal of the type 2 component in oral poliovirus vaccine in April 2016; and, noting the progress achieved in introducing inactivated poliovirus vaccine by end-2015, in particular in coordination with partners such as The GAVI Alliance,

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[1] Document A68/21.

[2] See the summary record of the Executive Board at its 136th session, seventh meeting.

[3] See document WHA66/2013/REC/3, summary record of Committee A, ninth meeting, section 2.

[4] WHO statement on the meeting of the International Health Regulations Emergency Committee concerning the international spread of wild poliovirus, available at http://www.who.int/mediacentre/news/statements/2014/polio-20140505/en/ (accessed on 16 March 2015).

1. URGES Member States with poliovirus transmission:

(1) to stop all wild poliovirus transmission by fully implementing all strategic approaches outlined in the Polio Eradication and Endgame Strategic Plan 2013–2018 and national emergency action plans;

(2) to ensure that all necessary measures are in place for the safe access of health workers to all communities and ensure the safety of health workers, including through the appropriate engagement with and support of community leaders and relevant law-enforcement, military, non-military and non-State entities;

(3) to implement fully the temporary recommendations under the International Health Regulations (2005) in order to reduce the risk of international spread of wild poliovirus;

(4) to intensify cross-border collaboration for improving both vaccination and surveillance activities;

2. URGES all Member States that currently use oral poliovirus vaccine to prepare for the global withdrawal of the type 2 component of the oral poliovirus vaccine in April 2016, including by:

(1) developing national plans, by end-September 2015, for the withdrawal of the type 2 component of oral poliovirus vaccine and its replacement with the bivalent oral poliovirus vaccine;

(2) expediting the registration of bivalent oral poliovirus vaccine for use in routine immunization programmes and, if required and in the interim, authorizing its use on the basis of prequalification granted by WHO;

(3) implementing national policy for the appropriate destruction of residual trivalent vaccine stocks;

(4) completing the introduction of inactivated poliovirus vaccine optimally before the withdrawal of the type 2 component of oral poliovirus vaccine in April 2016;

3. URGES all Member States:[1]

(1) to achieve and maintain certification-standard surveillance to detect polioviruses, and to respond fully to polioviruses detected from any source;[2] to immediately put in place national public health emergency measures, as appropriate, to respond to a new polio outbreak in a polio-free country following confirmation of detection of any circulating wild poliovirus, type 2 circulating vaccine-derived poliovirus or Sabin poliovirus following withdrawal of the type 2 component in the oral poliovirus vaccine; and by ensuring full implementation of revised

[1] And, where applicable, regional economic integration organizations.

[2] For example, any positive sample from a case of acute flaccid paralysis or its contacts, environmental surveillance, and targeted stool surveys.

outbreak response protocols[1] that build on the international outbreak response guidelines issued in resolution WHA59.1;

(2) to support the global expansion of environmental surveillance in strategically-selected high-risk locations to supplement acute flaccid paralysis surveillance for prompt detection of polioviruses;

(3) to support those Member States experiencing poliovirus transmission in their eradication efforts, including through political engagement and the provision of additional support as appropriate;

(4) to monitor for potential gaps in population immunity and implement measures to fill such gaps and further boost population immunity through timely and complete routine immunization and, where necessary, high-quality supplementary immunization activities;

(5) to make available urgently the financial resources required for the full and continued implementation of the Polio Eradication and Endgame Strategic Plan 2013–2018, including through the rapid and full operationalization of pledged funds and the filling of the remaining funding gap;

(6) to lead the development of national plans to ensure that polio assets, lessons learnt and knowledge acquired are applied to support other national health priorities, notably to routine immunization, and ensure that the potential legacy of polio eradication is fully realized;

(7) to implement appropriate containment of type 2 wild polioviruses in essential facilities by the end of 2015 and of type 2 Sabin poliovirus within three months of global withdrawal of the type 2 component in oral poliovirus vaccine in April 2016;[2]

(8) to establish procedures to authorize the importing and use of monovalent oral poliovirus vaccine type 2 from the global stockpile after its release has been authorized by the Director-General in the event of an emergency; whereas the Strategic Advisory Group of Experts on immunization has advised to maintain only a global stockpile of monovalent oral poliovirus vaccine type 2, Member States that decide to establish a national stockpile of this vaccine should maintain the stockpile in conditions of containment that are verified by the Regional Certification Commission for Polio Eradication to be compliant with the containment Global Action Plan,[2] and seek authorization of the Director-General of WHO before its release and use;

4. REQUESTS the Director-General:

(1) to continue to collaborate with all relevant actors, governments and administrators, in partnership with other organizations in the United Nations system and local and international nongovernmental organizations, to support national efforts for polio eradication to benefit children in all areas;

[1] Responding to a poliovirus outbreak. Standard operating procedures for a new polio outbreak in a polio-free country (February 2015), available at: http://www.polioeradication.org/Portals/0/Document/Resources/PolioEradicators/1a.PolioOutbreakGuideline20150220.pdf, (accessed 17 March 2015).

[2] WHO global action plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of OPV use. Geneva: World Health Organization; 2014, available at: http://www.polioeradication.org/Portals/0/Document/Resources/PostEradication/GAPIII_2014.pdf, (accessed 17 March 2015).

(2) to continue to coordinate with all relevant partners, including vaccine manufacturers, to ensure that Member States are fully supported for a globally-coordinated phased removal of oral poliovirus vaccines from all immunization programmes, beginning with the type 2 component in oral poliovirus vaccine in April 2016, including by ensuring a sufficient global supply of inactivated poliovirus vaccine for use in all countries introducing the vaccine in their routine immunization schedules;

(3) to ensure that prequalification of bivalent oral poliovirus vaccine for use in routine immunization programmes is done expeditiously in order to support its introduction by Member States;

(4) to establish a mechanism that assures the Director-General's authority for the release of a global stockpile of monovalent oral poliovirus vaccine type 2[1] in a timely and equitable way to all Member States, and develop a procedure for authorization of release by the Director-General and for use of monovalent oral poliovirus vaccine type 2 by the countries that maintain national stockpiles of this vaccine;

(5) to support Member States,[2] partners and stakeholders in developing plans that ensure that polio assets, lessons learnt and knowledge acquired are applied to support the broad immunization agenda and other health priorities and that the potential legacy of polio eradication is fully realized;

(6) to report annually up to the Seventy-second World Health Assembly on progress made towards achieving a lasting polio-free world, and to provide timely and transparent financial information, including details of any budgetary constraints or changes that could adversely affect full implementation of the Polio Eradication and Endgame Strategic Plan 2013–2018.

Ninth plenary meeting, 26 May 2015
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[1] Operational Framework for Monovalent Oral Poliovirus Type 2 (mOPV2) deployment and replenishment (during the endgame period), available at: http://www.polioeradication.org/Portals/0/Document/Resources/PostEradication/mOPV2_Operational_Framework.pdf (accessed 5 May 2015).

[2] And, where applicable, regional economic integration organizations.

Containment of Polioviruses

What is containment?

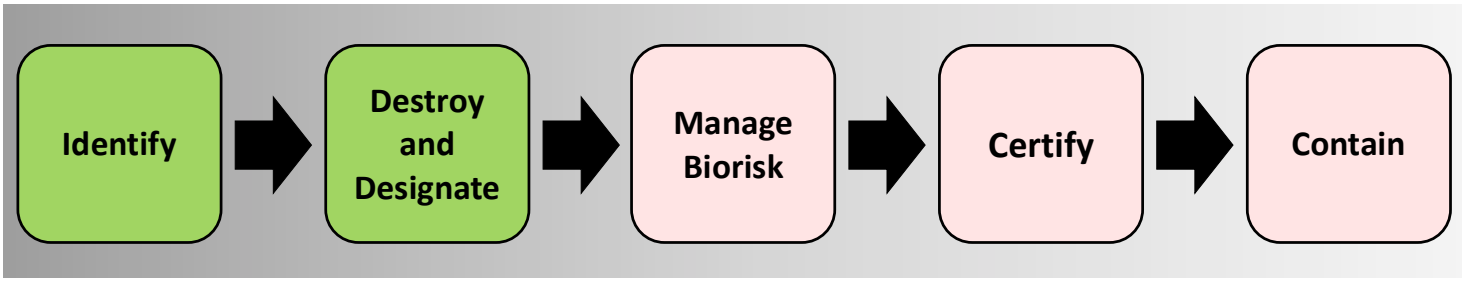
Poliovirus (PV) containment is a system for confining PV within a defined space.

Why must PV be contained?

Once polio is eradicated, laboratories and polio vaccine production sites handling or storing must minimize the risk of PV reintroduction into the community.

What must countries do to contain PV before the switch?

Poliovirus containment requirements are detailed in the WHO Global Action Plan III (GAPIII).



Identify
All countries survey all biomedical facilities to identify infectious or potentially infectious WPV2 materials and develop a national inventory of facilities that handle and/or store WPV2 materials.

Destroy and Designate
Countries request facilities to destroy all unneeded WPV2 material, and designate poliovirus-essential facilities (PEFs) that will store needed WPV2 materials following the requirements described in GAPIII.

Countries submit a report on the inventory, destruction and designation of PEFs to WHO through their Regional Certification Commission (RCC).

It is expected that most countries and facilities worldwide will destroy PV materials, and only a limited number of facilities in a limited number of countries will be designated as PEF.

Manage biorisk
Countries request facilities that store PV2 to implement Annex 2/3 of GAPIII. Countries request facilities that are likely to investigate new PV2 isolates to implement a non-retention policy for PV2, and Annex 6 of GAPIII.

Certify
National authorities for containment (NACs) apply the WHO GAPIII Containment Certification Scheme (CCS) to certify PEFs against GAPIII. Countries seek approval of certification from the global oversight body for containment (Global Certification Commission, GCC).

Contain
Certified PEFs handling and storing PV must implement and be regularly (e.g. annually) reassessed against GAPIII.

How will the GAPIII be implemented?

The global strategy for minimizing poliovirus (PV) facility-associated risk is implemented in 3 phases:

Phase I	Reduce the number of facilities containing PV2 before (WPV2) or shortly after (OPV2/Sabin2) OPV2 withdrawal
Phase II	Ensure appropriate containment of PV2 in PEFs until certification of eradication of all WPV
Phase III	Ensure appropriate containment of all types of PV after certification of eradication of all WPV

What is the progress towards Phase I completion?

AMRO, EURO, SEARO, WPRO

- All countries completed WPV inventories in the past
  → WPV2 inventory updates and PV-essential facility designations due by end-Sept (SEARO, WPRO), end-Nov (EURO) and end-Jan (AMRO)
- Considering PV-essential facility designations for laboratories, IPV or s-IPV producers: **42** estimated

AFRO & EMRO

- 15/47 (AFRO) and 18/21 (EMRO) countries completed inventories in the past
  → WPV2 inventories and PV-essential facility designations due by end-November
- Considering PV-essential facilities designations for s-IPV producers: **1** estimated

How does WHO support the timely completion of Phase I?

- **Global Work Plan**: a global work plan has been developed to accelerate the implementation of Phase I that includes specific activities, priorities, timelines for progress monitoring, and the identification of additional resources. Under this plan, human resources have already been increased in HQ, EURO, EMRO, and AFRO in support of containment implementation activities.
- **Communications**: a communications' strategy and work plan is being prepared to roll out a major communication drive immediately after SAGE to inform and engage all stakeholders.
- **Advocacy**: an advocacy work plan is being prepared that includes high-level engagement with countries at risk of not meeting the expected deadlines.

What has slowed down preparations for implementation of containment in Phase II?

- At national level:
  - In many concerned countries, national authorities for containment (NACs) with responsibility to certify containment against GAPIII still need to be designated
  - Most concerned countries still need to develop appropriate national containment regulations that are aligned with GAPIII
  - Technical expertise to support activities needs to be developed

- At laboratory or manufacturing facility level:
  - The implementation of GAPIII is not a regulatory requirement
  - Technical expertise, financial resources and time still need to be identified to support the appropriate implementation of GAPIII requirements

How does WHO support the implementation of containment in Phase II?

- **Advocacy**: An advocacy plan that targets the countries planning to host PV-essential facilities is being developed. The advocacy will target all relevant sectors of government (beyond health) to ensure buy-in and implementation;
- **Risk Management**: The Containment Certification Scheme (CSS) for the certification of PEFs was endorsed by the Global Commission for the Certification of Poliomyelitis Eradication (GCC) in September 2015. In order to effectively manage risks until full implementation of containment is completed, interim certification of containment is proposed.
- **Consultation and Training**: Consultations with IPV manufacturers and the NACs of their hosting countries are planned to address next steps. GAPIII implementation training for candidate PEFs and NACs will continue.
- **Verification of certified PV-Essential Facilities**: A Global Containment Advisory Group (GCAG) will be established to advise GCC on approving national certification against GAPIII provisions, as well as to ensure effective procedures are established and maintained for certification processes to function appropriately across sectors and geographies.

Plans for containment of poliovirus following type-specific polio eradication worldwide, 2015

Nicoletta Previsani,[a] Rudi Tangermann,[a] Graham Tallis,[a] Hamid Jafaria[a]

In 1988, the World Health Assembly (WHA) resolved to eradicate polio worldwide. In 2015, only Afghanistan and Pakistan have reported wild poliovirus (WPV) transmission.[1] Timely steps are needed for the containment of WPV and oral poliovirus vaccine (OPV)/Sabin virus materials in laboratories and vaccine manufacturing facilities. On 25 May 2015, all WHO Member States endorsed WHA resolution 68.3[2] on the full implementation of *the Polio Eradication and Endgame Strategic Plan 2013–2018*[3] (the Endgame Plan), and with it, the third Global Action Plan to minimize poliovirus facility-associated risk[4] (GAPIII). All Member States committed to implementing appropriate containment of type 2 WPV (WPV2) in essential facilities by the end of 2015 and of type 2 Sabin poliovirus (Sabin2) within 3 months of withdrawal of the type 2 component in OPV (OPV2) globally, planned for April 2016.[5] This report summarizes critical steps for essential laboratory and vaccine production facilities that intend to retain materials confirmed to contain or potentially containing type-2 WPV andvaccine-derived poliovirus (VDPV), or OPV/Sabin viruses as of the "Poliovirus type 2 containment period" (Phase II) planned to begin in 2016 and for facilities that may isolate polioviruses after initiation of Phase II. National authorities will need to certify that the essential facilities they host meet the containment requirements described in GAPIII. After certification of WPV eradication, the use of all OPV will cease; final containment of all polioviruses will minimize the risk of reintroduction of poliovirus into a polio-free world.

Background

The Endgame Plan[3] set the goal of eradicating wild poliovirus as well as VDPVs. Achieving this goal requires: (i) detection of circulating polioviruses and interruption of transmission; (ii) sequential cessation of the use of OPV to eliminate the risks for vaccine-associated paralytic poliomyelitis (VAPP),[6]

[1] See No. 21, 2015, pp. 253–258.

[2] WHA68.3. Available at http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R3-en.pdf; accessed on July 2015.

[3] Polio Eradication and Endgame Strategic Plan 2013–2018. Available at http://www.polioeradication.org/resourcelibrary/strategyandwork.aspx

[4] WHO Global Action Plan to minimize poliovirus facility-associated risk after types-pecific eradication of wild polioviruses and sequential cessation of OPV use. Geneva: World Health Organization, 2014. Available at http://www.polioeradication.org/Portals/0/Document/Resources/PostEradication/GAPIII_2014.pdf; accessed on July2015.

[5] See No. 27, 2015, pp. 337–342.

[6] Platt KR, Estivariz CF, Sutter RW. Vaccine-associated paralytic poliomyelitis: A review of the epidemiology and estimation of the global burden. J Infect Dis 2014:201:S380-9.

Plans pour le confinement des poliovirus après l'éradication de la poliomyélite par type spécifique à l'échelle mondiale, 2015

Nicoletta Previsani,[a] Rudi Tangermann,[a] Graham Tallis,[a] Hamid Jafaria[a]

En 1988, l'Assemblée mondiale de la Santé (WHA) a pris la résolution d'éradiquer la poliomyélite à l'échelle mondiale. En 2015, seuls l'Afghanistan et le Pakistan avaient signalé la transmission de poliovirus sauvages (PVS).[1] Il faudra prendre des mesures en temps utile pour confiner les PVS et les matériels contenant une souche virale du vaccin antipoliomyélitique oral (VPO)/virus Sabin dans des laboratoires et des installations de production des vaccins. Le 25 mai 2015, tous les États ont approuvé la résolution WHA68.[2] concernant la mise en œuvre dans son intégralité du *Plan stratégique pour l'éradication de la poliomyélite et la phase finale 2013 2018*[3] (Plan pour l'assaut final) et, avec elle, le troisième Plan d'action mondial visant à réduire au minimum le risque d'exposition au poliovirus sauvage associé aux établissements[4] (GAPIII). Tous les États Membres se sont engagés à mettre en œuvre le confinement approprié des poliovirus de type 2 (PVS2) dans des établissements essentiels d'ici à la fin de l'année 2015 et les poliovirus Sabin de type 2 (Sabin 2) dans un délai de 3 mois à compter du retrait de la composante de type 2 du vaccin antipoliomyélitique oral (VPO2) à l'échelle mondiale, prévu en avril 2016.[5] Le présent rapport récapitule les étapes critiques pour les laboratoires et les installations de production essentiels ayant l'intention de conserver des matériels susceptibles de contenir ou dont il est confirmé qu'ils contiennent des PVS2 et des poliovirus dérivés d'une souche vaccinale (PVDV) ou des souches virales entrant dans la composition du VPO/vaccin Sabin, à partir de la « phase de confinement des poliovirus de type 2 » (phase II), dont le début est prévu en 2016, et pour les établissements susceptibles d'isoler des poliovirus après le lancement de la phase II. Les autorités nationales devront certifier que les établissements essentiels installés sur leur territoire remplissent les exigences de confinement décrites dans le document GAPIII. Après certification de l'éradication des PVS, tous les VPO cesseront d'être utilisés; le confinement final de tous les poliovirus réduira au minimum le risque de réintroduction de poliovirus dans un monde exempt de poliomyélite.

Généralités

Le Plan pour l'assaut final[3] fixe comme objectif d'éradiquer les poliovirus sauvages et les PVDV. Réaliser cet objectif nécessite: 1) la détection des poliovirus circulants et l'interruption de la transmission; 2) l'arrêt séquentiel de l'utilisation du VPO pour éliminer les risques de poliomyélite paralytique associée au vaccin (PPAV),[6] d'infection chro-

[1] Voir N° 21, 2015, pp. 253-258.

[2] WHA68.3. Disponible sur http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R3-fr.pdf; consulté en juillet 2015.

[3] Plan stratégique pour l'éradication de la poliomyélite et la phase finale 2013-2018. Disponible sur http://www.polioeradication.org/resourcelibrary/strategyandwork.aspx; consulté en juillet 2015.

[4] WHO Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of OPV use. Geneva: World Health Organization, 2014. Disponible sur http://www.polioeradication.org/Portals/0/Document/Resources/PostEradication/GAPIII_2014.pdf; consulté en juillet 2015.

[5] Voir N° 27, 2015, pp. 337-342.

[6] Platt KR, Estivariz CF, Sutter RW. Vaccine-associated paralytic poliomyelitis: A review of the epidemiology and estimation of the global burden. J Infect Dis 2014:201:S380-9.

chronic VDPV infections of immunodeficient persons (iVDPV), and outbreaks of circulating VDPV (cVDPV);[7,8] and (iii) implementation of measures for the safe handling and containment of polioviruses to minimize the risks for facility-associated reintroduction of virus into polio-free communities.

The first step towards OPV cessation will be the withdrawal of OPV2, which has caused >90% of cVDPV cases since WPV2 was last reported in 1999. OPV2 withdrawal will be accomplished by replacing trivalent OPV (tOPV) with bivalent OPV (bOPV, protecting against types 1 and 3 in all countries using OPV for routine immunization.The introduction of at least one dose of inactivated poliovirus vaccine (IPV) will helpprotecti against all 3 virus types.[5] The final confirmation of April 2016 as the date for the switch from tOPV to bOPV is expected when a number of readiness criteria are met, including the implementation of Phase I poliovirus containment activities, with appropriate handling of residual type 2 materials (Phase II), as described below.

Methods

The Endgame Plan includes phased withdrawal of OPV strains. GAPIII was aligned to the Endgame Plan and describes the "Preparation for containment of poliovirus type 2" lasting until end-2015 (Phase I), the "Poliovirus type 2 containment period" lasting until regional certification of WPV elimination (Phase II), and the "Final poliovirus containment" (Phase III) (*Figure 1*). Countries are currently tasked with completing Phase I and preparing for the Phase II poliovirus containment activities of GAPIII (*Table 1*), referring to the need for all countries to:

- identify WPV2 and OPV2/Sabin 2 infectious and potentially infectious materials;
- destroy, transfer, or contain WPV2 infectious or potentially infectious materials (including VDPV2) by the end of 2015;
- destroy, transfer, or contain OPV2/Sabin 2 infectious or potentially infectious materials by July 2016.

The controls described in GAPIII have been developed to reflect current biocontainment best practices. These controls are largely derived from the CEN Workshop Agreement CWA15793 (2011) – Laboratory biorisk management,[9] which has recently entered the International Organization for Standardization (ISO) process. GAP III is a product of extensive review and inputs by leaders in the field of poliovirus transmission as well as biorisk.

[7] Burns CC, Diop OM, Sutter RW, Kew OM. Vaccine-derived polioviruses. J Inf Dis 2014;210:S283-93.

[8] See No. 25, 2015, pp. 309–320.

[9] CEN Workshop Agreement CWA15793 (2011) – Laboratory biorisk management available at http://www.uab.cat/doc/CWA15793_2011; accessed on July 2015.

nique par des PVDV chez les personnes immunodéficientes (PVDVi) et de flambée de PVDV circulant (PVDVc);[7,8] et 3) la mise en œuvre de mesures permettant la manipulation et le confinement sans risque des poliovirus en vue de réduire au minimum le risque de réintroduction de virus associé aux établissements dans des collectivités exemptes de poliomyélite.

La première étape vers l'arrêt du VPO sera le retrait du VPO2, qui a été à l'origine de >90% des PVDVc depuis le dernier signalement d'un PVS2 en 1999. Le retrait du VPO2 s'effectuera en remplaçant le vaccin VPO trivalent (VPOt) par le VPO bivalent (VPOb), protégeant contre les types 1 et 3 dans tous les pays utilisant le VPO pour la vaccination systématique. L'introduction d'au moins une dose de vaccin antipoliomyélitique inactivé (VPI) aidera à la protection contre les 3 types de virus.[5] On s'attend à ce que l'approbation finale confirmant en avril 2016 soit la date à laquelle le passage du VPOt au VPOb soit accordée, lorsqu'un certain nombre de critères seront remplis, dont la mise en œuvre des activités de confinement des poliovirus de phase I, avec une manipulation appropriée des matériels de type 2 résiduels (phase II), comme indiqué ci-après.

Méthodes

Le Plan pour l'assaut final inclut le retrait en plusieurs phases des souches entrant dans la composition du VPO. Le plan GAPIII a été aligné sur le Plan pour l'assaut final et décrit la «préparation du confinement des poliovirus de type 2» jusqu'à la fin 2015 (phase I), la «période de confinement des poliovirus de type 2» se poursuivant jusqu'à la certification régionale de l'élimination des PVS (phase II) et le «confinement final des poliovirus» (phase III) (*Figure 1*). Les pays ont actuellement reçu pour missions d'achever la phase I et de se préparer aux activités de confinement des poliovirus de la phase II prévues par le document GAPIII (*Tableau 1*), faisant référence à la nécessité pour tous les pays:

- d'identifier les matériels infectieux ou potentiellement infectieux contenant des PVS2 ou une souche virale entrant dans la composition du vaccin VPO2/Sabin 2;
- de détruire, transférer ou confiner les matériels infectieux ou potentiellement infectieux contenant des PVS2 (y compris les PVDV2) d'ici à la fin de l'année 2015;
- de détruire, transférer ou confiner les matériels infectieux ou potentiellement infectieux contenant une souche vaccinale entrant dans la composition du VPO2/Sabin 2 d'ici à juillet 2016.

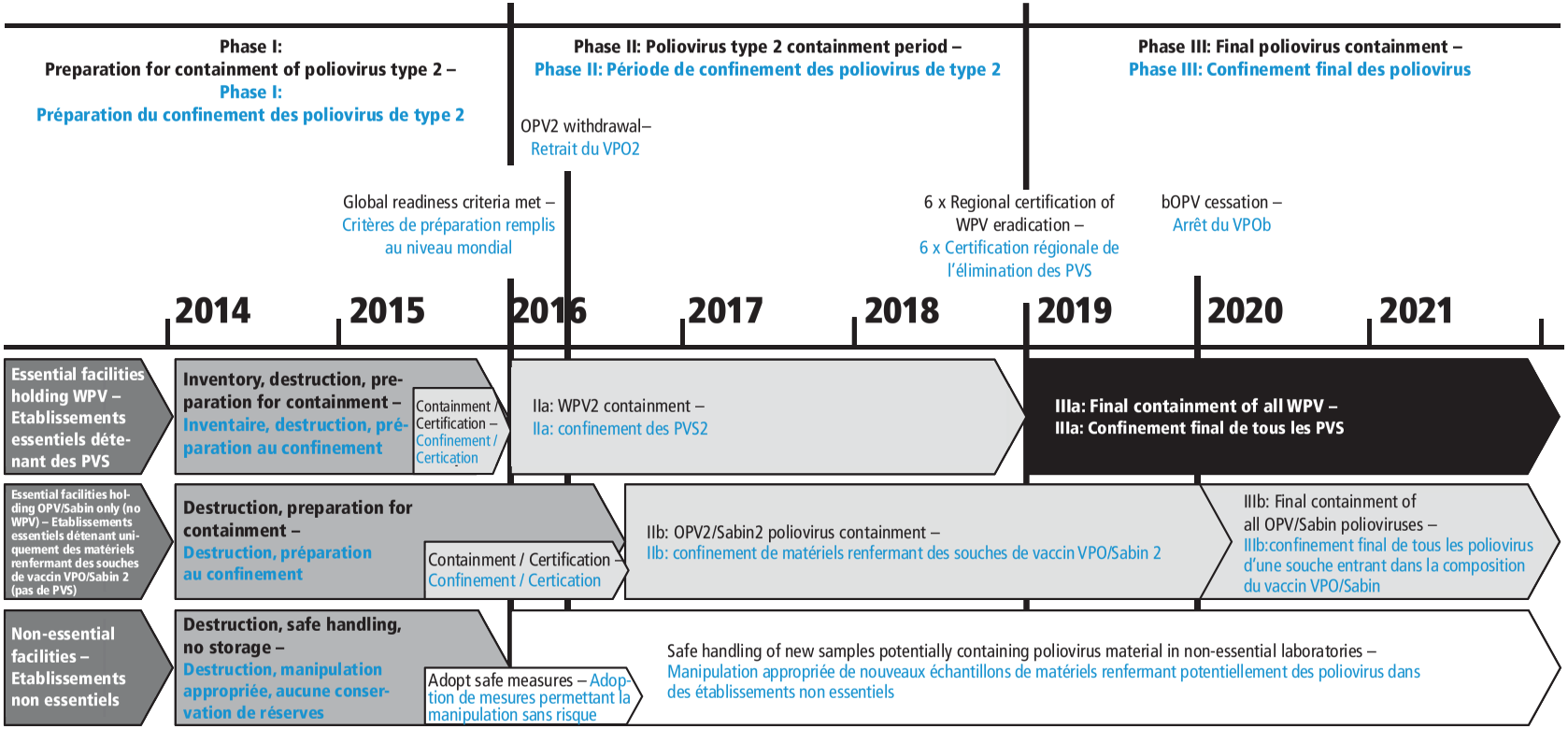
Les contrôles décrits dans le document GAPIII ont été conçus pour correspondre aux meilleures pratiques actuelles en matière de confinement biologique. Ces contrôles s'inspirent largement de l'Accord d'atelier du CEN 15793 (2011) – «*Laboratory biorisk management*»,[9] récemment entré dans le processus ISO (Organisation internationale de normalisation). Le document GAPIII est le produit de l'examen approfondi et des commentaires des principaux spécialistes dans les domaines de la transmission des poliovirus et de la gestion des risques biologiques.

[7] Burns CC, Diop OM, Sutter RW, Kew OM. Vaccine-derived polioviruses. J Inf Dis 2014;210:S283-93.

[8] Voir N° 25, 2015, pp. 309-320.

[9] Accord d'atelier du CEN CWA15793 (2011) – Laboratory biorisk management. Disponible sur http://www.uab.cat/doc/CWA15793_2011, consulté en juillet 2015.

Figure 1 **Schematic diagram of the phased poliovirus containment by type of facility, with expected associated timeline 2014–2021**
Figure 1 **Diagramme schématique du confinement par phases des poliovirus selon le type d'établissement (échéance attendues: 2014-221)**



No containment – Pas de confinement

Adoption of safe-handling measures – Mise en place de mesures permettant la manipulation sans risque des poliovirus

Containment of WPV2, OPV2/Sabin2; final containment of all OPV/Sabin polioviruses – Confinement des PVS2 et de matériels renfermant des souches de vaccin VPO/Sabin 2; confinement final de tous les poliovirus d'une souche entrant dans la composition du vaccin VPO/Sabin

Final containment of all WPV – Confinement final de tous les PVS

Global readiness criteria for OPV2 withdrawal: – Critères de préparation à l'échelle mondiale au retrait du VPO2:

1. **IPV:** Introduction of at least one dose of IPV; – **VPI:** l'introduction d'au moins une dose de VPI;
2. **bOPV:** Access to a bivalent oral polio vaccine that is licensed for routine immunization; – **VPOb:** accès au vaccine VPO bivalent qui est homologué pour la vaccination de routine;
3. **Surveillance and stockpile:** Implementation of surveillance and response protocols for type 2 poliovirus (including constitution of a stockpile of mOPV2); – **Surveillance and réserves:** mise en place de de protocols de surveillance et de réponse pour les poliovirus de type (y compris la constitution d'une réserve de VPOm2);
4. **Containment:** Completion of Phase I poliovirus containment activities, with appropriate handling of residual type 2 materials; – **Confinement:** achievement des activités de confinement des poliovirus de phase I;
5. **Verification:** Verification of global eradication of WPV2. – **Vérification:** vérification de l'éradication du PVS2 au niveau mondial

Trigger for setting a date for the withdrawal of OPV2: – Déclencheur pour déterminer une date pour le retrait du PVO2:
Absence of all persistent cVDPV2 – Absence de tout PVDV2c persistant

6 x Regional certification of WPV eradication: – 6 x Certification régionale de l'élimination des PVS:
The Regional Certification Commissions (RCC) will certify their regions as polio-free once WPV transmission is interrupted in that region, i.e. 36 months after the last WPV is detected. – Les Commissions régionales de certification certifierons que leurs régions sont exemptes de poliomyélite une fois que la transmission de PVS aura été interrompue dans la region concernée (par exemple, 36 mois après la detection du dernier cas de PVS).

Table 1 **Phased implementation of poliovirus containment**
Tableau 1 **Mise en œuvre en plusieurs phases du confinement des poliovirus**

Prerequisites – Prérequis	Phase – Phase	Begins – Début	Target completion date – Date d'achèvement visée	Key activities – Activités importantes
Phase I: Preparation for containment of poliovirusppoliovirusoliovirus type 2 – Phase I: Préparation au confinement des poliovirus				
	I: Inventory, destruction, preparation for poliovirus type 2 containment – I: Inventaire, destruction, préparation au confinement des poliovirus de type 2	Ongoing – En cours	Global readiness of OPV2 withdrawal – Préparation au retrait du VPO2 à l'échelle mondiale	Inventory, destruction, preparation for poliovirus type 2 containment – Inventaire, destruction, préparation au confinement des poliovirus de type 2 • survey/inventory of facilities handling or storing infectious or potentially infectious poliovirus materials. – enquête/inventaire dans les établissements manipulant des matériels infectieux ou potentiellement infectieux contenant des poliovirus Non-essential facilities: – Établissements non essentiels: • destroy unneeded poliovirus material; – détruire les matériels contenant des poliovirus inutiles ; • transfer needed poliovirus type 2 material to essential laboratory facilities; – transférer les matériels contenant des poliovirus de type 2 nécessaires dans des installations de laboratoire essentielles ; • adopt a non-retention policy for new WPV2/Sabin2 isolates, to be implemented as of Phase IIa. – adopter une politique de non conservation pour les nouveaux isolements de PVS2/Sabin 2, à mettre en œuvre à partir de la phase IIa. Essential facilities: – Établissements essentiels: • obtain national certification. – obtenir la certification nationale
Phase II: Poliovirus type 2 containment period – Phase II: Période de confinement des poliovirus de type 2				
Elimination of WPV2 – Élimination des PVS2 **Elimination of persistent cVDPV2 – Élimination des PVDV2c persistants**	**IIa: WPV2 *containment* – IIa: *Confinement des PVS2***	Global readiness of OPV2 withdrawal – Préparation au retrait du VPO2 à l'échelle mondiale	6 x regional certification of WPV eradication – 6 x certification régionale de l'éradication des PVS	Containment of WPV2 – Confinement des PVS2 Certified essential WPV2-holding laboratory and IPV production facilities: – Laboratoires essentiels certifiés détenant des PVS2 et installations de production de PVI: • handle and store WPV2 materials according to the "Containment of WPV2" provisions. – manipuler et stocker les matériels contenant des PVS2 conformément aux « Dispositions pour le confinement des PVS2 ». Non-essential facilities: – Établissements non essentiels: • destroy the remaining unneeded Sabin2 material; – détruire les matériels contenant une souche Sabin 2 non nécessaires; • transfer needed Sabin2 material to certified essential poliovirus facilities. – transférer les matériels contenant une souche Sabin 2 non nécessaires dans des établissements essentiels certifiés autorisés à détenir des poliovirus. Non-essential facilities investigating new WPV2; aVDPV2, cVDPV2, or iVDPV2 isolates; or new faecal and respiratory samples originating from recent OPV-using countries: – Établissements non essentiels étudiant de nouveaux isolements de PVS2, de PVDV2a, de PVDV2c ou de PVDV2i ; ou de nouveaux échantillons d'origine fécale ou respiratoire provenant de pays ayant utilisé récemment le VPO: • implement a non-retention policy; – mettre en œuvre une politique de non conservation; • destroy unneeded recently isolated poliovirus material; – détruire les matériels contenant des poliovirus récemment isolés inutiles; • transfer needed recently isolated poliovirus material to certified essential poliovirus facilities. – transférer les matériels contenant des poliovirus récemment isolés nécessaires dans des établissements essentiels certifiés autorisés à détenir des poliovirus.
Licensed and available bOPV – VPOb homologué et disponible **Global introduction of IPV – Introduction à l'échelle mondiale du VPI** **Global tOPV-bOPV switch – Passage à l'échelle mondiale du VPOt au VPOb**	**IIb: *OPV2/Sabin2 poliovirus containment (post tOPV-bOPV switch)* – IIb: *Confinement des poliovirus appartenant à une souche du vaccin VPO2/Sabin 2 (passage du VPOt au VPOb)***	Within 3 months of global tOPV-bOPV switch – Dans les 3 mois suivant le passage à l'échelle mondiale du VPOt au VPOb	Within 3 months of global bOPV cessation (bOPV cessation is planned one year after global certification of WPV eradication) – Dans les 3 mois suivant l'arrêt du VPOb à l'échelle mondiale (l'arrêt du VPOb est prévu un an après la certification de l'éradication des PVS à l'échelle mondiale)	Containment of OPV2/Sabin2 poliovirus – Confinement des poliovirus appartenant une souche du vaccin VPO2/Sabin 2 *Certified essential OPV2/Sabin2-holding laboratory, or OPV/Sabin-IPV production facilities: – Laboratoires essentiels certifiés détenant des souches entrant dans la composition du vaccin VPO2/Sabin 2, ou installations de production de VPO/VPI à partir d'une souche Sabin:* • handle and store OPV2/Sabin2 materials according to "Containment of OPV2/Sabin2 poliovirus" provisions. – manipuler et stocker les matériels contenant des souches du vaccin VPO2/Sabin 2 conformément aux « Dispositions pour le confinement des poliovirus appartenant à une souche du vaccin VPO2/Sabin 2 ».

Table 1 *(continued)* – Tableau 1 *(suite)*

Prerequisites – Prérequis	Phase – Phase	Begins – Début	Target completion date – Date d'achèvement visée	Key activities – Activités importantes
Phase III: Final poliovirus containment – Phase III: Confinement final des poliovirus				
Three years after isolation of last WPV – Trois ans après le dernier isolement d'un PVS	**IIIa: *Post-eradication* – IIIa: *Phase post-éradication***	6 x regional certification of WPV eradication – 6 x certification régionale de l'éradication des PVS	Long-term eradication (beyond global bOPV cessation) – Éradication à long terme (au delà de l'arrêt du VPOb à l'échelle mondiale)	Final containment of all WPV – Confinement final de tous les PVS Certified essential WPV-holding laboratory or IPV production facilities: – Laboratoires essentiels certifiés détenant des PVS ou installations de production de VPI: • handle and store all WPV materials in "Final containment of all WPV" provisions. – manipuler et stocker tous les matériels contenant des PVS conformément aux dispositions pour le « Confinement final de tous les PVS ».
Global bOPV cessation – Arrêt du VPOb à l'échelle mondiale	**IIIb: *Post-bOPV cessation* – IIIb: *Après l'arrêt du VPOb***	Within 3 months of global bOPV cessation (bOPV cessation is currently planned one year after global certification of WPV eradication) – Dans les 3 mois suivant l'arrêt du VPOb à l'échelle mondiale (l'arrêt du VPOb est actuellement planifié un an après la certification de l'éradication à l'échelle mondiale des PVS)	Long-term eradication (beyond global bOPV cessation) – Éradication à long terme (au delà de l'arrêt du VPOb à l'échelle mondiale)	Final containment of all OPV/Sabin polioviruses – Confinement final de tous les poliovirus appartenant à une souche du vaccin VPO/Sabin Certified essential OPV/Sabin-holding laboratory or Sabin-IPV production facilities: – Laboratoires essentiels certifiés détenant des souches du vaccin VPO/Sabin ou installations de production de vaccins VPI à partir d'une souche Sabin: • handle and store OPV/Sabin materials in "Final containment of all OPV/Sabin polioviruses" provisions. – manipuler et stocker tous les matériels contenant des souches de vaccin VPO/Sabin conformément aux dispositions pour le « Confinement final de tous les poliovirus appartenant à une souche du vaccin VPO/Sabin ».

Rationale

Reintroduction of WPV from a poliovirus facility poses a serious risk of re-establishing poliovirus transmission. When OPV use stops, many countries will continue vaccination. Some of these countries will have suboptimal IPV coverage, and still others may discontinue all national polio immunization activities. A reintroduction of an OPV/Sabin strain from a facility risks unrecognized virus transmission, reversion to cVDPV, and re-establishment of poliovirus transmission.

Most countries will have no need to retain polioviruses in the post-eradication and post-OPV era. Facility-associated risks in these countries can be eliminated by a thorough nationwide search for and destruction of all WPV, VDPV, and OPV/Sabin stocks and potentially infectious materials. Some countries will host a limited number of poliovirus facilities that serve critical international functions, including production of IPV and Sabin-IPV, production and storage of monovalent OPV stockpiles, vaccine quality assurance, diagnostic reagent production, virus diagnostic and reference functions, together with crucial research. Each essential poliovirus facility should manage biorisk appropriately to minimize the risk of virus reintroduction into the community, under effective national certification and international verification programmes to assure

Justifications

La réintroduction de PVS à partir d'un établissement détenant de tels virus constitue un risque sérieux de rétablissement de la transmission des poliovirus. Une fois que l'on aura cessé d'utiliser le VPO, de nombreux pays poursuivront la vaccination. Certains de ces pays présenteront une couverture sous-optimale par ce vaccin et d'autres encore pourront avoir interrompu toutes les activités nationales de vaccination contre la poliomyélite. La réintroduction d'une souche vaccinale entrant dans la composition du VPO/vaccin Sabin en provenance d'un établissement fait courir le risque d'une transmission virale sans qu'on en ait connaissance, la réversion d'une telle souche en PVDVc et le rétablissement de la transmission des poliovirus.

La plupart des pays n'auront pas besoin de conserver des poliovirus pendant l'ère postéradication et post-VPO. Les risques d'exposition à des poliovirus associés à des établissements de ces pays peuvent être éliminés par une enquête approfondie, à l'échelle nationale, à la recherche de tous les stocks de matériels contenant des PVS, des PVDV ou des poliovirus appartenant à une souche du VPO ou à la souche Sabin et de matériels potentiellement infectieux. Certains pays auront sur leur territoire un nombre limité d'établissements détenant des poliovirus qui exercent des fonctions internationales essentielles, dont la production de VPI ou de VPI à partir d'une souche Sabin, la production et la conservation de réserves de VPO monovalent, l'assurance de la qualité des vaccins, la fabrication de réactifs de diagnostic, le diagnostic et la conservation de références virales, ainsi que des recherches d'importance cruciale. Chaque établissement essentiel détenant des poliovirus devra gérer correc-

Table 2 **Synopsis of containment safeguards described in GAPIII**
Tableau 2 **Résumé des mesures de protection dans le cadre du confinement présentées dans le GAPIII**

	Poliovirus type 2 containment period – Période de confinement des poliovirus de type 2	Final poliovirus containment period – Période de confinement final des poliovirus	
	All type 2 polioviruses – Tous les poliovirus de type 2	All OPV/Sabin polioviruses – Tous les poliovirus appartenant à une souche du vaccin VPO/Sabin	All wild polioviruses – Tous les poliovirus sauvages
Primary safeguards: Prevent infection & release of contaminated materials – Mesures de protection primaires: Prévention de l'infection & de la libération de matières contaminées			
Operator protection[a] – Protection des opérateurs[a]	Yes – Oui	Yes – Oui	Yes – Oui
Decontamination of materials/equipment – Décontamination du matériel/des équipements	Yes – Oui	Yes – Oui	Yes – Oui
Dedicated effluent treatment plant – Unité de traitement des effluents dédiée	No[b] – Non[b]	No[b] – Non[b]	Yes[c] – Oui[c]
Air/exhaust treatment – Traitement de l'air/des gaz d'échappement	No – Non	No – Non	Yes[d] – Oui[d]
Secondary safeguards: Population immunity in country hosting the facility – Mesures de protection secondaires: Immunité des populations dans les pays où se trouvent les établissements			
IPV doses – Doses de VPI	≥1	≥1	≥3
IPV coverage – Couverture par le VPI	= DTP3 coverage[e] – = Couverture par le DTC3[e]	= DTP3 coverage[e] – = Couverture par le DTC3[e]	>90%
Tertiary safeguards: Environment & location – Mesures de protection tertiaires: Environnement & lieu			
Siting of facilities in areas with low transmission potential (R_0) for wild polioviruses – Implantation des établissements dans des zones où le potentiel de transmission des poliovirus sauvages est faible (R0)	No– Non	No– Non	Yes– Oui

[a] Since the operator is considered to be one of the sources of release of poliovirus from the facility, specific measures of protection are required, including e.g. the use of PPE, the use of primary containment devices, and vaccination.– Comme les opérateurs sont considérés comme l'une des sources potentielles de libération de poliovirus à partir des établissements, des mesures de protection spécifiques s'imposent, dont l'utilisation d'EPI, de dispositifs de confinement primaires et la vaccination.

[b] Untreated release into a closed sewage system with secondary effluent treatment in the facility location (Note: all waste from facilities, potentially containing live poliovirus, should be inactivated prior to release through adequate and validated inactivation procedures. For facilities without a dedicated effluent treatment plant, this would normally be done through the application of heat or chemicals as part of a validated treatment process. Under no circumstances should raw poliovirus containing effluents be discharged to drains, unless the effluent treatment plant has been designed and validated to handle such effluents, effectively acting as part of the primary containment system). – Rejets non traités dans un réseau d'égout fermé avec un traitement des effluents secondaires sur le site de l'établissement (note: tous les déchets provenant d'établissements susceptibles de contenir des poliovirus vivants devront être inactivés avant leur rejet selon des procédures d'activation appropriées et validées. Dans le cas des établissements ne disposant pas d'une unité de traitement dédiée, cette opération devrait normalement s'effectuer par application de chaleur ou de produits chimiques dans le cadre du processus de traitement validé. En aucune circonstance, des effluents contenant des poliovirus bruts ne devraient être rejetés dans le réseau de drainage, à moins que l'unité de traitement n'ait été conçue et validée pour traiter de tels effluents, pour jouer efficacement le rôle de système de confinement primaire).

[c] Facility effluent treatment before release into closed sewage system with secondary or greater effluent treatment in the facility location. – Traitement des effluents dans l'établissement avant leur rejet dans un réseau d'égout fermé, avec traitement des effluents de niveau secondaire et plus sur le site de l'établissement.

[d] HEPA (high efficiency particulate arresting) filtration on exhaust air. – Filtration HEPA (Haute efficacité d'interception des particules) de l'air extrait.

[e] Diphtheria–tetanus–pertussis vaccine third dose (DTP3) immunization coverage (http://www.who.int/gho/immunization/dtp3/en/). – Couverture vaccinale par 3 doses de vaccin antidiphtérique-antitétanique-anticoquelucheux (DTC3) (http://www.who.int/gho/immunization/dtp3/en/).

compliance with GAP III. The risk for a poliovirus reintroduction can in addition be minimized by ensuring that essential facilities are located in areas with high levels of population immunity, effective acute flaccid paralysis and environmental surveillance, supplemented by efficient public health and response capacity (*Table 2*). Minimizing the number of essential facilities worldwide further reduces the

tement les risques biologiques de manière à réduire au minimum le risque de réintroduction virale dans la collectivité, grâce à une certification nationale et des programmes de vérification internationaux efficaces qui assurent la conformité avec les exigences du GAPIII. D'autre part, il est possible de minimiser le risque de réintroduction de poliovirus en s'assurant que les établissements essentiels sont situés dans des zones où les populations bénéficient d'un fort taux d'im-

magnitude of the risk, facilitates national and international oversight, and strengthens the likelihood that global containment standards can be met and successfully maintained.

Policy and implementation

Phase I: Preparation for containment of poliovirus type 2. Phase I is in progress as part of global preparedness for OPV2 withdrawal (*Figure 1* and *Table 1*). Key activities during Phase I are: (i) governments, institutions, and facilities storing or handling poliovirus are informed about the upcoming need for type-specific poliovirus containment; (ii) national laboratory survey to identify poliovirus inventory are conducted; (iii) destruction of unneeded poliovirus type 2 materials; (iv) designated essential poliovirus facilities obtain national certification for containment; and (v) transfer of needed poliovirus type 2 materials to essential poliovirus facilities. The national laboratory surveys are to include not only known research or commercial facilities working with WPV2/VDPV2 but also all facilities working with OPV2/Sabin2 or with faecal or respiratory materials that could contain WPV2, VDPV2 or OPV2/Sabin2 (collected at a time and place when OPV was in use). All countries shall include in the survey new or other biomedical laboratories that might have collections of infectious or potentially infectious WPV2, VDPV2 or OPV2/Sabin2 materials of any origin that are maintained for any reason.

Laboratories that retain clinical specimens which may contain WPV2/VDPV2 viruses must destroy or contain such materials before Phase IIa. Laboratories that retain clinical specimens which may contain OPV2/Sabin2 viruses (i.e. faecal or respiratory samples collected at times and places when OPV was in use) must destroy or contain such materials before Phase IIb. Laboratories wishing to retain historic collections of clinical materials potentially containing polioviruses but not planning to implement the poliovirus containment measures described in GAPIII are required to explore options with designated essential poliovirus research and reference facilities for handling and storage arrangements.

Phase II: Poliovirus type 2 containment period. Phase II commences as soon as the criteria for global readiness of OPV2 withdrawal are met,[5] and continues until certification of global WPV eradication, for which:

munisation et où la surveillance de l'environnement et des paralysies flasques aiguës est efficace et appuyée par des capacités de santé publique et de réponse efficientes (*Tableau 2*). Limiter le plus possible le nombre d'établissements essentiels dans le monde permet de réduire davantage l'ampleur du risque, facilite la supervision nationale et internationale et accroît la probabilité que les normes de confinement mondiales soient respectées et maintenues avec succès.

Politique et mise en œuvre

Phase I: Préparation au confinement des poliovirus de type 2. La phase I se poursuit dans le cadre de la préparation à l'échelle mondiale du retrait de la composante VPO (*Figure 1* et *Tableau 1*). Les activités importantes à mener pendant cette phase sont: 1) l'information des gouvernements, des institutions et des établissements conservant ou manipulant des poliovirus de la nécessité imminente d'un confinement des poliovirus d'un type spécifique; 2) la réalisation d'une enquête dans les laboratoires nationaux afin d'établir un inventaire des poliovirus; 3) la destruction des matériels contenant des poliovirus de type 2 inutiles; 4) l'obtention de la certification nationale par les établissements essentiels détenant des poliovirus désignés; et 5) le transfert des matériels contenant des poliovirus de type 2 nécessaires dans les établissements essentiels autorisés à détenir des poliovirus. Les enquêtes dans les laboratoires nationaux devront non seulement inclure les établissements de recherche ou industriels travaillant avec des PVS2/PVDV2, mais aussi les installations dont l'activité fait intervenir une souche entrant dans la composition du vaccin VPO2/Sabin 2 ou des matières d'origine fécale et/ou respiratoire, susceptibles de contenir des PVS2, des PVDV2 ou une souche entrant dans la composition du vaccin VPO2/Sabin 2 (recueillies à un moment et à un endroit où le VPO était en usage). Tous les pays devront faire porter aussi leur enquête sur les nouveaux laboratoires biomédicaux et autres, susceptibles de détenir des collections de matériels infectieux ou potentiellement infectieux contenant des PVS2, des PVDV2 ou une souche entrant dans la composition du vaccin VPO2/Sabin 2, quelle qu'en soit l'origine et la raison de les conserver.

Les laboratoires qui conservent des échantillons cliniques susceptibles de renfermer des PVS2/PVDV2 doivent détruire ou confiner ces matériels avant la phase IIa. Ceux qui conservent des échantillons cliniques pouvant contenir des virus d'une souche entrant dans la composition du vaccin VPO2/Sabin 2 (c'est-à-dire des échantillons d'origine respiratoire ou fécale recueillis à des moments ou à des endroits où le VPO était en usage) doivent détruire ou confiner ces matériels avant la phase IIb. Enfin, ceux désireux de conserver des collections historiques de matériels cliniques renfermant potentiellement des poliovirus, mais ne prévoyant pas de mettre en œuvre les mesures de confinement décrites dans le plan GAPIII, devront étudier des options concernant les dispositions à prendre en termes de manipulation et de stockage avec les établissements de recherche et de référence essentiels désignés pour détenir des poliovirus.

Phase II: Période de confinement des poliovirus de type 2. La phase II débute dès que les critères de préparation à l'échelle mondiale au retrait du VPO2 sont remplis[5] et se poursuit jusqu'à la certification de l'éradication des PVS dans l'ensemble du monde, pendant laquelle:

- Essential poliovirus facilities are expected to implement GAPIII requirements in order to continue to work with and store polioviruses
- Hosting countries' National Authorities responsible for containment are expected to certify essential facilities in accordance with GAPIII criteria
- An international oversight mechanism will ensure a globally harmonized approach to containment verification (GAPIII Containment Certification Scheme, currently being developed).

This phase has 2 parts (*Figure 1* and *Table 1*), addressing the containment of WPV2/VDPV2 and OPV2/Sabin2: Phase IIa – Containment of all WPV2 and VDPV2 in certified essential poliovirus facilities; Phase IIb – Containment of OPV2/Sabin2 polioviruses in certified essential poliovirus facilities. Phase IIb commences within 3 months of OPV2 withdrawal (tOPV–bOPV switch). Certified essential poliovirus facilities handling and storing WPV2 or OPV2/Sabin2 materials in Phase II must implement, be certified and be regularly reassessed for implementing "WPV2 containment" measures, including primary and secondary safeguards (*Table 2*). Facilities that have not received formal national certification for "WPV2 containment" will no longer be allowed to handle and store WPV2 materials as of Phase II. Countries or concerned facilities may apply to WHOthrough their national authorities for verification of containment in essential poliovirus facilities, certified by the Ministry of Health or other designated national authority, and declared to meet all biorisk management criteria consistent with GAPIII.

Phase III: Final poliovirus containment. This phase also has 2 parts. Phase IIIa begins when all 6 WHO Regions have completed the certification of WPV eradication, at least 3 years after the last isolation of WPV. As of the start of Phase IIIa (*Figure 1* and *Table 1*), certified essential poliovirus laboratories and IPV production facilities handling and storing any WPV or VDPV materials must implement "Final containment of all WPV" provisions including primary, secondary, and tertiary safeguards (*Table 2*). Facilities that have not received formal national certification for final containment of all wild polioviruses will no longer be allowed to handle and store any WPV materials in Phase III. Global bOPV cessation is planned to take place 1 year after the global certification of WPV eradication. Phase IIIb begins 3 months after global bOPV cessation (*Figure 1* and *Table 1*). As of the start of Phase IIIb, certified essential poliovirus laboratory and Sabin-IPV production facilities handling and storing OPV/Sabin materials (but no WPV) must implement "Final containment of all OPV/Sabin polioviruses" provisions, including primary and

- il est attendu des établissements essentiels détenant des poliovirus qu'ils appliquent les exigences du GAPIII pour continuer à travailler avec de tels virus et les conserver;
- il est attendu des autorités nationales responsables du confinement dans les pays où se trouvent ces établissements essentiels qu'elles les certifient conformes aux critères GAPIII;
- un mécanisme de supervision internationale garantira une démarche harmonisée à l'échelle mondiale pour la vérification du confinement (schéma de certification du confinement selon le GAPIII, actuellement en cours d'élaboration).

Cette phase comporte 2 parties (*Figure 1* et *Tableau 1*): la phase IIa consacrée au confinement des PVS2/PVDV2 et des souches entrant dans la composition du vaccin VPO2/Sabin 2 et la phase IIb consacrée au confinement des poliovirus appartenant à une souche du vaccin VPO2/Sabin 2 dans les établissements essentiels détenant des poliovirus. La phase IIb débute dans les 3 mois suivant le retrait du VPO2 (passage du VPOt au VPOb). Les établissements essentiels certifiés détenant des poliovirus qui manipulent et conservent des matériels renfermant des PVS2 ou des souches de vaccin VPO2/Sabin 2 pendant la phase II doivent mettre en œuvre des dispositions de confinement des PVS2, et notamment des mesures de protection primaires et secondaires (*Tableau 2*), et être certifiés et régulièrement réévalués pour cela. Les établissements n'ayant pas obtenu de certification nationale formelle pour le « confinement des PVS2 » ne seront plus autorisés à manipuler et à conserver des matériels contenant des tels poliovirus à partir de la phase II. Les pays ou les établissements concernés peuvent demander à l'OMS, par le biais de leurs autorités nationales, la certification d'établissements essentiels détenant des poliovirus, certifiés par le ministère de la santé ou une autre autorité nationale désignée et déclarés comme remplissant tous les critères de gestion des risques biologiques en ligne avec le GAPIII.

Phase III: Confinement final des poliovirus. Cette phase comporte également 2 parties. La phase IIIa commence lorsque les 6 Régions de l'OMS ont obtenu la certification pour l'éradication des VPS et au moins 3 ans après le dernier isolement d'un PVS. À compter du début de la phase IIIa (*Figure 1* et *Tableau 1*), les laboratoires essentiels certifiés détenant des poliovirus et les installations de production de PVI manipulant ou conservant un quelconque matériel contenant des PVS ou des PVDV doivent appliquer les dispositions pour le « confinement final de tous les PVS », y compris les mesures de protection primaires, secondaires et tertiaires (*Tableau 2*). Les installations qui n'ont pas reçu une certification nationale formelle pour le confinement final de tous les poliovirus sauvages ne seront plus autorisées à manipuler ou conserver des matériels contenant des PVS, qu'elle qu'en soit la nature, pendant la phase III. Il est prévu que l'arrêt mondial de l'utilisation du VPOb intervienne 1 an après la certification de l'éradication des PVS à l'échelle mondiale. La phase IIIb débute 3 mois après l'arrêt de l'utilisation du VPOb à l'échelle mondiale (*Figure 1* et *Tableau 1*). À compter du début de la phase IIIb, les laboratoires essentiels certifiés détenant des poliovirus et les installations de production de vaccins VPI à partir d'une souche Sabin qui manipulent ou

secondary safeguards (*Table 2*). Facilities that have not received formal national certification for final containment of all OPV/Sabin polioviruses will no longer be allowed to handle and store OPV/Sabin materials. Within 6 months of bOPV cessation, all countries must submit documentation confirming that requirements for "Final containment of all OPV/Sabin polioviruses" have been met.

Discussion

Although available data estimate the number of facilities currently holding type 2 wild polioviruses to be around 500 worldwide, one of the goals of poliovirus containment will be to reduce this number substantially,[10] dissuading candidate facilities not meeting the GAPIII containment criteria from holding any polioviruses. Only designated 'essential facilities' that meet GAPIII containment criteria will store and handle polioviruses.

Polio diagnostic and research laboratories that hold type 2 poliovirus containing infectious or potentially infectious materials should begin preparations to comply with GAPIII in accordance with the timelines above. Considering the substantial investments and technical capacity that are required by facilities to become compliant with GAPIII it is expected that most diagnostic and research laboratories holding poliovirus materials will either destroy or transfer such materials to a laboratory that is GAPIII compliant.

Similarly, significant number of facilities maintain faecal or respiratory samples collected in areas where tOPV was in use at the time of collection. Successful management of poliovirus-associated risk requires such facilities to apply bio-safety and containment measures that reduce the risk of human exposure to live polioviruses from manipulation of such samples.

National authorities in countries that host designated essential facilities that store and handle polioviruses for the purpose of diagnosis, research or vaccine production, will be assisted by WHO to implement the international scheme to certify containment in compliance with GAPIII.

Manufacturing of IPV involves amplification of wild polioviruses at an industrial scale, thus requiring extraordinary measures to mitigate the risk of facil-

[10] Dowdle WR, van der Avoort H, de Gourville E, et al. Containment of polioviruses after eradication and OPV cessation: Characterizing risks to improve management. Risk Anal 2006;26:1449–1469.

conservent des matériels contenant une souche vaccinale entrant dans la composition du vaccin VPO/Sabin (mais pas de PVS) doivent appliquer les dispositions pour le « confinement de tous les poliovirus appartenant à une souche entrant dans la composition du vaccin VPO ou Sabin », y compris les mesures de protection primaires et secondaires (*Tableau 2*). Les installations n'ayant pas reçu de certification nationale formelle pour le confinement final de tous les poliovirus d'une souche entrant dans la composition du vaccin VPO/Sabin ne seront plus autorisées à manipuler ou à conserver des matériels contenant une telle souche. Dans les 6 mois suivant l'arrêt du VPOb, tous les pays doivent soumettre une documentation confirmant que les exigences pour le « confinement final de tous les poliovirus d'une souche entrant dans la composition du vaccin VPO/Sabin » ont été remplies.

Discussion

Si, d'après les données disponibles, le nombre d'installations détenant des poliovirus sauvages de type 2 est estimé à 500 environ dans le monde, un des objectifs du confinement des poliovirus sera de réduire ce nombre de façon substantielle[10] et de dissuader les établissements ne remplissant pas les critères de confinement du GAPIII de conserver des poliovirus. Seuls les établissements désignés comme "essentiels" et remplissant les critères de confinement du GAPIII seront habilités à conserver et manipuler des poliovirus.

Les laboratoires de diagnostic de la poliomyélite et de recherche sur cette maladie qui détiennent des matériels infectieux ou potentiellement infectieux contenant des poliovirus de type 2 devront commencer à se préparer à une mise en conformité avec les exigences du plan GAPIII, en respectant le calendrier ci-dessus. Compte tenu des investissements et des moyens techniques substantiels nécessaires pour que les établissements soient conformes aux exigences du GAPIII, on s'attend à ce que la plupart des laboratoires de diagnostic ou de recherche qui détiennent des matériels contenant des poliovirus les détruisent ou transfèrent ces matériels dans un laboratoire en conformité avec le plan GAPIII.

De manière similaire, un nombre important d'établissement conservent des échantillons d'origine respiratoire ou fécale recueillis dans des zones où le VPOt était alors en usage. Pour gérer correctement les risques liés aux poliovirus, les établissements doivent appliquer des mesures de sécurité biologique et de confinement capables de réduire les risques d'exposition humaine à des poliovirus vivants, découlant de la manipulation de ces échantillons.

Les autorités nationales des pays hébergeant sur leur territoire des établissements essentiels désignés qui conservent et manipulent des poliovirus à des fins de diagnostic, de recherche et de production vaccinale, recevront le soutien de l'OMS pour mettre en œuvre le schéma international permettant de certifier la conformité du confinement de ces poliovirus avec les exigences du GAPIII.

La fabrication de VPI suppose l'amplification de poliovirus sauvages à l'échelle industrielle, ce qui exige des mesures extraordinaires pour limiter les risques de propagation de

[10] Dowdle WR, van der Avoort H, de Gourville E, et al. Containment of polioviruses after eradication and OPV cessation: Characterizing risks to improve management. Risk Anal 2006;26:1449–1469.

ity associated risk of poliovirus spread. WHO has kept IPV manufacturers informed about the phased approach to containment of all polioviruses, starting with the type 2 poliovirus. WHO is working with national authorities and vaccine manufacturers to assure appropriate risk management and ultimately full GAPIII compliance.

WHO has planned the provision of technical assistance and training to national authorities, managers of essential laboratories and vaccine manufacturers to facilitate compliance with GAPIII, and implementation of the international containment certification scheme.

The timeline cited in GAPIII for the type-specific containment of polioviruses is short for candidate essential poliovirus facilities to be assessed and certified in accordance with GAPIII and for the national authorities responsible for containment to deliver containment certificates. However, continuation of polio vaccine production, surveillance and essential research activities are considered critical and must continue. Thus, in order to help manage practical challenges associated with the implementation of containment for essential facilities, an additional status of interim certification of containment is introduced. This allows the containment certification scheme to proceed in the endgame phases of eradication in a controlled and structured manner, while managing potential delays that may be associated with meeting the requirements for full containment within pressing timelines. The proposed mechanisms will provide some degree of flexibility while facilities make the required changes, and countries and other bodies develop the required capability and capacity to implement the certification scheme.

The final containment of all infectious materials and WPV/VDPVs, including types 1 and type 3 polioviruses is also approaching. The initial process to contain PVS2 is also an opportunity to learn how containment of all polioviruses can best be achieved. After WPV transmission has been stopped, final containment will minimize the risk of reintroduction into a polio-free world once all OPV use has been phased-out. As for variola virus, containment requirements will have to be regularly assessed and maintained, until a global decision is made to destroy all remaining poliovirus materials and prohibit any de novo synthesis.

Author affiliations

[a] Polio Operations and Research Department, World Health Organization, Geneva, Switzerland States (Corresponding author: Nicoletta Previsani, previsanin@who.int). ■

poliovirus à partir d'un établissement. L'OMS a tenu les fabricants de VPI informés de la démarche par phases appliquée au confinement de tous les poliovirus, en commençant par le type 2. Elle collabore avec les autorités nationales et les fabricants de vaccins pour garantir une gestion appropriée des risques et, au final, la conformité totale avec les exigences du GAPIII.

L'OMS a prévu de fournir une assistance technique ainsi qu'une formation aux autorités nationales, aux responsables des laboratoires essentiels et aux fabricants de vaccins pour permettre la mise en conformité avec les exigences du GAPIII et la mise en œuvre du schéma international permettant de certifier la conformité du confinement de ces poliovirus.

Le délai mentionné dans le GAPIII pour le confinement des poliovirus par type spécifique est court pour permettre l'évaluation des installations essentielles détenant des poliovirus et leur certification comme conformes aux exigences du GAPIII et pour la délivrance par les autorités nationales responsables du confinement de certificats relatifs à cette opération. Néanmoins, il est considéré comme essentiel que les activités de production, de surveillance et de recherche d'importance se poursuivent. En conséquence, pour aider à gérer les difficultés pratiques que pose le confinement pour les installations essentielles, un statut supplémentaire de certification provisoire pour le confinement est introduit. Il autorise le déroulement, de manière contrôlée et structurée, du schéma de certification pour le confinement pendant les phases finales de l'éradication, tout en permettant de répondre, dans des délais serrés, aux problèmes rencontrés dans la satisfaction des exigences requise pour obtenir un confinement complet. Les mécanismes proposés fourniront un certain degré de flexibilité pendant que les installations procèdent aux changements requis et que les pays et les autres organismes développent les capacités et les moyens nécessaires pour mettre en œuvre le schéma de certification.

La phase de confinement final de tous les matériels infectieux et des PVS/PVDV, y compris les types 1 et 3, approche. Le processus initial de confinement des PVS2 représente aussi une occasion d'apprendre à confiner tous les virus de la meilleure manière qui soit. Après l'arrêt de la transmission des PVS, le confinement final permettra de réduire au minimum le risque de réintroduction de ces virus dans un monde exempt de poliomyélite jusqu'à ce que tous les usages des VPO soient supprimés. Comme pour le virus de la variole, les exigences de confinement devront être régulièrement évaluées et maintenues jusqu'à ce que la décision soit prise au niveau mondial de détruire tous les matériels contenant des poliovirus restants et interdire toute synthèse de novo.

Affiliations des auteurs

[a] Département Poliomyélite: opérations et recherche, Organisation mondiale de la Santé, Genève (Suisse) (Auteur principal: Nicoletta Previsani, previsanin@who.int). ■

Monitoring the Switch from tOPV to bOPV

The World Health Assembly endorsed the SAGE recommendation for a synchronized switch from tOPV to bOPV in all 155 OPV using countries and territories during a two week period in April 2016 (April 17-May 1, 2016, to be endorsed by SAGE in October 2015). A key component of a successful switch involves effective monitoring of health facilities after the National Switch date in all countries to ensure that tOPV is no longer available for administration. Ensuring that tOPV is no longer being administered or in the cold chain is a responsibility of Member States. This document summarizes **the GPEI's recommended monitoring strategy** for withdrawal of all tOPV from cold chain storage points. **Full Guidelines for Developing National Monitoring Plans are available on the website.**

Objectives of the monitoring strategy

1) Conduct site visits at **all cold chain stores** from the national to the district levels (where the largest quantities of tOPV will generally be stored at the time of the switch), as well as **selected service delivery points** (health facilities), in order to verify removal of these stocks from the cold chain;
2) Take corrective action to remove tOPV stocks from the cold chain if found and mark these stocks for disposal;
3) Assess performance of the switch; and
4) Assess the status of bOPV and IPV distribution at monitored facilities.

Monitoring the withdrawal of tOPV from cold chain stores and service points is a distinct process from the certification of containment or destruction of poliovirus at laboratories and vaccine production facilities.

Timelines for the monitoring process

The monitoring process will take place in the 2 weeks following the national switch date. During these 2 weeks monitors should validate the withdrawal of tOPV from cold chain stores and delivery points.

The monitoring process should be developed in advance of the switch, following a number of phases similar to the switch process itself.

Example of a timeline of activities for planning and implementing the monitoring process

Independent Monitoring Period	**Plan**	**By September 2015** – Develop monitoring structure – Determine timeline of activities – Develop indicators for switch validation – Identify human and financial resources needed
	Prepare	**October 2015 – February 2016** – Develop questionnaires and data collection tools – Develop training materials – Create roster of facilities to monitor – Recruit supervisors and monitors – Train supervisors and monitors – Develop micro-plans – Develop contingency plans
	National Switch Day	**A day chosen during April 17 – May 1, 2016** ***(to be endorsed by SAGE in October 2015)***
	Validate	**April-May 2016 - During the two weeks after the National Switch Day** – Monitors visit cold chain stores and service delivery points – Data reported and aggregated – Develop validation report
Follow-up Monitoring Period	**Follow-Up**	**2-3 months ongoing after the switch** – Additional monitoring of tOPV withdrawal as needed – Correcting identified problems – Monitoring tOPV disposal as desired

Management and implementation of the monitoring process

1. Switch Management Committee: plans, manages, and oversees all activities relating to the switch, including identification of the sites to be monitored at the regional and national levels and takes appropriate programmatic action in case large amounts of tOPV are found at cold chain stores or service points and/or IPV and bOPV is not available.

2. National Switch Validation Committee: A body independent from switch implementation activities that is authorized by the government to validate the switch and certify that tOPV has been withdrawn from the cold chain. A country's National Certification Committee could be used for this purpose if it is active, or members of the National Switch Validation Committee could be drawn from the National Certification Committee or other authorities not part of the Switch Management Committee.

3. Independent Monitors: Persons who will assess the cold chain storage sites and service points with a questionnaire. These persons should not be directly involved with the organizations implementing the switch itself because their independence from those organizations is important for allowing them to provide honest assessments.

Identification of facilities for monitoring (sampling)

The goal is to identify which facilities in the cold chain need to be visited for the efficient validation of tOPV withdrawal and bOPV introduction. The recommended risk-based purposive (non-random) sampling monitoring strategy is intended to rapidly identify the cold chain stores and service points possibly holding the largest stocks of tOPV after the switch and facilitate immediate corrective action.

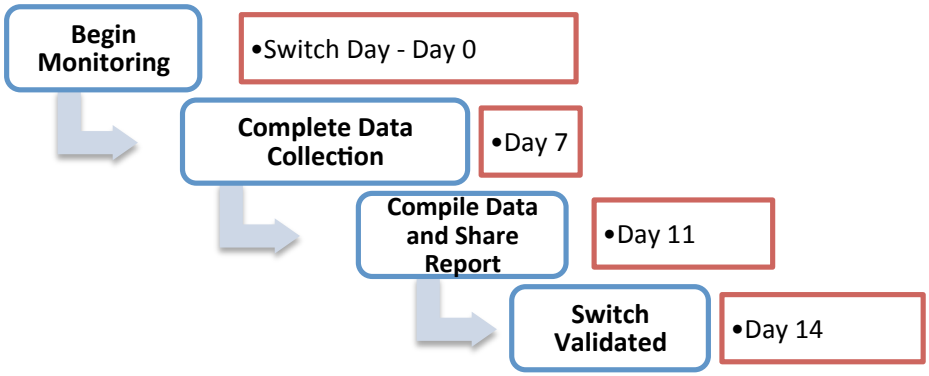
Steps:

1. Cold chain stores that stock tOPV from the national to the district level (in other words, all national, regional, and district cold chain stores) along with their last known tOPV stock levels (if possible). Monitors should **visit all of these stores.**
2. Service points that can store tOPV in a working refrigerator or freezer for more than 1 night. The monitors, based on standardized criteria set by the national level, should **visit a sample of these service points**. Select 10% of the service points with the highest population. Priority is given to facilities that have:
    - tOPV received just before the switch
    - A history of non-compliance with immunization program policies
    - DPT3 coverage <80%
    - Management issues
    - Other high risk characteristics

This strategy will provide complete information on all cold chain stores from the national to the district level and will provide information on many service points. These data will provide reasonable assurance of a successful national switch within two weeks of the national switch date.

Results from the sampled service points will not be generalizable to all service points. Therefore, countries are encouraged to ensure tOPV withdrawal from all service points through supportive supervision during the 2-3 months that follow the completion of independent monitoring.

Validation of the of the switch



In case one or more tOPV vials (opened or unopened) are found in the cold chain of the service points:

- The monitor will remove the vials from the cold chain and transport them to the nearest district or region disposal site according to the disposal plan. The monitor may wait to transport the tOPV to the disposal site until after he or she has completed his or her other monitoring activities.
- The supervisor will select an additional 5% of health facilities for monitors to visit.

If one or more tOPV vials containing vaccine (opened or unopened) are found in the additional 5% of visited facilities, a sweep of all service points should be conducted for the whole district. Sweeping would mean an intensified monitoring exercise with involvement of more district, regional and national staff, etc.

Validation report

After the National Switch Validation Committee has concluded whether the country can validate that there is no longer tOPV being administered or present in the cold chain after the National Switch Day, the committee should report its findings to the national government. The national government should in turn report on the status of the switch, including a validation of the switch, to the country and regional office of the World Health Organization.

Proceedings and Draft Recommendations from the Fifth Meeting of the SAGE Working Group on Measles and Rubella 3-4 September 2015, Geneva

Executive Summary

The 2014 Annual Report on the Global Vaccine Action Plan (GVAP) noted that while substantial progress has been made in reducing the burden of measles and rubella, the 2015 global measles control targets would not be achieved on time, and, except for the Americas, the regional measles and rubella elimination goals were off-track.

Reports on the status of measles elimination and rubella elimination were presented to the SAGE Decade of Vaccines Working Group at their meeting on 31 August 2015. Their assessment was similar to the 2014 GVAP report that concluded vaccination coverage was "*a very long way from the 95% in every district that will be required to eliminate measles". A huge amount of work and political commitment lies ahead if elimination goals are to be achieved…"*

With this background, the SAGE Measles Rubella Working Group met on 3-4 September to review progress and discuss refinements to existing immunization policies that would protect more individuals and increase population immunity. The specific objectives of their September 2015 meeting were:

1. to review most recent progress and challenges in worldwide efforts to control and eliminate measles and rubella and discuss the need for a mid-term review of the Global Measles and Rubella Strategic Plan, 2012-2020
2. to review the evidence to determine the epidemiological circumstances under which it should be recommended to provide a zero dose of MCV to infants <9 months of age
3. to review the evidence for recommendations to guide countries on how to use coverage, surveillance, seroprevalence and other sources of data to determine the target age range for a measles or measles-rubella supplementary immunization activities (SIAs) in order to interrupt endemic transmission of measles and rubella
4. to review the evidence to determine if HIV-infected children receiving HAART should be revaccinated against measles.

This report has 4 sections, one for each of the meeting objectives. Each section provides a summary of the information presented and puts forward conclusions and draft recommendations (only for objectives 2 and 4) for consideration by SAGE at their October 2015 meeting. The draft recommendations for administration of a zero dose of MCV to infants <9 months of age are presented on page 13. Draft recommendations for revaccination of HIV-infected children on HAART can be found on page 28. Work is ongoing to develop more operational guidance on determining the target age range for measles or measles-rubella SIAs.

1. Measles and Rubella Status Report

In 2010, the sixty-third World Health Assembly endorsed three global measles targets for 2015 as milestones towards global eradication of measles,[1] and in 2012, the World Health Assembly (WHA) endorsed the Global Vaccine Action Plan (GVAP) and its objective to eliminate measles in 4 WHO Regions and rubella in 2 WHO Regions by 2015 and eliminate measles and rubella in 5 WHO regions by 2020. Below is an update of the progress and challenges towards these milestones.

Between 2010 and 2014, global routine measles vaccine coverage remained at 85%[2] – well below the 2015 target of ≥90%. By region, three of the six WHO regions have sustained MCV1 coverage above 90% (Region of the Americas, European Region and Western Pacific Region), one region achieved coverage between 80 and 90% (South-East Asia Region) and two regions achieved coverage below 80% (African Region and Eastern Mediterranean Region). The number of Member States achieving the global MCV1 coverage target at the national level remained the same in 2014 when compared to 2010; 122 Member States achieved the ≥90% MCV1 national coverage target[3].

Since 2010, global reported measles incidence has decreased by 21% from 50.1 cases per million population in 2010 to 39.8 in 2014 with only one region (Region of the Americas) meeting the global 2015 milestone target of fewer than five cases per million population. During the same period, there was a decrease in the number of Member States (98 Member States in 2014 compared to 114 Member States in 2010) meeting the global 2015 incidence target.

Between 2000 and 2013, estimated measles deaths decreased by 75% (from 544 200 to 145 700) and all regions reported substantial reductions in estimated measles mortality. However, progress since 2010 has been too slow (from 69% mortality reduction in 2010 to 75% in 2013) making it highly unlikely that the target of a 95% mortality reduction can be achieved by the end of 2015.

In 2014, 154 (79%) Member States had introduced a second dose of MCV (compared to 136 (70%) in 2010) and MCV2 global coverage was 56% (compared to 40% in 2010). Among those 154 countries, 53 provide MCV2 to infants less than 2 years of age *and* have reported coverage

[1] The global milestones endorsed are to: 1) exceed 90% coverage with the first dose of MCV nationally and exceed 80% vaccination coverage in every district or equivalent administrative unit; 2) reduce annual measles incidence to fewer than five cases per million and maintain that level; 3) reduce measles mortality by 95% or more in comparison with 2000 estimates.

[2] data source: Joint Reporting Forms (JRFs) for disease incidence and WHO-UNICEF estimates of national immunization coverage (WUENIC) data for coverage rates

[3] It should be noted that the 90% MVC1 coverage target for 2015 is a milestone towards elimination. In order to achieve the regional elimination targets, vaccination coverage needs to be >95% for two doses of MCV administered through routine immunization or routine immunization and SIAs. To prevent measles outbreaks, this high level of coverage needs to be achieved uniformly across all districts and across people in all age groups born since the introduction of measles vaccine.

both for MCV1 and MCV2. In these 53 countries,[4] the difference between MCV1 and MCV2 reached 16% in 2014 (87% MCV1 compared to 71% MCV2). This highlights the missed opportunities and routine system weaknesses that contribute to suboptimal population immunity and the inability to interrupt measles virus transmission.

In decreasing order, the following six large Member States had the highest number of susceptible infants in 2014 and accounted for more than two-thirds of the measles mortality burden in 2013: India, Nigeria, Pakistan, Indonesia, Ethiopia and Democratic Republic of the Congo. Measles disease is an indicator of weaknesses and gaps in the immunization and health systems. Indeed, these six countries are characterised by weak health systems (low MCV1 coverage, low density of nursing and midwifery personnel per 10 000 population, poor data quality, etc.) and this highlights the importance of strengthening health systems in order to achieve higher immunization coverage and optimise child health programmes.

As of December 2014, 140 (72%) Member States had introduced Rubella containing vaccines (RCV), a 49% (46 countries) increase from 2000. Of the 54 Member States that had not introduced RCV into their routine immunization programme, 42 (78%) are eligible for GAVI Alliance support. Average coverage globally has gradually increased from 41% in 2010 to 46% in 2014. However, it varies from 12% in the South-East Asia Region to 94% in the European Region. In 2014, an additional three Member States introduced rubella vaccine in their routine programme and introduction of rubella vaccine is ongoing in six Member States in 2015.

The global incidence of rubella has decreased from 14 per million population in 2012 (reported by 176 (91%) of member states) to 4.8 per million population in 2014 (reported by 161 (84%) of Member States). While this suggests progress, it is hard to interpret because the proportion of Member States reporting rubella cases has also declined. The same trend can be seen with Congenital rubella syndrome (CRS) reporting. In total 111 (57%) Member States reported CRS incidence in 2014 (4.32 per 100,000 live births) compared with 130 (67%) in 2012 (2.01 per 100,000 live births). The very low reported incidence is probably a reflection of very limited or non-existent CRS surveillance systems outside the Americas and a few other Member States.

Many countries regularly supplement routine immunization efforts through the use of supplementary immunization activities (SIAs). Approximately 197 million children in 33 Member States were vaccinated during SIAs with measles-containing vaccines in 2013 and an additional 215 million children in 28 Member States in 2014. Among 34 countries that conducted SIAs between 2012 and 2014 and that conducted a coverage evaluation survey of the SIA, less than half (16 Member States) were able to reach the target of 95% national coverage.

The Region of the Americas achieved measles elimination in 2002 and sustained the elimination for more than 10 years. The reestablishment of endemic measles transmission in Brazil in 2014 highlights the constant risk of spread from importations, especially in communities with low vaccination coverage. In 2014, more than 80% of measles cases in Brazil, Canada and the

[4] Countries that had introduced MCV2 in 2014 were excluded from this comparison,

United States were not vaccinated and, as a whole, the region has witnessed a decline in routine MCV1 coverage since 2012 with heterogeneous coverage at the subnational level where many municipalities have less than 80% coverage. Experience in the Americas indicates that maintaining measles elimination may be more challenging than achieving it because of the problems of complacency, hesitancy, declining routine coverage, decreasing quality of surveillance and competing public health priorities[5]. The Region achieved its 2010 rubella elimination goal in 2009 and very few cases of rubella and CRS have been reported in the region since then. The Region has the longest standing regional Verification Commission (RVC) called the International Expert Committee (IEC). As of December 2014, 98% of its Member States were verified as having achieved measles elimination. The IEC awaits interruption of measles transmission in Brazil and fulfilment of verification criteria by an external team, to declare the elimination of measles in the Americas. In 2015, the region was verified by the IEC as having eliminated rubella and CRS (table 1).

In the African Region many countries continued to experience measles outbreaks in 2014, with large outbreaks occurring in Angola, Ethiopia, Democratic Republic of the Congo, Nigeria and South Sudan. Outbreaks are mainly the result of stagnating coverage levels, with MCV2 coverage lagging behind MCV1 coverage, and poor quality of SIAs in many countries. Funding gaps also led to countries limiting the age ranges covered by SIAs despite a wider age range being indicated, and delaying MCV2 and RCV introduction owing to uncertainty about future financial commitments. The African Region does not have a rubella control or elimination target and, in 2014, reported the highest incidence of rubella of all WHO regions. This is not surprising given the low uptake of RCV in the region. By the end of 2014, seven (15%) countries had introduced RCV. Of these, four countries are GAVI eligible. The Region has not yet established a RVC.

The Eastern Mediterranean Region has seen a decline in reported measles cases since 2012. However in 2013- 2014, measles outbreaks occurred in Afghanistan, Pakistan, Somalia, Sudan, Yemen and in the Syrian Arab Republic and neighbouring countries hosting Syrian refugees. The majority of the reported measles outbreaks in the Region affect children under 10 years of age, indicating poor implementation of routine vaccination and poor quality of SIAs. In addition, the deteriorating security situation, and/or inadequate funds hamper adequate implementation of elimination strategies. Although the Region has not yet set a rubella elimination goal, 13 countries (60%) have set a national target for rubella/CRS elimination and 12 countries are now implementing CRS surveillance. In 2014, 2945 confirmed cases of rubella were reported by the countries of the Region, the majority of these (95%) were reported from four countries[6] which had not yet introduced RCV. So far, only one of the six GAVI-eligible countries (i.e. Yemen) has benefited from GAVI support to conduct SIAs with RCV. Although no RVC has yet been established, National verification Commissions (NVC) were established in 9 of 21 Member States. Three countries in the region (Bahrain, Oman and Palestine) are ready for verification of

[5] Ad-hoc Meeting of the International Expert Committee: Paving the road for the regional verification process April 22-23, 2015. PAHO, Washington DC

[6] Afghanistan, Pakistan, Sudan and Yemen

measles elimination, as they have reported zero cases for the past three years in the presence of a nationwide measles case-based surveillance and high coverage with both MCV1 and MCV2.

Following the establishment in 2013 of a measles elimination and rubella/CRS control target of 2020 in the South-East Asia Region, all countries have developed national plans of action to achieve these goals. By the end of 2014, regional coverage with MCV1 had increased to 84% and MCV2 to 59%. However, measles continued to circulate widely in most countries of the Region primarily due to underutilization of measles vaccine. Of the 40 625 measles cases reported in the region in 2014, India continued to report the most cases, followed by Indonesia, Sri Lanka and Nepal. Six of the 11 countries in Region had introduced RCV by the end of 2014, 2 countries introduced RCV in 2015, and the remaining 3 (accounting for 87% of children under 1 year of age in the region) have committed to introducing the vaccine in the next few years. The majority of rubella cases reported from the region in 2014 were reported from India followed by Indonesia and Nepal. CRS surveillance is routinely conducted in three countries in the region, Bangladesh, Nepal and Sri Lanka. The remaining countries in the region have agreed in principle to establish sentinel surveillance for CRS. There is no measles RVC in the Region yet however, it is likely to be established in 2015.

The European Region reported the lowest level of measles incidence since 2010 with 50% fewer measles cases reported in 2014 (14 020) than in 2013 (26 385). However, in 2014 outbreaks occurred in Bosnia and Herzegovina, Georgia, Italy, Russian Federation and Ukraine with the majority of the reported cases (78%) being either unvaccinated or of unknown vaccination status and more than half of those affected were 15 years of age or older. All 53 Member States in the Region use the combined measles, mumps and rubella (MMR) vaccine (except for Tajikistan that uses combined measles-rubella (MR) vaccine) in a two-dose schedule. Based on JRF data, the number of rubella cases reported in the region dropped by 98% between 2013 (39614) and 2014 (640). However, only 19 countries in the Region reported rubella cases in the 2015 JRF. Most of the cases occurred in Poland even though no cases were reported in their JRF. In the Region, 50 of 53 Member States have established NVCs and at the RVC meeting in November 2014, 22 (41%) and 23 (43%) of the Member States were verified to have interrupted endemic measles and rubella transmission, respectively (table 1).

Measles incidence (per 1 million population) in the Western Pacific Region increased from 5.9 in 2012 to 17.2 in 2013 and 70.6 in 2014. This is largely the result of a resurgence of transmission in endemic countries (China and the Philippines) and outbreaks following importation in countries with a period of low or no documented transmission (e.g. Papua New Guinea and Viet Nam). The region is witnessing increased incidence of measles among people outside the target group of current immunization strategies for measles elimination (i.e. infants aged <8 months, adolescents and adults). In 2014, the Regional Committee endorsed a regional rubella elimination goal and a 2020 target date will be discussed by Member States at the 2015 Regional Committee meeting. The number of reported rubella cases has been declining in the Region since 2011 (from 76 022 in 2011 to 12 814 in 2014) with the majority of cases being reported from China and Japan. Reported CRS cases have also declined in the region (44 in

2013 and 12 in 2014) with most cases being reported from China. CRS surveillance remains weak in some countries in the region. At the 2014 Regional RVC meeting in 2014, Australia, Macao (China), Mongolia and Republic of Korea were verified as having achieved measles elimination based on a verification-standard epidemiological surveillance system supported by accredited laboratories. Three additional countries were included in 2015: Brunei Darussalam, Cambodia and Japan.

Conclusions

1. Measles remain an important cause of mortality among children. For example, from 2000 to 2008, the decrease in measles mortality has accounted for 24% of the overall decrease in childhood mortality[7]. Continued efforts to reach the measles mortality reduction targets will be an important contributing factor towards achieving Sustainable Development Goal 3.2[8]
2. Although in 2014 some improvement was seen in MCV2 immunization coverage and a small reduction was reported in measles incidence (compared to 2010), based on current trends and programme performance, the 2015 global milestone targets will not be achieved.
3. To achieve the 2015 global measles incidence and mortality reduction milestone targets, it is essential to strengthen immunization systems as a whole in the six Member States with the highest measles disease burden. A strategic cross-cutting approach by all immunization stakeholders is needed in these countries to address the combined challenges of lack of health infrastructure and human resources as well as civil conflict in some areas.
4. Measles is a highly infectious disease, and its elimination requires very high and homogeneous population immunity and a high-quality surveillance system. Without a robust routine programme, elimination is very difficult to achieve and cannot be sustained. For Member States that are now at <90% coverage nationally, reaching ≥95% coverage will require substantial additional investment over a sustained period. The gap between MCV1 and MCV2 coverage highlights the missed opportunities and routine system weaknesses that contribute to suboptimal population immunity and ongoing measles transmission.
5. Rubella and CRS surveillance systems are weak and cases remain underreported, particularly in Member States that have not yet introduced RCV and/or do not have rubella control or elimination goals. Hence, global rubella and CRS surveillance data do not reflect the true burden of these diseases. Failure to fully integrate prevention of rubella and CRS with measles elimination activities represents a major missed opportunity for immunization.
6. Except for the Americas, the WHO regions are not on track to achieve measles and rubella elimination. Substantially greater commitment and investment by Member States and the global immunization community will be required to achieve the GVAP goal of measles and rubella elimination in five WHO regions by 2020.
7. Financial support from the GAVI Alliance together with the leadership, coordination and technical expertise from the Measles & Rubella Initiative (M&RI), provide an opportunity for Member States and regions to accelerate progress in rubella control and CRS prevention.

[7] Van den Ent et al. Measles Mortality Reduction Substantially Contributes to Lower Under-Five Mortality d JID 2011:204 (Suppl 1) 18-23.

[8] The SDG 3.2: By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births

Table 1: Progress towards measles and rubella elimination, by WHO region (as of 31 December 2014)

WHO region	Target year for measles/ rubella elimination in region	RVC established	Regional measles elimination verification report provided in 2015 by RVC for 2013/ 2014 data	Member States that have established an NVC n (% of total)	Established NVCs that submitted annual status reports[a] n (% of total)	Member States that were verified free of endemic measles based on 2013 reporting n (% of total)[b]	Member States that were verified free of endemic rubella based on 2013 reporting n (% of total)
African Region	2020	No	No	Unknown	Not applicable	Not applicable	Not applicable
Region of the Americas	2000	Yes	Verification reports sent in 2013. No need to send updates in 2014	24 (100%)	Reports not submitted on annual basis	43/44 (98%)	44/44 (100%)
Eastern Mediterranean Region	2015	Yes	No	9	Not applicable	Not applicable	Not applicable
European Region	2015	Yes	Yes (for2013)	50 (94%)	46 (87%)	22 (41%)[c]	23 (43%)
South-East Asia Region	2020	No	No	Unknown	Not applicable	Not applicable	Not applicable
Western Pacific Region	2012	Yes	Yes (for 2014)	17[d] (100%)	17 (100%)[d]	3 (11%)	Not applicable

a Percentage is out of the total number of established NVCs, not the total number of Member States. Note that a total of 46 reports were submitted to the European RVC. Percentage is based on Member States submitting reports in time for RVC review in October 2013.

b Percentage is out of the total number of Member States, and not the total number of established NVCs.

c These 22 countries were not verified as having been free of endemic measles for 36 months or longer, but were documented to have interrupted endemic measles transmission in 2013 (see Table 5).

2. Under what epidemiological circumstances is it recommended to provide a zero dose of MCV to infants <9 months of age?

Background

Recent measles outbreaks have manifest a bi-modal age distribution with an increased proportion of cases either too young to receive their scheduled first dose of MCV or in adolescents and young adults who are not usually targeted for vaccination. Recent examples of outbreaks with a high proportion of measles cases among infants include China, Mongolia, Sri Lanka, and Papua New Guinea.

In response to these outbreaks countries have recommended, or wanted to recommend, that infants at risk receive a dose of measles containing vaccine starting at 6 months of age. However, neither the current measles (2009) nor the current mumps (2007) vaccines position papers recommend vaccine use at a younger age during outbreaks. In contrast, the 2011 rubella vaccines position paper does recommend use of rubella containing vaccine (RCV) starting at 6 months of age during measles outbreaks. In addition, most manufacturer package inserts provide indications for measles (M) and MMR vaccine starting at age 9 months, however the indication for use of MMR vaccine manufactured by Serum Institute of India is from 12 months to 10 years. Hence, there is need for standardized global recommendations on use of MCVs (M, MR, MMR) under the age of 9 months that will enable countries to provide earlier protection to infants at risk of measles during outbreaks and for other specific indications.

Current recommendations on use of MCVs <9 months of age

The 2009 measles position paper[9] recommends that all national immunization programmes should provide children with 2 doses of MCV delivered through routine services and/or periodically through supplemental immunization activities. Where risk of measles mortality among infants remains high, the first dose of MCV (MCV1) should be administered at 9 months of age. In countries with low risk of measles infection among infants (i.e., near elimination), MCV1 can be administered at or after 12 months, because higher sero-conversion rates are achieved at 12 months. Increasing the age of administration of MCV1 from 9 months to 12 months represents a rational and desirable policy change. Before increasing age of MCV1, policy-makers should review local measles epidemiology and programmatic data on vaccination.

The 2011 Rubella Position Paper[10] recommends that RCVs: be administered at age 12–15 months, but may be administered to children aged ≥9–11 months and to older children, adolescents and adults. In most countries, rubella vaccine is given as MR or MMR, and the age of administration follows the schedule for measles. Thus, the first dose is usually given 9 months or 12–15 months and a second dose at 15–18 months or 4–6 years. During outbreaks of measles, RCVs may be administered to infants as young as 6 months. Because of the possibility of lower seroconversion, the dose administered at 6 months should not be counted as a valid dose, and the child should be vaccinated with subsequent dose(s) of RCVs according to the usual national immunization schedule.

[9] WHO. Measles vaccines: WHO position paper. Weekly epidemiological record, 2009. 35:84, 349-360.
[10] WHO. Rubella vaccines: WHO position paper. Weekly epidemiological record, 2011. 29:86, 301-316.

The 2007 Mumps Position Paper[11] recommends that the first dose of the mumps vaccine (monovalent or MMR) be given at the age of 12–18 months. For this reason, countries planning to add mumps vaccine should first reduce measles transmission to low levels to enable them to increase the age of administration of the first dose of measles vaccine to 12 months before considering adding mumps vaccine to their schedule.

At their November 2013[12] meeting, SAGE recommended that in countries using a two-dose schedule of MCV, both doses should be the same formulation of M, MR or MMR; that is, the same vaccine should be used for both doses irrespective of the age of administration of the first dose.

The 2009 WHO guidelines on Response to Measles Outbreaks in Measles Mortality Reduction Settings[13], recommend that as soon as a measles outbreak is suspected, all children six to 59 months of age (or other target age group determined by the local disease epidemiology) presenting to a health facility or an outreach vaccination site without a history of measles vaccination (either written or verbal), should be vaccinated. Children receiving measles vaccine before the age of nine months must be revaccinated after the age of nine months (with at least a one-month interval between the doses).

The 2012 WHO International Travel and Health[14] recommends that for infants travelling to countries experiencing extensive measles transmission, a dose of vaccine may be given as early as 6 months of age. However, children who receive the first dose between 6 and 8 months of age should subsequently receive the two conventional doses according to the national schedule.

WHO Regional recommendations for MCV administration under 9 months emphasize use in outbreak settings, humanitarian emergencies and for travellers to endemic areas. They are summarized below:

WHO Regional recommendations for use of MCV at <9 months
Africa: Outbreaks: M ≥6 months; Preventive M SIAs: 6-59 months
Americas: Outbreaks: MCV0 at 6-11 months
Eastern Mediterranean: Outbreaks: MCV0 at 6 months
Europe: Outbreaks: MCV0 at 6 months
SE Asia: Emergencies or outbreaks: Supplementary M dose at 6 months
Western Pacific: Outbreaks or travellers to endemic areas: MCV0 at 6 months

[11] WHO. Mumps vaccines. WHO position paper. 2007. Weekly epidemiological record, 2009. 7:82, 49-60.
[12] WHO. Meeting of the Strategic Advisory Group of Experts on immunization, November 2013– Conclusions and recommendations. Weekly epidemiological record, 2014. 1:89, 1-20.
[13] WHO. Response to Measles Outbreaks in Measles Mortality Reduction Settings. WHO/IVB/09.03
[14] WHO. International Travel and Health. Vaccine Preventable Diseases Update, 2014 ; Ch 6, pg 25.

Systematic review & meta-analysis of the safety, immunogenicity and effectiveness of measles vaccine administered to children <9 months of age

A comprehensive systematic review and meta-analysis of measles containing vaccines administered to children <9 months of age was conducted by the National Institute for Public Health and the Environment (RIVM) in the Netherlands[15]. The authors concluded that humoral immunogenicity depends on age of MCV1, as well as on the vaccine strain and presence of maternal antibodies. In meta-analyses of 20 studies meeting inclusion criteria, the age-specific seroconversion proportions were: 4 months - 50%; 5 months - 67%; 6 months – 76%; 7 months – 72%; 8 months – 85% (see figure below).

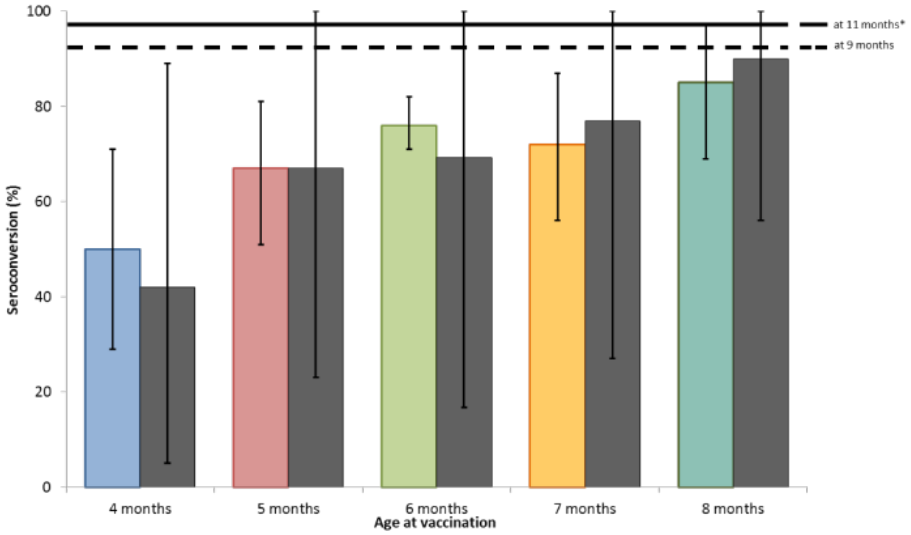


Figure 1. Proportion seroconverted by age MCV1 (4-8 months), pooled estimates derived from 20 studies (coloured blocks) and the proportion seroconverted by age of MCV1 (4-8 months) from a previous review (grey blocks).[16] Error bars present 95% confidence intervals. * The horizontal lines represent the median proportion of infants responding to MCV1 at 9 months (dashed line) and 11 months (filled line).[15]

Seroconversion rates <9 months of age are lower than the reference values of 92% and 98% for MCV1 at 9 months and 11 months, respectively. Seroconversion rates depended on measles strain used in the vaccine formulation, with Edmonston-Zagreb Mexico having the highest sero-conversion rate (95% at 6 months; (95% CI 92-97%)). Limited data on head-to-head comparisons found significantly higher seroconversion rates after vaccination with Edmonston-Zagreb compared to Schwarz (difference: 18%, (95% CI 3-34%)). Substantially lower geometric mean titres (GMT) of anti-measles IgG measured by the plaque reduction neutralization test (PRNT) were found comparing infants <9 months (283 mIU/ml) to infants ≥9 months (615 mIU/ml). The pooled estimate of vaccine effectiveness (VE) against clinical measles after MCV1 <9 months was 72%, compared to a VE of 77% between 9-11 months and 92% ≥12 months estimated in a previous review.[17] The current review found a larger

[15] L. Nic Lochlainn, N. van der Maas, B. de Gier, N. Rots, R. van Binnendijk, H. de Melker, S. Hahné. Measles vaccination below 9 months of age: Systematic literature review of effects and safety (available to SAGE members as a background document on the web)
[16] The immunological basis for immunization series. Module 13: Measles. 2008.
[17] Uzicanin and Zimmerman. Field effectiveness of live attenuated measles-containing vaccines: A review of published literature. JID 2011:204.

difference in VEs between MCV1 given at <9 months versus MCV1 given at ≥9 months of 18% (95% CI 15-20%) when considering within study comparisons only.

Limited evidence suggests avidity of measles specific antibodies to be significantly lower after MCV1 at 6 months compared to 9 and 12 months of age, whilst T cell proliferation was not dependent on age at MCV1. Regarding duration of immunity, one of three studies found significantly faster waning after MCV1 <9 months. Regarding blunting of the immune response to subsequent doses of MCV, early MCV1 was not found to affect seropositivity rates after MCV2. Limited evidence suggested avidity to be lower after MCV2 when MCV1 was given <9 months of age. Three studies reported GMTs after MCV2 with MCV1 administered <9 months versus MCV1 ⩾9 months. GMTs were lower after a two dose MCV schedule starting <9 months compared to MCV1 ⩾9 months of age. However, this difference was significant in only one of the three studies. No evidence of blunting was found considering VE. The pooled VE of two studies for a two dose schedule with MCV1 <9m was 93%, whilst the reference VE for two doses with MCV1 ≥9 months was 94%[16].

Regarding adverse events, fever after MCV1 occurred more often in infants <9 months of age than in infants aged 9 months or older, but in the absence of studies with control groups, it is impossible to know whether this is attributable to vaccination or to higher age-specific background rates. No reports of serious adverse events were found for infants given MCV1 <9 months, although this observation is limited by a small sample size.

Overall, the strength of the evidence from the review was limited by the nature of the study designs, which were mostly observational, as well as the limited comparability of the various laboratory assays used. However, the available information suggests that an early (<9 months) dose of MCV is effective and safe, although not as effective as a first dose at an older age (≥9 months).

Is there blunting of the immune response following MCV given at <9 months?
A review of the literature[18] showed a high prevalence of seropositivity following an early two-dose schedule with the first dose given at <9 months and no evidence of "immunological tolerance" – that is the non-reactivity of the immune system to an antigen as a consequence of specific immunologic mechanisms by which auto-reactive B and/or T cells are either deleted or rendered anergic. However, some evidence did exist for lower antibody concentrations and avidity, but not T cell proliferation, in children who received MCV1 younger than 9 months of age, which persisted after receipt of MCV2. The likely biological mechanism for this phenomenon is the presence of pre-existing neutralizing antibodies that impede replication of vaccine virus. In one VE study conducted during an outbreak in Niger, VE among those vaccinated at 9 months (95%) was similar to VE for those vaccinated at 6 months and 9 months (93%)[19]. In another study in Florida, VE of an "early" two-dose schedule (99.5%) was found to be similar to the VE for a single dose administered at 6-11 months (97.6%) or 12-18 months (99.7%).

[18] Presentation by William Moss, Is immunological tolerance a real concern? (available to SAGE members on the website)
[19] Kaninda AV, Legros D, Jataou IM et al. Measles vaccine effectiveness in standard and early immunizaiotn strategies, Niger, 1995. Pediatr infect Dis J. 1998; 17:1034-9.

Safety and immunogenicity of mumps and rubella vaccines (MR, MMR) among children <9 months of age

A literature review on safety and immunogenicity of the mumps and rubella components of MR and MMR among children < 9 months of age was conducted by CDC/Atlanta. Both the mumps and rubella components had comparable immunogenicity when administered to infants <9 month of age compared with infants ≥12 months; efficacy and effectiveness data were lacking. No significant adverse events were associated with MR or MMR in children <12 months old.

Impact of maternal vaccination on decay of maternally-derived measles and rubella antibodies among infants < 9 months of age

A specific concern relates to the duration of protection from maternally-derived measles and rubella specific antibodies in women with vaccine-induced immunity (as opposed to naturally-derived immunity). A review of the literature on the decay of maternally-derived measles and rubella antibodies was conducted by CDC/Atlanta. In a study comparing the decay of maternal antibodies in infants born to vaccinated and unvaccinated mothers in Netherlands, the half-life of IgM antibodies was found to range from 35 to 64 days and the duration of protection ranged from 3.5 months in infants born to mothers with vaccine induced immunity to 5.5 months in infants born to mothers with natural induced immunity [20]. Cross-sectional studies also supported the hypothesis that infants born to women with measles vaccine-induced immunity receive fewer measles maternal antibodies and therefore have shorter protection than infants born to women with naturally acquired immunity. For rubella, no strong evidence was found that maternal antibody levels are different between vaccinated versus naturally immune mothers, and transplacental transfer of antibodies is higher in women with low antibody levels. The decay of maternal rubella antibodies is variable, ranging from 30 to 45 days.

Programmatic considerations

Implementing a change in the recommended schedule of routinely administered vaccines has substantial implications for health workers and parents. Specific considerations of a six month dose include integration into the current vaccination schedule and the impact on wastage and cold-chain logistic issues. Resources are required for introductions, such as communication, training and creating new recording materials. In most developing countries, giving MCV at 6 months of age would require an additional visit and, depending on the national schedule, the issue of multiple injections would need to be considered. In countries with high MCV wastage, wastage may decrease, and in countries with cold chain logistics issues, capacity to provide an additional dose would need to be considered. The country experience with a dose of MCV at 6 months and at 9 months (e.g., Papua New Guinea and Saudi Arabia) is limited with problems related to recording doses and confusion in providers and parents. In settings where timeliness of routine vaccination is an issue, the dose at 6 months may be administered closer to 9 months, creating questions about optimal spacing for the next MCV dose.

[20][9] Leuridan, E., et al. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. BMJ, 2010. 340: p. c1626.

Non-specific beneficial effects of MCV on mortality were considered, but the evidence related to measles control was the dominant consideration in formulating recommendations.

Conclusions
Available evidence on immunogenicity, effectiveness and safety supports the use of MCV among infants aged 6 to 8 months and suggests a significant proportion of these infants will be protected against measles. The scientific evidence on immunogenicity suggests that MCV doses given before 9 months may be adequate if a subsequent routine dose is administered on schedule. Limited data on a two dose schedule starting <9 months suggests it leads to high seropositivity but may result in lower avidity antibodies and lower GMTs; T cell proliferation seems unaffected. The clinical relevance of this is unclear. Lower GMTs after an early two dose schedule may indicate that the duration of protection could be affected over the longer term.

Draft Recommendations
SAGE recommends that infants from 6 months of age receive a dose of measles containing vaccine in the following epidemiological circumstances: 1) in the presence of a measles outbreak as part of intensified service delivery; 2) during supplementary immunization activities (i.e., mass vaccination campaigns) in settings where risk of measles among infants remains high; 3) for internally displaced populations and refugees, and populations in conflict zones; 4) for individual children at high risk of contracting measles (exposed or at high risk of exposure to measles); 5) for infants travelling to countries experiencing extensive measles transmission; and 6) for infants known to be HIV positive (see section 4 below).

Because immunogenicity and effectiveness is lower than for doses administered at a later age, and because of the concern about the long term effectiveness of an early two dose schedule, a dose administered more than a month prior to the recommended age of MCV1 should be considered a “zero dose” (MCV0) rather than the first dose. Children who receive an early dose of MCV (i.e., MCV0) should then receive subsequent measles containing vaccines at the recommended ages according to the national schedule.

Available evidence on safety and immunogenicity of rubella and mumps-containing vaccines support their use down to 6 months of age. Thus, in countries using measles vaccine in combination with rubella vaccine or rubella-mumps vaccines (i.e., MR or MMR) in their national routine schedule, the combined vaccine rather than measles-only formulations of MCV should also be administered to children under 1 year of age. SAGE recognizes that this is an off-label recommendation and recommends that governments do not restrict the use of the vaccine in this age group for this reason only, and that manufacturers consider obtaining licensure down to 6 months of age.

Research needs
While it is possible that an early 2 dose schedule of MCV at 6 and 9 months is as effective as 9 and 12 months, evidence is lacking to support a SAGE recommendation for administration of MCV1 at 6 months of age. A particular concern is that coverage with the second dose is often much lower (than with the first dose) and, hence, many young children would be left unprotected after a single dose administered at 6 months of age. A clearer understanding of the biological basis for the observed immunological blunting after MCV given at 6 months would be helpful. Further research, including vaccine effectiveness and

immunogenicity studies, is needed to better understand whether a dose of MCV given <9 months should be counted as MCV1 or MCV0. Further modelling would be helpful to identify the optimal 1 dose and 2 dose schedule as a function of birth rate, coverage, age-specific vaccine effectiveness and incidence, and impact on overall population immunity. In addition, it would be helpful to perform more head-to-head comparisons of different vaccine strains.

Epidemiologically, it would be useful to document whether there is clear evidence of an increasing incidence of measles in infants below 9 months of age.

Further studies of the non-specific effects of measles-containing vaccines on overall mortality, and severity of measles vaccine failures compared to non-vaccinated cases should be conducted.

In addition, operational research on the programmatic impact of implementing and operating different schedules would be helpful. The impact of changing the age of a routine dose or adding a dose may be significantly disruptive for programs. Whether an earlier dose would increase uptake of measles vaccine (or other vaccines) and overall coverage is unknown.

3. How can data on vaccination coverage, surveillance, seroprevalence and other sources be used to determine the target age range for measles or MR SIAs in order to stop measles and rubella transmission?

Introduction

As pioneered in the Region of the Americas (AMR), the classic SIA strategy for measles control and elimination is for programmes with low to moderate MCV1 coverage (<90%) to conduct a wide age-range "catch-up" supplementary immunization activity (SIA) targeting children <15 years of age, followed by regular "follow-up" SIAs targeting children <5 years of age. Some countries with high coverage with two doses of MCV (i.e., >90%) have done only a "catch-up" targeting older children and adolescents, based on low coverage in earlier years, surveillance or seroprevalence data. When these SIAs are successful countries report low numbers of cases. After several years of low measles incidence, countries in AFR reaching high coverage of routine MCV1 and reported high coverage during follow-up SIAs experienced large outbreaks with an increase in the proportion of cases in older age groups. In response these countries conducted a second SIA targeting children <15 years of age and have not had large outbreaks since but also have not yet achieved elimination. Other countries in AFR and EMR experienced initial decreases in measles incidence after initial catch-up SIAs, but after 3-4 follow-up SIAs began to have large outbreaks with a high proportion of cases >5 years of age. Some of these countries have targeted wider target age ranges in subsequent follow-up SIAs. Gavi, the Vaccine Alliance, has focussed their support on SIAs targeting children <5 years of age, because this age group experiences the highest mortality risk from measles.

Rubella vaccine currently has not yet been introduced into the immunization programmes of 54 countries. Some of these countries have increasing susceptibility to rubella among women of childbearing age (WCBA) due to demographic factors (e.g., declining birth rates). Identifying these countries will be important in order to avoid outbreaks in adults which may lead to cases in pregnant women resulting in children born with congenital rubella syndrome (CRS). An algorithm has been developed to guide countries and partners in determining if the SIA to introduce MR vaccine should target adolescents 15 years of age and older. If validated the results of this algorithm could be used for resource mobilization, given that currently most donor funding is restricted to SIAs targeting children <15 years of age.

Current Global and Regional Recommendations

The 2009 measles position paper [21] recommends that follow-up SIAs be conducted nationwide every 2–4 years and target children aged 9–59 months. Data on vaccination coverage should be used to monitor the accumulation of susceptible people and follow-up SIAs conducted before the number of susceptible children of pre-school age reaches the size of the birth cohort.

The 2009 WHO guidelines on Response to Measles Outbreaks in Measles Mortality Reduction Settings [22], recommend that the target age range for a non-selective SIA be chosen depending upon the susceptibility profile of the population. Key elements to consider are 1) routine vaccination coverage and coverage during SIAs in each birth cohort; 2) age-

[21] WHO. Measles vaccines: WHO position paper. Weekly epidemiological record, 2009. 35:84, 349-360.
[22] WHO. Response to Measles Outbreaks in Measles Mortality Reduction Settings. WHO/IVB/09.03

specific attack rates; and 3) absolute number of cases. All age groups contributing to cases should be considered for vaccination. Even if the attack rate is low in some age groups, especially in older age groups, they may represent a large proportion of cases and large potential groups at risk of contracting measles and of transmitting the infection to younger persons.

The 2011 Rubella Position Paper [23] recommends that countries undertaking the elimination of rubella and CRS begin with MR vaccine or MMR vaccine in a campaign targeting a wide age range, followed immediately by the introduction of MR or MMR vaccine into the routine programme. Depending on their targeted goal, burden of disease and available resources, countries may choose to accelerate their progress towards elimination by conducting campaigns targeting a wide range of ages of both adult males and females.

At their November 2013 [24] meeting, SAGE recommended that countries integrate their surveillance, demographic, survey and (if available) seroprevalence data together with vaccination coverage information, history of MCV and RCV use, and local knowledge to determine the age distribution of susceptibility and hence the target age range of measles and MR SIAs. Additional information to consider in relation to MR SIAs is rubella immunity among women of child-bearing age, the epidemiology of rubella and CRS, age-specific fertility rates, and the age of mothers of CRS-affected infants.

WHO Regional recommendations on the target age range for measles follow-up SIAs are summarized below:

Region (Document)	**Recommended interval between SIAs**	**Recommended target age range**
AFR (TAG, 2005)	MCV1 >80% - interval of 4 y MCV1 60-79% - interval of 3 y MCV1 <60% - interval of 2 y	9-59 m 9-47 m 9-35 m
AFR (SIA Guide, 2015)		Determined according to the epidemiology: the age breakdown of confirmed measles cases & deaths, age specific incidence rates
AMR (13th TAG, 1999)	When number of susceptibles approaches the size of a birth cohort	1-4 years
EMRO (N Teleb, personal communication)		Depends on epidemiology of the disease and previous vaccination activities
EURO (MR Strat Plan 2003)	Every 3-5 years	Children not targeted by previous mass campaign
SEARO (Strategic Plan	Every 3-5 years, depending on the quality of the initial national wide-	Monitor the age specific population immunity with

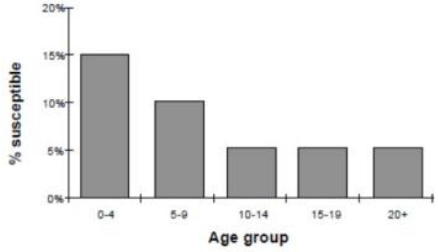
[23] WHO. Rubella vaccines: WHO position paper. Weekly epidemiological record, 2011. 29:86, 301-316.
[24] WHO. Meeting of the Strategic Advisory Group of Experts on immunization, November 2013– Conclusions and recommendations. Weekly epidemiological record, 2014. 1:89, 1-20.

for measles elimination and rubella control, 2015)	age range MR SIA and coverage with MCV1 and MCV2	laboratory supported case-based surveillance, the use of the MSP tool, the use of the sub-national risk assessment tool and other data as available. Cover ages with population immunity <95%
WPRO (Measles Elimination Guide 2013)		<2y or <5y, depending on national SIA guidelines

The 16th Technical Advisory Group meeting for PAHO recommended that rubella-endemic countries conduct SIAs targeting men and women in rubella endemic countries from 15-29 or 15-39 years of age, depending on susceptibility in adults, with adult susceptibility determined by year of introduction of the MMR vaccine in the national schedule, the extent of follow-up MR or MMR vaccination campaigns to maintain measles elimination, and the rubella epidemiology in the country.

The only recommendation on how to use age-specific susceptibility data for measles is from the EUR 1999 Strategic Framework for the Elimination of Measles. This guidance was developed and validated by Nigel Gay based on data from England, Denmark and Canada. It recommends separate cut-offs by 5-year age groups: 15% for 0-4 years, 10% for 5 – 9 years, and 2% for every 5-year age group 10 years of age or older. Keeping susceptibility below these thresholds would maintain R < 1. However, these cut-offs were based on interpersonal contact patterns from studies done in Europe and assume a low birth rates, and therefore may not be appropriate for other settings.

Figure. Susceptibility targets for measles elimination, European Strategic Framework for the Elimination of Measles, 1999.



Global and regional recommendations for follow-up measles SIAs are to monitor accumulation of susceptible children and conduct an SIA targeting <5 years of age when that number equals the size of one birth cohort. Recommendations are not different for control or elimination settings. For CRS prevention and rubella elimination, global and regional recommendations are to start with an SIA targeting at minimum children <15 years of age, though elimination can be accelerated with an SIA targeting men and women. More recent recommendations are to assess gaps in immunity to measles or rubella by age group, using a susceptibility profile, age-specific attack rate, percentage or numbers of cases, serosurveys, and programme history. Outside of the European context, there are no fixed

cut-offs to decide when the immunity gap is large enough that an age group should be targeted by an SIA.

Review of impact of different SIA strategies on measles incidence – a multi-country analysis

A multi-country analysis of the impact of different SIA strategies on measles incidence is being done by CDC / Atlanta. Preliminary results reviewed the measles prevention strategies that have been used, their impact on measles incidence, and regional differences. Data on cases, coverage, vaccine introductions, and SIAs were accessed from WHO IVB and population data from the UN Population Division projections, 2012 revision. Countries were grouped as to their use of SIAs and / or MCV2 in routine (Table).

Table. Measles vaccination strategies

Abbreviation	Strategy defined according to intervention order
MCV_2	MCV1 + MCV_2 in routine schedule
SIA_{WA}	MCV1 + a wide-age SIA and regular follow-ups
SIA_{WA}/MCV2	MCV1 + a wide-age SIA and routine MCV2
MCV2+SIA_{WA}	MCV1 + MCV2 routine + wide-age SIA
SIA_{WA}+MCV2	MCV1 + wide-age SIA with regular follow-ups +MCV2 routine

Each added intervention, first adding a second dose (through routine or SIAs) and second adding both SIAs and MCV2 in routine, decreased median measles incidence 10-fold, as shown in the figure.

Figure. Median measles incidence per million by vaccination strategy, 1985 – 2014.

Between 2000 and 2014, most countries experienced years with excellent control (<5 cases / million), though countries in AFR, EMR and SEAR spent more time with poor (50-100 cases / million) or “no control” (>100 cases / million). Future work will look at characteristics of measles SIAs that are most effective in reducing disease incidence.

Comparison of age distribution of cases and seroprevalence studies

A literature review done at CDC / Atlanta of measles and rubella seroprevalence studies published between 2000-2014 identified 14 studies. Rubella testing only was done in four while 10 included testing for both measles and rubella. Eight were done only in WCBA and one (from Nepal) was done after a measles-rubella SIA targeting children <15 years of age. Annual numbers of measles and rubella cases reported through the JRF were used to calculate disease incidence and identify countries with high incidence (>20 cases per million population) in the year before, during or after the survey. Case-based measles data from countries with both high incidence and available serosurveys was then used to calculate age-specific incidence. Preliminary results from this work were difficult to interpret and further analysis of data from seroprevalence studies will include countries in elimination or

near-elimination settings to determine the age-specific seroprevalence associated with achieving elimination.

Modelling of age distribution of cases from outbreaks to determine vaccination strategies

Modelling is ongoing to assess the marginal benefit of wide age-range SIAs in four countries, with a deeper look at sub-national dynamics in Ethiopia[25]. Because mathematical modelling using achievement of elimination as the outcome is challenging, the approach being taken is to model the conditions needed to maintain elimination. When the effective reproduction number is below one (R < 1) persistent measles transmission is unlikely and measles has been eliminated. When the routine immunization programme cannot reach and immunize all children born, R increases with time until an effective SIA immunizes previously susceptible children and decreases R. When R<1, outbreaks are possible but will be small and self-limited whereas when R>1 they are more frequent, larger, and more likely to persist. This analysis looks at the outbreak risk over 15 years, normalized to be 1 for the least aggressive strategy. The strategies involve SIAs repeated every 4 years with different target age ranges, and different proportions of susceptible children immunized by the SIA. In the figures "coverage" or "immunization" is not the proportion of children in the target population reached, but rather the proportion of susceptible children immunized. The least aggressive strategy is targeting children <5 years of age and reaching 70% of susceptible children.

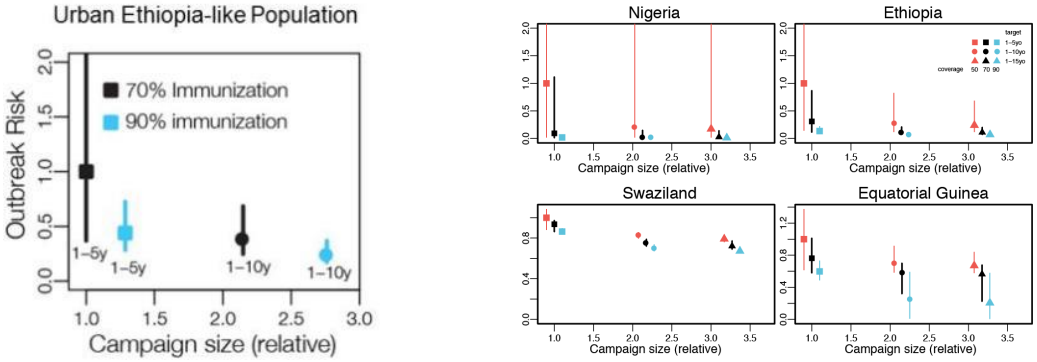


Figure. Comparison of relative outbreak risk and campaign size for different choices of target age range and proportion of susceptible children immunized by SIAs. Left panel is for a population like urban Ethiopia, right panel is for Nigeria, Ethiopia, Swaziland and Equatorial Guinea. SIA targeting <5 years represented by squares, <10 years by circles, and <15 years by triangles.

In a setting like urban Ethiopia, where most susceptibility is in children <5 years of age, increasing from 70% to 90% the proportion of susceptible children immunized and targeting <5 years in follow-up SIAs reduces the 15-year outbreak risk by 50%. The same results can be achieved when the follow-up SIAs target is increased to <10 years of age while still reaching only 70% of susceptible children. Using national data from Ethiopia, Equatorial Guinea, Nigeria and Swaziland and adding <15 year follow-up SIAs, in urban Ethiopia, Equatorial Guinea and Nigeria, where routine coverage is low and most susceptibility is in children <5 years, outbreak risk is most affected by SIA quality. Increasing the target age of follow-up SIAs to <10 years also reduces outbreak risk, but extending to <15 years provided

[25] Presentation by Dr Matthew Ferrari, Penn State University, given at the Measles Rubella Working Group Meeting, 3-4 September 2015

little additional benefit. In Swaziland, where routine coverage is high and susceptibility is low, the benefit of targeting wider age ranges is less marked. This analysis shows that follow-up SIAs targeting children < 5 years of age are sufficient to maintain herd immunity when they reach high coverage in unvaccinated children in SIAs. However, where high quality follow-up SIAs are difficult to achieve, targeting children <10 years can achieve similar effect. Repeated follow-up SIAs targeting children <15 years of age have little marginal impact on outbreak risk.

In larger countries subnational variations in susceptibility may require subnational variation in strategies. The age distribution of cases was compared for each region in Ethiopia. Ethiopia started accelerated disease control in 2002 with a multi-year, rolling SIA targeting children < 15 years of age and reaching 90% coverage. Since that SIA the country has done four SIAs targeting children <5 years of age (except for a target of <4 years in 2010) that reached 88 – 106% coverage. Routine MCV1 coverage has gone from 36% in 2002 to 70% in 2014. Reported cases initially decreased to low levels but have been increasing since 2006. Despite SIAs reaching 90% of children in recent SIAs (confirmed by survey), large outbreaks have been occurring since 2013 with increasing incidence and proportion of cases in children >5 years of age (see Annex 2).

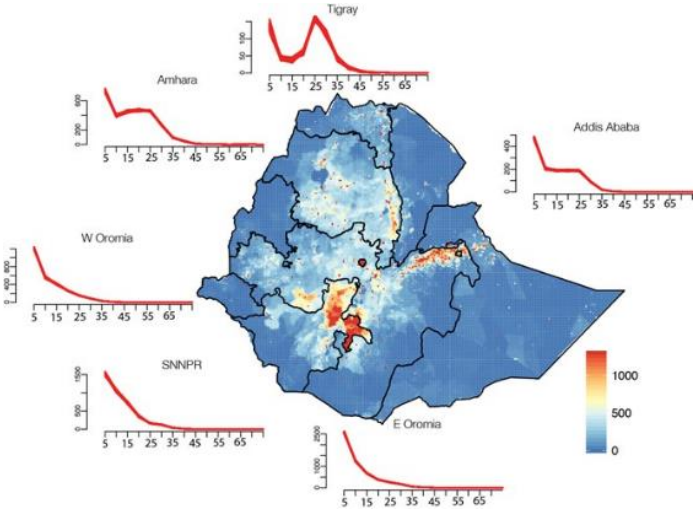


Figure. Map of Ethiopia showing density of children <5 years susceptible to measles and age distribution of confirmed measles cases by age (2004-2014).

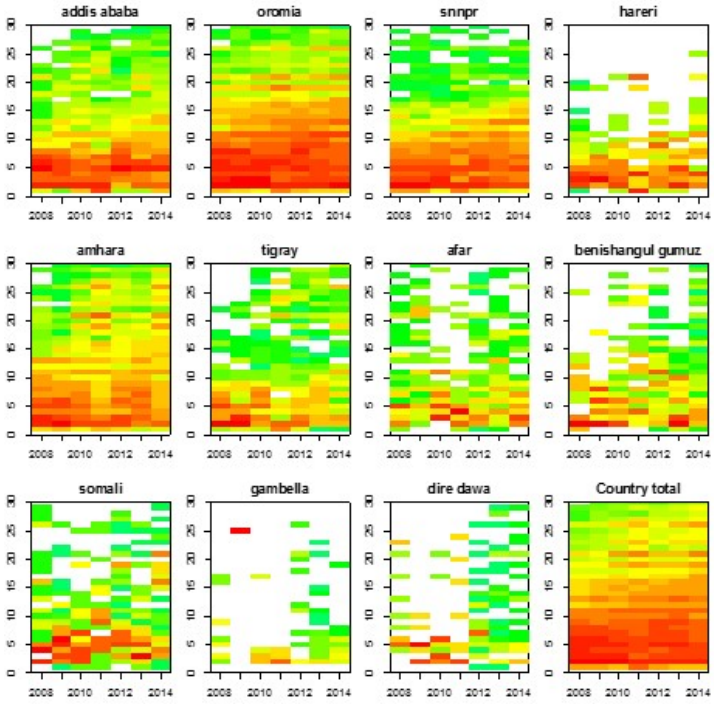


Figure. Time trends in the age distribution of measles cases by region in Ethiopia from 2008-2014. Cases increase as the colour changes from green to red.

In Northern Ethiopia a larger proportion of cases are in older age groups, reflecting the strength of the programme in this area and the lower risk of exposure to measles (see figures). Here, SIAs should target accumulated susceptibility by covering a wider age group (<35 years). In Southern Ethiopia a larger proportion of cases are in younger age groups, reflecting endemic transmission. SIAs in the South should target transmission in those age groups. However, in the most populated Southern regions of Oromia and SNNPR, large outbreaks have been occurring in 2013-2015 with high incidence in children 5-14 years of age (see Annex), so SIAs should continue to target children up to 10 – 15 years of age.

Taxonomy of measles control regimes and its relation to the age distribution of cases
A group at Johns Hopkins University has been developing a taxonomy approach using two indicators: adjusted measles incidence vs. coefficient of variation. A state-space model was used to adjust for under-reporting of measles cases. Lexis diagrams are used to estimate the susceptible proportion by age, given adjusted cases, along with routine and supplementary vaccination. As countries move to higher coefficient of variation, they are more likely to have susceptibility in older ages.

This work suggests that the current approach, based on a the current or past age distribution of cases, may not be as effective as basing SIA target age ranges on predicted age group likely to have immunity gaps in the future. Using the current approach, SIAs have targeted only younger ages as they experience the highest incidence but may be missing pockets of susceptibility in older age groups. Data from Africa from 2006-2014 show that the current approach did not predict the large multi-country outbreak in 2009-2011 affecting children >5 years of age.

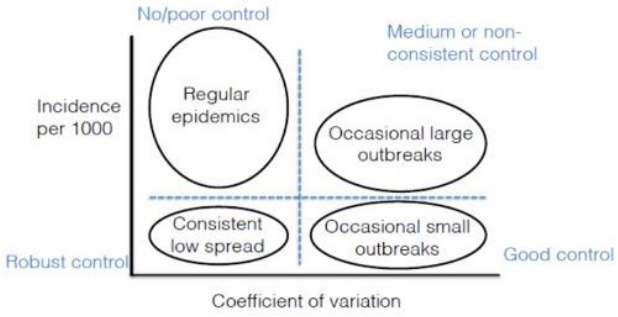


Figure. Taxonomy of measles control to help guide future SIA target age range.

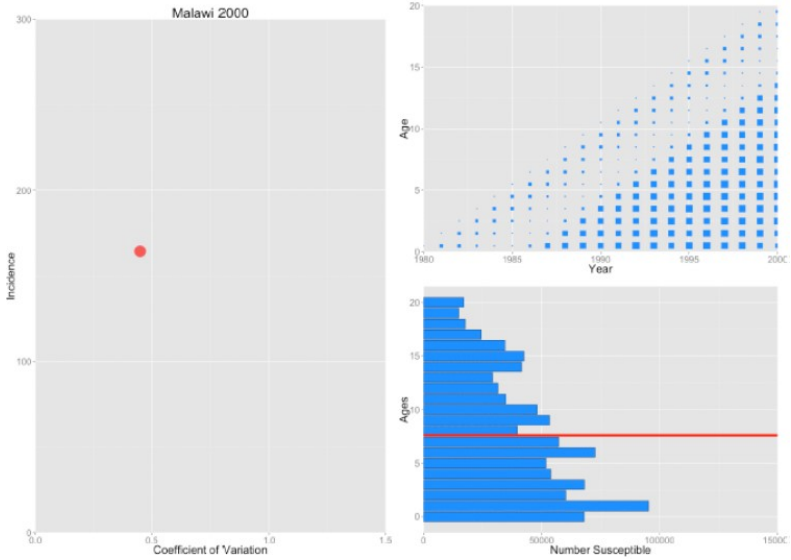


Figure. Taxonomy of measles control – example of Malawi. Red line is the mean age of adjusted cases.

The taxonomic approach suggests common dynamics as countries approach elimination, implying that there is a fundamental process underpinning this evolution. Though the results are not definitive, the approach after further refinement may help guide countries without the need for a detailed serological survey.

Algorithm for determining upper age limit for rubella introduction SIAs

Based on projections using disease transmission models, effective rubella control requires at least 80% of the population to be immune. When introducing RCV into an immunization schedule, programmes are often faced with the question of what criteria would require them to target older adolescents or young adults. An algorithm has been developed to guide programmes. In general, when >=80% of WCBA are immune to rubella, the initial MR catch-up campaign does not need to target age groups over 15 years of age. When immunity is below that level then the older age groups should be considered for inclusion into the target population for the catch-up SIA.

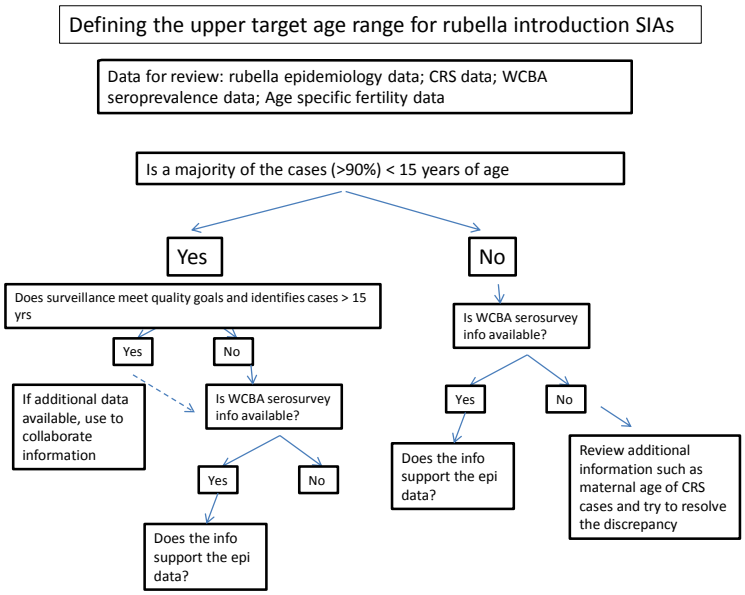


Figure. Proposed algorithm for determining if an introductory SIA for MR should target people >15 years of age.

The algorithm assesses the proportion of rubella cases <15 years of age, serosurvey data from WCBA, and additional data such as age of mothers of CRS cases and country fertility rates. This algorithm was applied to available data from Egypt, Ghana and Nepal and compared rubella incidence after the SIA. In Egypt rubella cases in 2007 were mostly aged 10-20 years and a serosurvey done in 2002 showed low immunity in children below 11 years of age. After an MR SIA in 2007-2008 targeting people 2 – 20 years of age, annual incidence of reported rubella sharply decreased and since 2010 has been <1 case per million population. In Ghana and Nepal the majority of reported rubella cases were <15 years of age and serosurveys in WCBA showed high immunity in women >15 years of age. MR SIAs were done targeting children <15 years of age and since then both countries have had an annual incidence of lab-confirmed rubella <1 per million population.

Based on these country examples the 80% cut-off for determining age range predicts successful prevention of rubella and CRS. The recommendations based on the algorithm may have been more robust for these countries as seroprevalence data were available. Monitoring rubella incidence in countries applying the algorithm and modelling results expected when following the algorithm should help to validate it and possibly refine the parameters used. A similar algorithm should be developed for measles to guide decisions on including older age groups in follow-up SIAs, providing an integrated process for determining the target age range for measles-rubella SIAs.

Conclusions

Current recommendations are for countries to monitor the accumulation of susceptible children and conduct an SIA when the number reaches the size of one birth cohort, targeting children from the age of routine MCV1 to at least 59 months. Recent experience suggests significant pockets of susceptibility to measles exist in older age groups, but outside of Europe no explicit criteria exist to determine when to include age groups >5 years of age. For rubella introduction, no clear WHO guidance exists on when to target age groups >15

years of age. Analyses of the impact of SIA strategies and the comparison of surveillance and susceptibility data are still at an early stage. Dynamic disease models for four countries shows that immunization of susceptible children through an SIA is a critical indicator of the impact of the SIA on reducing transmission. Countries can maintain R < 1, and lower the risk of outbreaks, more efficiently when the proportion of susceptibles immunized is high. When SIAs have difficulty reaching a high (90%) proportion of susceptibles, a wider target age range will be equally effective but less efficient. Data from Ethiopia show that throughout the country susceptibility is high in children <15 years of age, with pockets in young adults in regions with stronger immunization programmes. A taxonomy using adjusted incidence and the coefficient of variation of incidence looks promising to help predict when significant susceptibility exists in older age groups.

An algorithm to guide the inclusion of older age groups in introductory MR SIAs, when applied in selected countries, appears to result in very low rubella incidence. Additional examples and modelling is needed to confirm the applicability of the algorithm and adjust its parameters. A similar algorithm for inclusion of older (>5 years of age) age groups for measles SIAs is needed, allowing for an integrated measles-rubella approach.

4. Should an additional dose of measles-containing vaccine be recommended for HIV-infected children receiving highly active antiretroviral therapy?

Introduction

Human immunodeficiency virus (HIV)-infected children are at increased risk of measles morbidity and mortality and could play a role in sustaining measles virus transmission in regions of high HIV prevalence. Protective antibody concentrations wane following measles vaccination of HIV-infected children as a consequence of impaired immunity. Until the widespread introduction of antiretroviral therapy, the high mortality rate of HIV-infected children prevented the build-up of a sizeable pool of measles susceptible children. Highly active antiretroviral therapy (HAART) is effective in prolonging survival in HIV-infected children by suppressing viral replication and restoring immune function. However, immune reconstitution in children is primarily achieved through the generation of naïve T-cells rather than the expansion of memory T-cells and antiretroviral therapy does not restore measles vaccine-induced immunity established prior to therapy. As a consequence, HIV-infected children are at increased risk of measles morbidity and mortality despite measles vaccination. In countries with a high prevalence of HIV infection, susceptible children receiving HAART could become sufficiently numerous to sustain measles virus transmission despite high levels of measles vaccine coverage.

In 2012, the Advisory Committee on Immunization Practices recommended measles revaccination of persons with perinatal HIV infection who were vaccinated before establishment of effective antiretroviral therapy with two appropriately spaced doses of MMR vaccine once effective ART has been achieved. In low and middle-income countries, particularly those in sub-Saharan Africa that bear the greatest burden of pediatric HIV infection, antiretroviral treatment programs have scaled-up dramatically, increasing access to life-prolonging treatment for HIV-infected children. To protect these children against measles, and ensure high levels of population immunity, revaccination with MCV after immune reconstitution with HAART should be recommended.

Evidence in Support of the Recommendations

An increasingly large number of HIV-infected children will receive antiretroviral therapy

As of December 2013, an estimated 740,000 HIV-infected children in low and middle-income countries were receiving antiretroviral therapy, with 630,300 (85%) residing in Africa. These children represent only 23% (21-25%) of the estimated 3.2 million (2.9 to 3.5 million) children younger than 15 years of age living with HIV.

Measles case fatality ratio is higher in HIV-infected children

In the largest prospective study of measles mortality among hospitalized HIV-infected children, involving 1227 Zambian children with confirmed measles and HIV infection status, death during hospitalization occurred in 23 HIV-infected children (12.2%) and 45 HIV-1-uninfected children (4.3%, P <0.001). After adjusting for age, sex and measles vaccination status, HIV infection (OR 2.5, 95% CI: 1.4, 4.6) and the presence of a desquamating rash were significant predictors of measles mortality.

Measles seroprevalence is lower in HIV-infected than uninfected children after vaccination

The Global Advisory Committee on Vaccine Safety (GACVS) published a report on the immunogenicity and effectiveness of measles vaccination in HIV-infected children in 2009 based on a systematic review and meta-analysis. Serological assessments of measles antibody levels after vaccination showed that measles vaccination at the age of 6 months resulted in similar levels of antibody in HIV-positive children and children who had not been exposed to HIV. However, by the age of 9 months, fewer HIV-positive children responded to measles vaccine than did children who had not been exposed to HIV. At the time of the review there were scant data about the effects of HAART on responses to measles vaccination.

The systematic review was updated based on articles published after the availability of HAART in 1996 through February 2015. For the five studies reporting on children vaccinated at nine months of age, the seroprevalence ratio comparing HIV-infected to uninfected children ranged from 0.44 to 1.05, although the confidence intervals for individual studies were wide. Heterogeneity across studies precluded meta-analysis. The updated systematic review did not find evidence contradicting the earlier review.

Protective measles antibody levels wane in HIV-infected children not receiving HAART
Two prospective studies documented waning measles antibody levels in HIV-infected children not receiving antiretroviral therapy. In a prospective study of the immunogenicity of measles vaccine administered at 9 months of age to HIV-infected and uninfected children in Lusaka, Zambia, 88% of 50 HIV-infected children developed antibody levels of ≥120 mIU/mL, compared with 94% of 98 HIV-unexposed children and 94% of 211 HIV-exposed, uninfected children, suggesting a good primary response to measles vaccine. By 27 months after vaccination, however, only half of the 18 HIV-infected children who survived and returned for follow-up maintained measles antibody levels ≥120 mIU/mL, compared with 89% of 71 uninfected children

Low measles seroprevalence at the time of starting treatment provides supportive evidence that antibody levels wane in HIV-infected children not receiving antiretroviral therapy. In the largest study, involving HIV-infected children receiving antiretroviral therapy in the United States, only 52% of 193 children had protective antibody concentrations at the time of starting antiretroviral therapy. Among 61 HIV-infected Zambian children starting antiretroviral therapy, only 23% were measles seropositive.

Antiretroviral therapy does not restore measles immunity in the absence of revaccination
In a study of the impact of HAART on measles vaccine immunogenicity in Lusaka, Zambia, HAART was not associated with measles seroconversion in 46 children who were seronegative at enrolment nor was there a trend indicating that seroconversion was more likely with increased time on HAART after adjusting for baseline age and $CD4^+$ T lymphocyte percentage.

Antiretroviral therapy improves responses to measles vaccine
In six published studies, measles seroprevalence following revaccination of HIV-infected children receiving antiretroviral therapy ranged from 64% to 95%, with a mean of 83%. The two largest studies also had longer follow-up. In a study of 51 HIV-infected children receiving highly active antiretroviral therapy in Thailand, measles seroprevalence was 90% one month after measles revaccination and 85% three years after revaccination. In a study of 193 HIV-

infected children receiving highly active antiretroviral therapy in the United States, measles seroprevalence was 89% eight weeks after measles revaccination and 80% 80 weeks after revaccination. These two studies provide the best evidence of the long-term immunogenicity of measles revaccination in children receiving HAART.

Measles vaccine is safe in HIV-infected children
GACVS published a report on the safety of measles vaccination in HIV-infected children in 2009 based on a systematic review. The Committee concluded that the evidence does not demonstrate a serious risk in using measles vaccine in HIV-positive children. Although millions of doses of measles vaccine have been administered to HIV-positive children, only one case report was identified that suggested possible severe adverse events following immunization. However, ascertainment of such events may be incomplete, particularly given the need for molecular detection and sequencing to distinguish wild-type from vaccine measles virus.

An updated systematic review through February 2015 found no additional evidence of severe adverse events attributable to measles vaccine in HIV-infected children. Deaths after vaccination were reported in six studies, with a case fatality of 19% in 309 HIV-infected children who received measles vaccine. However, no deaths were attributed to measles vaccine and there were no reported cases of pneumonitis, measles inclusion body encephalitis or thrombocytopenia. Any potential increased risk of adverse events following measles vaccination of HIV-infected children is likely to be substantially lower in children who achieve immune reconstitution following antiretroviral therapy.

Optimal timing of measles revaccination in relation to antiretroviral therapy
The optimal timing of vaccination after initiation of antiretroviral therapy is not known. Most cross-sectional and prospective studies found that higher $CD4^+$ T lymphocyte counts and lower HIV viral loads were crudely or independently associated with seropositivity after measles vaccination of HIV-infected children receiving antiretroviral therapy, suggesting standard markers of immune reconstitution are associated with improved responses to measles vaccine.

HIV-infected children who start antiretroviral therapy prior to or shortly after the first dose of MCV may not require revaccination
Age at initiation of antiretroviral therapy in relation to the timing of measles vaccination may be important in enhancing vaccine responses. In one study, children who initiated antiretroviral therapy younger than 12 months had higher levels of protective immunity than children who initiated antiretroviral therapy later in childhood, with levels of immunity comparable to uninfected children of the same age. Little data exist on the immunogenicity of measles vaccine in children who start HAART prior to 9 or12 months of age.

Revaccination of HIV-infected children should be programmatically feasible
HIV-infected children receiving antiretroviral therapy have intensive follow-up, most often at clinics devoted to the care of HIV-infected children and adults where they are typically evaluated every 3 months, particularly after the start of antiretroviral therapy. Frequent follow-up visits would facilitate revaccination against measles. However, a policy to revaccinate HIV-infected children against measles will require coordination between the clinics that provide HIV care and those that provide routine immunizations to children.

Evidence to recommendations

1. The quality of evidence is moderate for benefits and harms as it is based on prospective and cross-sectional observational studies and not randomized controlled trials.
2. There is strong evidence that the benefits of providing an additional dose of MCV to HIV-infected children receiving HAART outweigh the risks of measles vaccine.
3. There is confidence in the estimate of the relative importance of preventing measles in HIV-infected children and that this would be preferred by caregivers.
4. The costs associated with an additional dose of MCV are trivial compared to the cost of treating and caring for HIV-infected children.

Draft Recommendations

These draft recommendations emphasize current World Health Organization recommendations and expand them to include an additional dose of MCV for HIV-infected children receiving HAART.

1. Early diagnosis of HIV infection is critical to allow early initiation of HAART, immune reconstitution and better responses to vaccines.
2. In areas where there is a high incidence of both HIV infection and measles, the first dose of MCV may be offered as early as age 6 months to provide protection to HIV-exposed infants, as currently recommended by the World Health Organization, followed by two doses of MCV.
3. Age-appropriate MCV should be administered to HIV-infected children according to World Health Organization recommendations and country immunization schedules, including measles supplementary immunization activities. Current World Health Organization recommendations are that measles vaccination should be routinely administered to potentially susceptible, asymptomatic HIV positive children and adults. Vaccination may be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to conventional definitions.
4. An additional dose of MCV should be administered to HIV-infected children receiving HAART following immune reconstitution:
    a. Where $CD4^+$ T lymphocyte counts are monitored, an additional dose of MCV should be administered when immune reconstitution has been achieved, e.g. when $CD4^+$ T lymphocytes are ≥ 20 to 25%.
    b. Where $CD4^+$ T lymphocyte monitoring is not available, children should receive an additional dose of MCV 9-12 months after initiating HAART.
5. HIV-infected children who start HAART prior to the first dose of MCV may develop protective immunity to measles virus. Current evidence is insufficient to recommend revaccination of these children.
6. A supplementary dose of MCV should be considered shortly after diagnosis of HIV infection in children older than 6 months of age who are not receiving HAART, and for whom the risk of measles is high, to provide protection until they are revaccinated after immune reconstitution with HAART. This additional dose should be administered at least one month after a prior dose of MCV.
7. Long-term immune responses to measles vaccine should be monitored in HIV-infected children revaccinated after starting HAART and in HIV-infected children who start HAART prior to receiving their first dose of MCV.

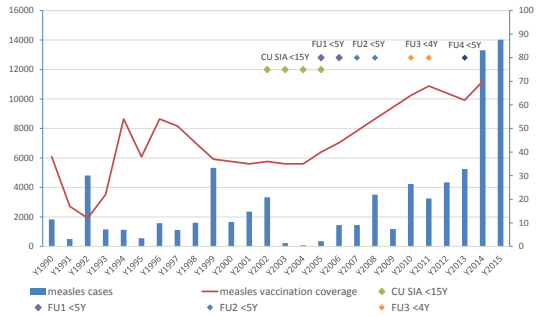
Annex 1: Acronyms

AFR	WHO African Region
AMR	WHO Region of the Americas
CRS	congenital rubella syndrome
EMR	WHO Eastern Mediterranean Region
EUR	WHO European Region
HAART	highly-active antiretroviral therapy
HIV	human immunodeficiency virus
JRF	joint reporting form
MCV	measles-containing vaccine
MCV0	early, supplemental dose of MCV
MCV1	first dose of MCV
MCV2	second dose of MCV, typically implying dose is part of routine immunization schedule
MMR	measles-mumps-rubella vaccine
MR	measles-rubella vaccine
PAHO	Pan-American Health Organization
R	effective reproduction number
RCV	rubella-containing vaccine
SEAR	WHO South-East Asian Region
SIA	supplementary immunization activity
WCBA	women of childbearing age
WPR	WHO Western Pacific Region

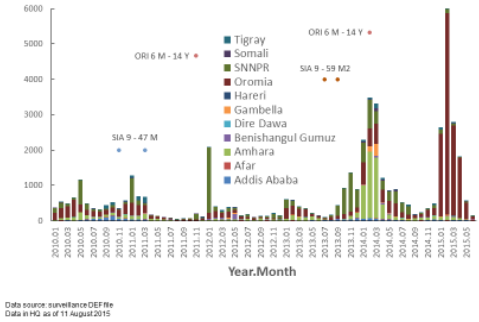
Annex 2: Measles Epidemiology in Ethiopia

SIA	Year	Admin	Survey
Catch-up	2002	98%	
	2003	92%	
	2004	89%	
	2005	82%	
Follow-up 1	2005	97%	
	2006	87%	
Follow-up 2	2007	98%	
	2008	92%	
Follow-up 3	2010	107%	88%
	2011	98%	93%
Follow-up 4	2013	98%	91%

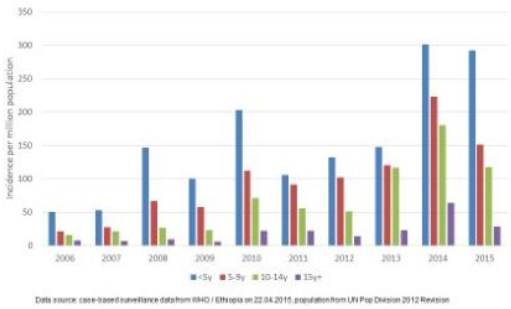
Reported measles cases, routine MCV1 coverage, and SIAs, 1990-2015, Ethiopia



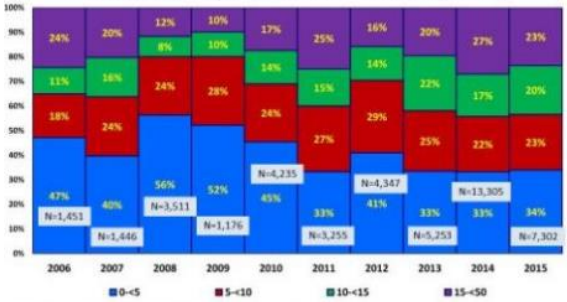
Ethiopia, confirmed measles cases by month and province and SIA dates, 2010-2015



Incidence of confirmed measles per million, by age group, Ethiopia, 2006-2015

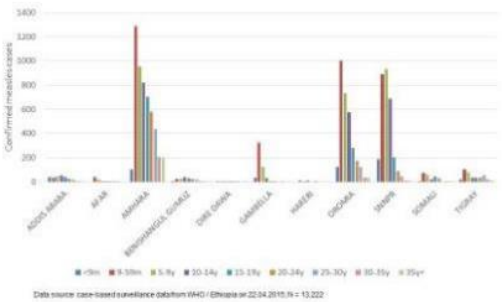


Age Distribution of Confirmed Measles Cases, Ethiopia, 2006 – 2015 (June)

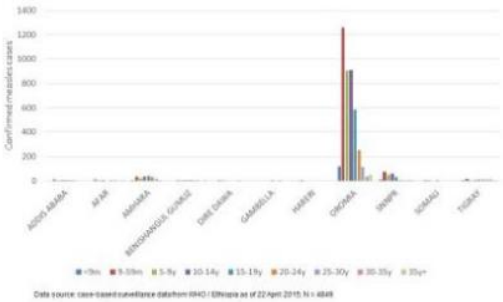


Yearly totals from JRF (2006-2014), country updates (2015)

Confirmed measles, by age group and region, Ethiopia, 2014



Confirmed measles, by age group and region, Ethiopia, 2015



World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

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Global Advisory Committee on Vaccine Safety, 10–11 June 2015

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides WHO with scientifically rigorous advice on vaccine safety issues of potential global importance.[1] GACVS held its 32nd meeting in Geneva, Switzerland, on 10–11 June 2015.[2] The Committee examined WHO's experience with monitoring the dissemination of vaccine safety information via the internet and methodological issues related to developing and maintaining information sheets on vaccine safety. It also reviewed recent data related to the safety of novel vaccines against Ebola virus and dengue and preparation for the introduction of a vaccine against malaria.

The WHO Vaccine Safety Net – improving global communication on vaccine safety

An update on the Vaccine Safety Net (VSN) had been provided during the December 2014 meeting.[3] VSN is a WHO initiative supported by GACVS that responds to the growing number of websites providing misinformation on the internet related to vaccine safety. Through the VSN, websites providing useful and reliable information

[1] See No. 41, 1999, pp. 337–338.

[2] GACVS invited additional experts to present and discuss evidence related to particular topics. These experts included persons affiliated with: University of Maryland School of Medicine, Baltimore MA, USA; Centers for Disease Control and Prevention, Atlanta GA, USA; US Military HIV Research Program, Rockville MD, USA; National Institute of Allergy and Infectious Diseases, Bethesda MD, USA; Kenya Medical Research Institute, Nairobi, Kenya; Centre Médical Universitaire, Genève, Switzerland; CHUV, Lausanne, Switzerland; GAVI, Geneva, Switzerland; Bambino Gesù Children's Hospital, Rome, Italy; GSK Biologicals, Wavre, Belgium; Merck & Co, West Point PA, USA; NewLink Genetics, Ames IA, USA; Sanofi Pasteur, Lyon, France.

[3] See No. 4, 2015, pp. 22–23.

Comité consultatif mondial de la sécurité vaccinale, 10-11 juin 2015

Le Comité consultatif mondial de la sécurité vaccinale (GACVS) est un organe consultatif indépendant composé d'experts cliniques et scientifiques qui fournissent à l'OMS des conseils d'une grande rigueur scientifique sur des problèmes de sécurité vaccinale susceptibles d'avoir une portée mondiale.[1] Le GACVS a tenu sa trente deuxième réunion à Genève (Suisse) les 10 et 11 juin 2015.[2] Il a examiné les efforts déployés par l'OMS pour surveiller la diffusion sur Internet des informations sur la sécurité des vaccins et étudié les questions de méthodologie liées à la préparation et à la tenue à jour des fiches d'information sur la sécurité des vaccins. Il a par ailleurs examiné les dernières données disponibles sur l'innocuité de nouveaux vaccins contre le virus Ebola et la dengue, ainsi que l'avancement des activités de préparation à l'introduction d'un vaccin antipaludique.

Le Réseau pour la sécurité des vaccins de l'OMS: pour une meilleure information sur la sécurité des vaccins à l'échelle mondiale

Un point sur les activités du Réseau pour la sécurité des vaccins (VSN) avait été présenté à la réunion de décembre 2014.[3] Le VSN est une initiative menée par l'OMS, avec le soutien du GACVS, en réaction au nombre croissant de sites Web diffusant des informations trompeuses sur la sécurité des vaccins. Dans le cadre du VSN, les sites Web qui fournissent

[1] Voir N° 41, 1999, pp. 337-338.

[2] Le GACVS a invité d'autres experts à présenter et à analyser les données relatives à des sujets particuliers. Il s'agissait notamment de personnes affiliées aux organismes suivants: Faculté de Médecine de l'Université du Maryland, Baltimore MA, (États-Unis); Centers for Disease Control and Prevention, Atlanta GA (États-Unis); US Military HIV Research Program, Rockville MD (États-Unis); National Institute of Allergy and Infectious Diseases, Bethesda MD (États-Unis); Kenya Medical Research Institute, Nairobi (Kenya); Centre médical universitaire, Genève (Suisse); CHUV, Lausanne (Suisse); GAVI, Genève (Suisse); Hôpital Bambino Gesù de Rome (Italie); GSK Biologicals, Wavre (Belgique); Merck & Co, West Point PA (États-Unis); NewLink Genetics, Ames IA (États-Unis); Sanofi Pasteur, Lyon (France).

[3] Voir N° 4, 2015, pp. 22-23.

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and meeting quality and content standards, are recognized and listed on the WHO website.[4]

During the past year, a working group has been updating several areas of the VSN including the evaluation criteria to meet current web standards and new information-sharing technologies. The VSN secretariat has also been considering the challenges of expanding the network to list selected social media platforms, and is planning to create an expert working group and a community of practice based on VSN members.

At this meeting, the committee endorsed the updated evaluation criteria as well as a set of screening criteria, and was presented with the VSN work plan for 2015–2016. Additional documentation will be issued to current and potential member sites, some of which will also be made available on the VSN portal page. This will include a guidance document elaborating the evaluation criteria (as requested by GACVS from the December 2014 meeting) and a template to capture summarized key website information that will accompany each member site's listing on the VSN portal. The criteria will be finalized over the next few months and posted on the website.

In addition, the committee was provided with web analytics showing how visitors use the VSN relative to other WHO vaccine safety web pages. There are currently 35 websites listed under the VSN, and another 10 which have requested to join and are currently being evaluated. Snapshots of analytics for the first 6 months of both 2014 and 2015 showed about 15 000 visitors per year to the VSN homepage, from just over 90 000 visitors to the parent WHO Vaccine Safety homepage.

Acknowledging trends in safety communication over its >10 years of existence, the VSN is undergoing upgrades to bring it in line with evolving information technologies. In addition to revising the evaluation criteria for websites, resources are being made available to include more countries and more languages, by providing limited technical support on request, and by increasing capacity to periodically review websites to ensure they continue to meet best practices. A VSN "logo" is being designed so that websites can readily demonstrate their compliance with the criteria as well as provide a link back to the VSN portal and thus indirectly to other member sites. The VSN website will undergo upgrades to increase its utility, enhance and standardize the description of recognized participating sites. As mentioned, both a network of expertise and a community of practice will be created: the former to provide ongoing advice to the VSN on best practices in communications and the latter to bring together member sites so they may assist each other, especially when a vaccine safety issue arises. A survey of VSN sites is also planned, along with an initiative to assist existing member sites

des informations utiles et fiables, répondant à des normes de qualité et de contenu, sont reconnus et inscrits dans une liste publiée sur le site Web de l'OMS.[4]

Au cours de l'année écoulée, un groupe de travail a régulièrement mis à jour différents aspects du VSN, notamment les critères d'évaluation visant à satisfaire aux normes actuelles sur le Web et les nouvelles technologies de partage de l'information. Le secrétariat du VSN a également réfléchi aux défis associés à l'expansion du Réseau à certaines plateformes sociales et prévoit de créer un groupe de travail d'experts à ce sujet, ainsi qu'une communauté de pratique composée de membres du VSN.

Lors de cette réunion, le Comité a approuvé les critères d'évaluation mis à jour, ainsi qu'un ensemble de critères de sélection. Il a également pris connaissance du plan de travail 2015-2016 du VSN. Des documents complémentaires seront diffusés auprès des sites qui sont membres actuels ou potentiels du Réseau. Certains de ces documents seront par ailleurs disponibles sur la page d'accueil du VSN. Parmi cette documentation figurent un document d'orientation, qui détaille les critères d'évaluation (comme l'avait demandé le GACVS lors de sa réunion de décembre 2014), ainsi qu'un modèle permettant de synthétiser les informations clés relatives à chaque site Web, qui seront affichées au regard du nom du site sur le portail du VSN. Les critères définitifs seront arrêtés dans les mois qui viennent et publiés sur le site Web.

En outre, le Comité a pris connaissance des données d'analyse Web montrant l'usage que font les visiteurs du VSN par rapport aux autres pages de l'OMS traitant de la sécurité vaccinale. Actuellement, 35 sites Web apparaissent sur la liste du VSN; 10 autres, qui ont demandé à se joindre au Réseau, font actuellement l'objet d'une évaluation. Les instantanés des données d'analyse Web pour les 6 premiers mois de 2014 et de 2015 ont montré que la page d'accueil du VSN attirait environ 15 000 visiteurs par an, contre un peu plus de 90 000 visiteurs pour la page mère de l'OMS sur la sécurité vaccinale.

Conscient des tendances qui ont marqué les communications sur la sécurité au cours de ses >10 ans d'existence, le VSN procède à des mises à niveau pour suivre l'évolution des technologies de l'information. Outre la révision des critères d'évaluation pour les sites Web, le VSN consacre des ressources à l'inclusion d'une plus grande variété de pays et de langues, en fournissant sur demande un appui technique limité et en augmentant sa capacité à mener un examen périodique des sites Web pour vérifier qu'ils continuent de satisfaire aux meilleures pratiques. Un «logo» VSN, en cours de conception, pourra être affiché par les sites Web pour attester de leur respect des critères, permettant en outre un lien de retour vers le portail du VSN, et donc indirectement vers les autres sites membres. Le site du VSN sera mis à niveau pour en accroître l'utilité et améliorer et harmoniser la description des sites participants reconnus. Comme évoqué, un réseau d'experts et une communauté de pratique seront mis en place. Le premier aura pour fonction de fournir un avis au VSN sur les meilleures pratiques en matière de communication, et la seconde visera à regrouper les sites membres au sein d'une même communauté pour qu'ils s'entraident, en particulier lorsque survient un problème de sécurité vaccinale. Il est également prévu de procéder à une

[4] Vaccine safety net. Accessible at http://www.who.int/vaccine_safety/initiative/communication/network/vaccine_safety_websites/en/

[4] Réseau pour la sécurité des vaccins. Disponible à l'adresse: http://www.who.int/vaccine_safety/initiative/communication/network/vaccine_safety_websites/fr/.

in collecting web metrics. This should help in identifying patterns of use and improve both collaboration and communication among participating sites. Finally, evaluation criteria are being developed for new resources that were not in existence 10 years ago, such as social network and mobile devices apps. GACVS supports the process of improving the VSN to keep up with the evolving range of vaccine safety communications.

Observed rates of adverse vaccine reactions

WHO has, since 2000, published information on the observed rates of adverse reactions following vaccination. Since 2012, this information has been included in a number of information sheets available from the WHO global vaccine safety website.[5] Each information sheet is specific for an individual vaccine antigen and supports the position paper[6] that provides the WHO recommendations for the use of this vaccine. An information sheet provides a brief overview of the vaccine and the observed rates of adverse reactions (mild/moderate and severe) as identified by experts from a review of published and non-published evidence. The intended audience for this information is immunization programme managers and health-care providers involved in vaccine administration. These information sheets describe known and expected reactions to vaccines to assist with safety communication and investigation of adverse events following immunization (AEFI). They also provide an indication of the expected rates of adverse reactions to facilitate comparison of observed AEFI rates measured through vaccine safety surveillance and determine whether any reactions have been reported with a higher frequency than expected. In addition, this information is referenced and used during WHO vaccine safety training. It also provides an estimation of known vaccine risks as part of WHO position papers.

The aim of this GACVS session was to discuss a revised approach for updating the existing information sheets and for developing new ones for newly available vaccines. This methodological revision also provides an opportunity to enhance the systematic approach to reviewing the relevant literature, and to evaluate the quality of the evidence available. WHO has previously adopted the GRADE methodology for assessing quality of evidence and has published guidelines on evaluating evidence for the purpose of preparing public health guidelines.[7] The revised methodology will incorporate these recommendations wherever possible. However, as most serious vaccine safety issues are rare events, established methods of assessing the quality of evidence (including GRADE) are not readily applicable: whereas common adverse reactions to a vaccine can usually be

[5] http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/

[6] http://www.who.int/immunization/policy/position_papers/en/

[7] WHO handbook for guideline development available at http://www.who.int/entity/kms/handbook_2nd_ed.pdf

enquête auprès des membres du VSN et de lancer une initiative pour les aider à recueillir des indicateurs sur la fréquentation de leurs sites. Cela devrait contribuer à une meilleure identification des caractéristiques d'utilisation des sites et favoriser une collaboration et une communication plus étroites entre les sites participants. Enfin, des critères d'évaluation sont en cours d'élaboration concernant de nouvelles ressources qui n'existaient pas il y a 10 ans, comme les réseaux sociaux et les applications pour appareils mobiles. Le GACVS est favorable à la démarche adoptée pour améliorer le VSN et veiller à ce qu'il reste en phase avec l'évolution des modes de communication en matière de sécurité vaccinale.

Taux observés de réactions postvaccinales indésirables

Depuis 2000, l'OMS publie les données relatives aux taux observés de réactions indésirables consécutives à la vaccination. Depuis 2012, ces données sont incluses dans plusieurs fiches d'information disponibles sur la page Web de l'OMS consacrée à la sécurité mondiale des vaccins.[5] Chaque fiche d'information traite d'un antigène vaccinal spécifique et étaye la note de synthèse publiée par l'OMS,[6] qui présente les recommandations de l'Organisation quant à l'utilisation du vaccin concerné. Les fiches d'information donnent un bref aperçu du vaccin et présentent les taux observés de réactions indésirables (légères/modérées ou graves), déterminés par des experts sur examen des données publiées et non publiées. Cette information est essentiellement destinée aux administrateurs des programmes de vaccination et aux agents de santé impliqués dans l'administration des vaccins. Les fiches décrivent les réactions connues et attendues pour chaque vaccin, guidant ainsi la communication en matière de sécurité vaccinale et l'investigation des manifestations postvaccinales indésirables (MAPI). Elles donnent également une indication des taux escomptés de réactions indésirables, facilitant la comparaison avec les taux de MAPI observés, mesurés par la surveillance de l'innocuité des vaccins, et permettant de déterminer si certaines réactions ont été signalées plus souvent qu'escompté. En outre, cette information, consignée comme référence, est utilisée dans le cadre de la formation sur la sécurité vaccinale dispensée par l'OMS. Elle permet enfin d'estimer les risques connus de la vaccination, figurant dans les notes de synthèse de l'OMS.

L'objectif de cette réunion du GAVCS était de discuter d'une nouvelle approche pour la mise à jour des fiches d'information existantes et l'élaboration de celles portant sur les nouveaux vaccins. Cette révision de la méthodologie employée est également l'occasion d'améliorer l'approche systématique d'examen de la documentation pertinente et d'évaluer la qualité des données disponibles. L'OMS utilise déjà la méthodologie GRADE pour évaluer la qualité des données et a publié des lignes directrices sur l'évaluation des données aux fins d'élaboration de directives de santé publique.[7] La méthodologie révisée incorporera dans la mesure du possible ces recommandations. Cependant, comme la majorité des problèmes graves de sécurité vaccinale sont des manifestations rares, les méthodes établies pour évaluer la qualité des données (y compris GRADE) ne sont pas aisément applicables: si les réactions indésirables postvaccinales courantes peuvent souvent être identifiées lors d'essais cliniques

[5] http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/fr/.

[6] http://www.who.int/immunization/policy/position_papers/en/.

[7] WHO handbook for guideline development, disponible à l'adresse: http://www.who.int/entity/kms/handbook_2nd_ed.pdf.

identified during randomised controlled clinical trials, severe or unusual reactions are generally ascertained only later from observational studies after the product has been available for large-scale use. Most studies which provide relevant vaccine safety information on rare events are post-licensure case-based studies or retrospective cohort studies. Whilst GACVS acknowledges the importance of using the GRADE methodology whenever it is applicable, alternative tools specifically designed for assessment of unusual and rare events recorded in observational studies also need to be included in a vaccine safety review process.

The proposed revised approach for WHO vaccine safety information sheets will focus on specific safety questions that will be formulated by a GACVS subcommittee dedicated to AEFI monitoring. The subcommittee will identify events that have been suspected to be causally associated with the vaccine and will formulate the safety issues requiring review of the evidence. An example of such a question would be: *"what is the attributable risk of intussusception following rotavirus vaccination?"*. The committee will focus on severe reactions and reactions of special interest. Where appropriate, safety reviews will also be prioritized based on the development of WHO position papers on vaccines, following discussions with the WHO Strategic Advisory Group of Experts on immunization (SAGE); vaccine risk information is an essential component of the WHO position papers on vaccines as the recommendations are based on a benefit-risk assessment. Review of the specific safety question will include both published and unpublished (for example, product information) evidence. Individual articles or review articles will be categorized according to a methodology including the assessment of the quality of the evidence. This information will be included in tables summarizing the findings and be further simplified for inclusion in the revised information sheets. The source and summary information will be available, for reference, on the internet.

Safety of two candidate Ebola virus vaccines

In response to the unprecedented Ebola outbreak in West Africa, in August 2014 WHO called for accelerated production of preventive vaccines that could potentially help control the outbreak. Criteria proposed for selection of vaccine candidates included prior demonstration of full protection against lethal Ebola virus challenge in non-human primates and production in facilities that met good manufacturing practices. Two vaccines, both based on insertion of an Ebola virus glycoprotein gene into a viral vector, had entered Phase 1 development by September–October 2014. By early 2015 Phase 2/3 studies with both products were under way in highly affected countries of West Africa.[8]

[8] In addition to the two candidate vaccines described above, more recently two other Ebola vaccine programmes have met the initially proposed pre-clinical trial criteria. These are a heterologous combination of two replication deficient recombinant vectors: human adenovirus 26 and modified vaccinia virus Ankara, both expressing ZEBOV GP (Johnson & Johnson) and a baculovirus expressing recombinant ZEBOV GP nanoparticle vaccine (Novavax). Both of these programmes have initiated Phase 1 trials; currently neither programme has clinical trial data available from sub-Saharan Africa..

contrôlés randomisés, les réactions graves ou inhabituelles sont généralement déterminées uniquement dans le cadre des études d'observation réalisées une fois que le produit est utilisé à grande échelle. La plupart des études qui fournissent des informations de sécurité vaccinale pertinentes sur les manifestations rares sont des études de cas après homologation ou des études rétrospectives de cohortes. Le GACVS reconnaît l'utilité de la méthode GRADE, qu'il convient d'employer lorsqu'elle est applicable, mais estime que le processus d'évaluation de l'innocuité des vaccins doit également recourir à d'autres outils, conçus spécifiquement pour l'évaluation des manifestations rares ou inhabituelles identifiées lors des études d'observation.

L'approche révisée qui a été proposée pour ces fiches d'information sera axée sur des questions spécifiques de sécurité qui seront formulées par le sous-comité du GACVS chargé du suivi des MAPI. Ce sous-comité identifiera les manifestations pour lesquelles un lien de causalité avec le vaccin est soupçonné et déterminera les questions de sécurité exigeant une analyse des données. Les questions pourront par exemple être formulées comme suit: «*Quel est le risque attribuable d'invagination après la vaccination antirotavirus?*». Le Comité se concentrera sur les réactions graves ou présentant un intérêt spécifique. Le cas échéant, les évaluations de l'innocuité des vaccins seront menées selon des priorités établies en fonction du processus d'élaboration des notes de synthèse de l'OMS, après discussion avec le Groupe stratégique consultatif d'experts sur la vaccination (SAGE); les informations sur les risques liés aux vaccins forment un élément essentiel des notes de synthèse de l'OMS, les recommandations de l'Organisation étant fondées sur une analyse risques-avantages. L'examen de chaque question relative à l'innocuité des vaccins s'appuiera aussi bien sur des données publiées que non publiées (par exemple information sur les produits). Les articles individuels et les articles d'analyse seront catégorisés selon une méthodologie tenant compte de l'évaluation de la qualité des données. Cette information sera consignée dans des tableaux récapitulatifs des résultats, qui seront ensuite simplifiés pour être inclus dans les fiches d'information révisées. Les informations d'origine et le récapitulatif seront disponibles sur Internet à titre de référence.

Innocuité de 2 vaccins candidats contre le virus Ebola

En août 2014, face à la flambée sans précédent de maladie à virus Ebola qui frappait l'Afrique de l'Ouest, l'OMS a appelé à la production accélérée de vaccins préventifs susceptibles de juguler cette flambée. Selon les critères de sélection proposés, les vaccins candidats devaient avoir donné la preuve de leur capacité à conférer une protection contre une inoculation d'épreuve mortelle par le virus Ebola chez les primates non humains et être produits dans des installations respectant les bonnes pratiques de fabrication. Deux vaccins, reposant tous 2 sur l'insertion d'un gène de la glycoprotéine du virus Ebola dans un vecteur viral, étaient déjà entrés en phase 1 de développement en septembre-octobre 2014. Au début de 2015, des études de phase 2/3 des 2 produits étaient en cours dans les pays les plus durement touchés d'Afrique de l'Ouest.[8]

[8] Outre les deux vaccins candidats décrits ci-dessus, deux autres programmes plus récents répondent aux critères initialement proposés avant les essais cliniques. Il s'agit, d'une part, d'une association hétérologue de deux vecteurs recombinants à réplication défectueuse, l'adénovirus humain 26 et le virus de la vaccine Ankara modifié, exprimant tous deux la ZEBOV GP (Johnson & Johnson) et, d'autre part, d'un vaccin recombinant à base de nanoparticules de ZEBOV GP exprimant le baculovirus (Novavax). Les essais cliniques de phase 1 ont démarré pour ces deux programmes; à l'heure actuelle, aucun des deux ne dispose de données d'essai issues d'Afrique subsaharienne.

One candidate vaccine, developed by the US National Institute of Allergy and Infectious Diseases and GlaxoSmithKline plc, uses a replication incompetent chimpanzee adenovirus 3 (ChAd3) vector with the E1 and E4 genes deleted. An Ebola virus Zaire (EBO-Z) glycoprotein (GP) gene cassette has been inserted in place of the E1 deleted region. Another candidate vaccine, developed by the Public Health Agency of Canada and subsequently licensed to NewLink and Merck & Co., Inc., uses an attenuated vesicular stomatitis virus (VSV) as the vaccine vector. The VSV G gene has been deleted and replaced with a EBO-Z GP expression cassette. The resulting recombinant virus is attenuated but remains replication competent.

Phase 1 studies of the ChAd3 vaccine began in September 2014 with limited data already published.[9, 10] A total number of 271 healthy adults were vaccinated with ChAd3-EBO-Z in Phase 1 studies in the United States, the United Kingdom, Mali and Switzerland, with doses ranging from 10^{10} to 10^{11} viral particles. An additional Phase 1 study including 2 arms testing monovalent ChAd3-EBO-Z (n=34) was undertaken in Uganda. Based on safety and immunogenicity data from Phase 1 studies, the 10^{11} viral particle dose was selected for further clinical testing. Phase 2 studies in healthy adults and in children are planned in West African countries adjacent to the current outbreak zone. A Phase 2/3 study, in collaboration with the U.S. National Institutes of Health, was begun in Liberia in February 2015 but safety data were not available at the time of the GACVS meeting.

In the Phase 1 studies, dose-related reactogenicity was observed, with injection-site pain and fever mainly occurring within the first 24 hours after vaccination. In most recipients, fever resolved within 24 hours. Transient clinically non-significant reductions in lymphocyte and platelet counts were observed, as is seen with many live virus vaccines. No serious adverse events ascribed to the vaccine or other unexpected serious adverse reactions were found.

Phase 1 studies of the rVSV-ZEBOV-GP vaccine began in October 2014 with limited data already published.[11, 12] In total, 248 volunteers were vaccinated across 7 studies in the United States, Switzerland, Germany, Gabon, Kenya and Canada; enrollment for all studies was completed by May 2015. Collection of long-term safety and immunogenicity data from these studies is ongoing. A Phase 1b dose-ranging study, with 256 volunteers receiving doses

L'un des vaccins candidats, mis au point par le National Institute of Allergy and Infectious Diseases des États-Unis et GlaxoSmithKline plc, utilise un vecteur dérivé d'un adénovirus de chimpanzé de type 3 (ChAd3) à réplication défectueuse, avec suppression des gènes E1 et E4. Une cassette du gène de la glycoprotéine (GP) du virus Ebola Zaïre (EBO-Z) a été insérée à l'emplacement où se trouvait le gène E1 supprimé. L'autre vaccin candidat, qui a été mis au point par l'Agence de la santé publique du Canada et dont la licence d'exploitation a ensuite été octroyée à NewLink et Merck & Co., Inc., utilise un virus atténué de la stomatite vésiculaire (VSV) à titre de vecteur. Le gène G du VSV a été supprimé et remplacé par une cassette exprimant la glycoprotéine du virus EBO-Z. Le virus recombinant qui en résulte est atténué mais demeure apte à la réplication.

Les études de phase 1 du vaccin ChAd3 ont démarré en septembre 2014 et des données en nombre limité sont déjà publiées.[9, 10] En tout, 271 adultes en bonne santé ont été vaccinés par le ChAd3-EBO-Z dans le cadre d'études de phase 1 menées aux États-Unis, au Mali, au Royaume-Uni et en Suisse, avec des doses variant de 10^{10} à 10^{11} particules virales. Une étude de phase 1 supplémentaire, comprenant 2 groupes d'essai du ChAd3-EBO-Z monovalent (n = 34), a été entreprise en Ouganda. Sur la base des données d'innocuité et d'immunogénicité issues des études de phase 1, la dose de 10^{11} particules virales a été choisie pour les essais cliniques ultérieurs. Il est prévu de mener des études de phase 2 chez des adultes et des enfants en bonne santé dans les pays d'Afrique de l'Ouest qui jouxtent la zone de flambée actuelle. Une étude de phase 2/3, menée en collaboration avec les National Institutes of Health des États-Unis, a commencé au Libéria en février 2015, mais les données sur l'innocuité provenant de cette étude n'étaient pas disponibles à la date de la réunion du GACVS.

Dans les études de phase 1, une réactogénicité liée à la dose a été observée, avec une douleur au point d'injection et de la fièvre susceptibles d'apparaître principalement dans les premières 24 heures après la vaccination. Chez la majorité des sujets, la fièvre avait disparu dans un délai de 24 heures. Une diminution transitoire, non significative sur le plan clinique, de la numération des lymphocytes et des plaquettes a été observée, comme cela est le cas pour de nombreux vaccins à virus vivants. Aucune manifestation indésirable grave imputable au vaccin et aucune réaction indésirable grave inattendue n'ont été constatées.

Les études de phase 1 du vaccin rVSV-ZEBOV-GP ont démarré en octobre 2014 et des données en nombre limité sont déjà publiées.[11, 12] En tout, 248 volontaires ont été vaccinés dans le cadre de 7 études menées en Allemagne, au Canada, aux États-Unis, au Gabon, au Kenya et en Suisse; en mai 2015, le recrutement était achevé pour toutes les études. La collecte des données sur l'innocuité et l'immunogénicité à long terme provenant de ces études est en cours. Une étude de phase 1b d'évaluation du

[9] Ledgerwood JE, De Zure AD, Stanley DA et al. Chimpanzee adenovirus vector vaccine – preliminary report. N Engl J Med 2014 Nov 26. [Epub ahead of print].

[10] Rampling T[1], Ewer K, Bowyer G et al. A monovalent chimpanzee adenovirus Ebola vaccine - Preliminary report. N Engl J Med. 2015 Jan 28. [Epub ahead of print].

[11] Regules JA, Beigel JH, Paolino KM et al. A recombinant vesicular stomatitis virus Ebola vaccine - Preliminary report. N Engl J Med. 2015 Apr 1. [Epub ahead of print].

[12] Agnandji ST, Huttner A, Zinser ME et al. Phase 1 trials of rVSV Ebola vaccine in Africa and Europe - Preliminary report. N Engl J Med. 2015 Apr 1. [Epub ahead of print].

[9] Ledgerwood JE, De Zure AD, Stanley DA et al. Chimpanzee adenovirus vector vaccine – preliminary report. N Engl J Med 2014 Nov 26. [Publication électronique avant impression].

[10] Rampling T[1], Ewer K, Bowyer G et al. A monovalent chimpanzee adenovirus Ebola vaccine – Preliminary report. N Engl J Med. 2015 Jan 28. [Publication électronique avant impression].

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[12] Agnandji ST, Huttner A, Zinser ME et al. Phase 1 trials of rVSV Ebola vaccine in Africa and Europe – Preliminary report. N Engl J Med. 2015 Apr 1. [Publication électronique avant impression].

of rVSV-ZEBOV ranging from 3 x 10^3 to 3 x 10^6 or placebo (n=74) was initiated in the United States in December 2014.

In those studies, pain at the injection site was common as were systemic symptoms including fever, malaise, and "flu-like symptoms" (chills, myalgia, headaches and fatigue) were common after vaccination and generally lasted 1 to 3 days. Administration of rVSV vaccine results in viraemia that is detectable by polymerase chain reaction (PCR) during the first and sometimes second week after vaccination, with a peak found on day 2. Vaccine virus was detected by PCR in urine and saliva in <10% of subjects. No vaccine-related serious adverse reactions have been reported to date from Phase 1 or 1b studies. Arthralgia, arthritis, dermatitis, rash and cutaneous vasculitis were reported, with varying frequency between study sites, in the 2nd week following vaccination; these reactions are associated with vaccine virus replication in the joints and the skin as demonstrated by PCR testing of specimens collected from those sites and evidence of local viral gene expression documented by immunohistochemistry. In subjects with arthritis, pain generally lasted 2–3 weeks, but occasionally more than 3 months. Joint reactions did not occur more frequently with higher doses of vaccine, but were more common among older subjects. A small number of skin vesicles and mouth ulcers were also observed and limited data did not indicate that virus had been detected by PCR. Transient, non-clinically significant reductions in neutrophil and lymphocyte counts were found in some recipients in the first few days following vaccination.

The rVSV vaccine is currently being tested in Phase 2/3 studies in Liberia, Guinea, and Sierra Leone; safety data are not yet available from those studies. Additional assessment of joint and skin events is planned in upcoming clinical studies.

Safety data from Phase 1 studies of both ChAd3 and rVSV vaccines indicate an acceptable safety profile in healthy adults. Ongoing studies will provide additional experience in adults, and will allow more extensive assessment of safety. No data are currently available regarding the safety of these vaccines in subjects with underlying disease or medical conditions. There are also no data regarding the safety of these products in paediatric and pregnant subjects.

Preparing for RTS,S malaria vaccine introduction

At the December 2014 GACVS meeting, the manufacturer of RTS,S vaccine (GSK Biologicals) presented the post-booster results from the Phase 3 multicentre clinical trial. Those results had shown 2 safety signals, meningitis and febrile convulsions, recently published,[13]

[13] RTS,S partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet 2015 (epub) PMID:25913272

dosage, comptant 256 volontaires recevant des doses de rVSV-ZEBOV allant de 3 x 10^3 à 3 x 10^6 ou un placebo (n = 74), a été lancée aux États-Unis en décembre 2014.

Dans le cadre de ces études, la douleur au point d'injection ainsi que des symptômes systémiques tels que fièvre, malaise ou symptômes «grippaux» (frissons, myalgies, céphalées, fatigue) étaient des réactions postvaccinales courantes et duraient généralement 1 à 3 jours. L'administration du vaccin rVSV entraîne une virémie pouvant être décelée par amplification en chaîne par polymérase (PCR) au cours de la première semaine après vaccination, voire de la seconde semaine, culminant au jour 2. Le virus vaccinal a été détecté par PCR dans l'urine et la salive de <10% des sujets. Aucune réaction indésirable grave liée au vaccin n'a été signalée à ce jour dans le cadre des études des phases 1 et 1b. Les réactions suivantes ont été signalées dans la seconde semaine après la vaccination, avec une fréquence variable d'un site d'étude à l'autre: arthralgie, arthrite, dermatite, éruption cutanée et vascularite cutanée; ces réactions sont liées à la réplication du virus vaccinal dans les articulations et la peau, comme l'indiquent l'analyse PCR des échantillons recueillis sur ces sites et les données signalant une expression locale du gène viral, mise en évidence par analyse immunohistochimique. Chez les sujets présentant une arthrite, la douleur durait généralement 2 à 3 semaines, mais pouvait parfois persister plus de 3 mois. Les réactions articulaires n'étaient pas plus fréquentes pour une dose de vaccin croissante, mais apparaissaient plus souvent chez les sujets plus âgés. Chez quelques personnes, des vésicules cutanées et des ulcérations buccales ont également été observées et les données limitées disponibles n'indiquaient pas de détection du virus par PCR. Une réduction transitoire, non significative sur le plan clinique, de la numération des lymphocytes et des neutrophiles a été observée chez certains sujets dans les premiers jours après la vaccination.

Le vaccin rVSV fait actuellement l'objet d'études de phase 2/3 au Libéria, en Guinée et en Sierra Leone; les données sur l'innocuité issues de ces études ne sont pas encore disponibles. Une évaluation complémentaire des manifestations de nature articulaire et cutanée est prévue dans le cadre des prochaines études cliniques.

Les données dérivées des études de phase 1 des vaccins ChAd3 et rVSV signalent un profil d'innocuité acceptable chez les adultes en bonne santé. Les études en cours fourniront davantage de données chez les adultes et permettront une analyse plus détaillée de l'innocuité des vaccins. On ne dispose actuellement pas de donnée sur l'innocuité de ces vaccins chez les sujets atteints de pathologies ou d'affections sous-jacentes. Aucune donnée ne renseigne non plus sur l'innocuité de ces produits chez les enfants et les femmes enceintes.

Préparation à l'introduction du vaccin antipaludique RTS,S

Lors de la réunion du GACVS de décembre 2014, le fabricant du vaccin RTS,S (GSK Biologicals) a présenté les résultats obtenus après administration de la dose de rappel dans le cadre de l'essai clinique multicentrique de phase 3. Ces résultats, récemment publiés,[13] mettaient en évidence 2 signaux liés à la sécu-

[13] RTS,S partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet, 2015 (epub) PMID:25913272

which had already been observed after the primary dose.[14, 15] Febrile convulsive seizures are a clearly identified adverse reaction in the 7 days following primary vaccination among subjects aged 5–17 months. Febrile seizures are also observed within 7 days after the booster dose irrespective of age at primary vaccination. All the febrile convulsions occurring within 7 days post vaccination resolved, without long term adverse outcomes reported to date. Meningitis cases occurred substantially more frequently in the groups that received RTS,S/AS01, especially in the older age group (5–17 months). The cases, however, are of varying etiologies, show no significant evidence of temporal clustering after vaccination and there is currently no clear causative relationship. The committee considered that meningitis should therefore be regarded as a potential signal which requires further assessment post-licensure. GACVS also reviewed safety data from a randomized control trial of 200 known HIV-positive children aged 6–17 weeks. There was a higher frequency of pneumonia in the RTS,S/AS01 group over the first 30 days after vaccination, although this difference was not statistically significant. At month 14, frequencies of pneumonia were very similar in both groups. So far, no safety signal has been detected in HIV-positive children.

A malaria vaccine GACVS sub-group has further developed guidance on post-licensure safety surveillance for the RTS,S/AS01 vaccine. Several adverse events of special interest have been considered, including meningitis, convulsive seizures, autoimmune disorders and those studied during the introduction of another inactivated vaccine (meningococcal A conjugate MenAfriVac) in sub-Saharan Africa through sentinel monitoring.[16] With respect to evaluating the meningitis safety signal, GACVS acknowledges that it will be necessary to propose case definitions and investigation procedures adapted to the health-care resources available in the sites where early RTS,S introduction would take place. It would be desirable that those early introduction sites be selected based on their ability to promptly identify cases compatible with meningitis and conduct proper investigation, including etiological diagnosis.

Several African experts in autoimmunity were consulted to consider the feasibility and need for studies of autoimmune disorders following RTS,S/AS01 introduction. This concern was raised out of theoretical considerations related to the use of AS01, a potent new adjuvant, although there is currently no evidence in experimental or human situations suggesting AS01 could be a trigger for autoimmune disorders. The experts highlighted the numerous practical constraints linked to the establish-

rité vaccinale, la méningite et les convulsions fébriles, qui avaient déjà été observés après la primovaccination.[14, 15] Les convulsions fébriles constituent une réaction indésirable clairement identifiée dans les 7 jours suivant la primovaccination chez les sujets âgés de 5 à 17 mois. Elles sont également observées dans les 7 jours suivant la dose de rappel, quel que soit l'âge lors de la primovaccination. Toutes les réactions de convulsion fébrile survenues dans les 7 jours après la vaccination ont ensuite disparu, sans issue défavorable à long terme signalée à ce jour. Les cas de méningite étaient notablement plus fréquents chez les groupes ayant reçu le RTS,S/AS01, en particulier dans la tranche d'âge supérieure (5 à 17 mois). Toutefois, ces cas étaient d'étiologies diverses, ne présentaient pas de regroupement temporel manifeste après la vaccination et aucun lien de causalité clair n'a été mis en évidence à ce jour. Le Comité a donc jugé que la méningite devrait être considérée comme un signal potentiel nécessitant une évaluation approfondie après homologation. Le GACVS a également examiné les données sur l'innocuité obtenues dans le cadre d'un essai contrôlé randomisé de 200 enfants séropositifs pour le VIH, âgés de 6 à 17 semaines. Le groupe ayant reçu le RTS,S/AS01 présentait une plus grande incidence de pneumonie dans les 30 jours suivant la vaccination, la différence observée n'étant toutefois pas significative sur le plan statistique. Au mois 14, l'incidence de la pneumonie était comparable dans les 2 groupes. À ce jour, aucun signal relatif à la sécurité vaccinale n'a été détecté chez les enfants séropositifs pour le VIH.

Le sous-groupe du GACVS consacré au vaccin antipaludique a apporté de nouvelles améliorations aux orientations relatives à la surveillance de l'innocuité du vaccin RTS,S/AS01 après homologation. Plusieurs manifestations indésirables d'intérêt spécifique ont été abordées, dont la méningite, les convulsions, les affections autoimmunes et les manifestations ayant fait l'objet d'une surveillance sentinelle lors de l'introduction d'un autre vaccin inactivé (antiméningococcique A conjugué MenAfriVac) en Afrique subsaharienne.[16] Pour l'évaluation du signal de sécurité relatif à la méningite, le GACVS reconnaît que les définitions de cas et les procédures d'investigation proposées devront être adaptées aux ressources sanitaires existant sur les sites d'introduction préliminaire du RTS,S. Il serait souhaitable que ces sites d'introduction préliminaire soient sélectionnés en fonction de leur capacité à identifier rapidement les cas compatibles avec la description clinique de la méningite et à mener les enquêtes nécessaires, y compris un diagnostic étiologique.

Plusieurs experts africains sur l'autoimmunité ont été consultés pour évaluer la possibilité et la nécessité de réaliser des études sur les affections autoimmunes après l'introduction du RTS,S/AS01. Ce souci émanait de considérations théoriques liées à l'utilisation du AS01, un nouvel adjuvant puissant, bien que rien n'indique actuellement que l'AS01 puisse déclencher des affections autoimmunes, que ce soit en situation expérimentale ou humaine. Les experts consultés ont souligné les nombreuses contraintes pratiques associées à la mise en place d'un système

[14] See No. 4, 2015, pp. 18-20.

[15] RTS,S clinical trial partnership. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med 2011;365:1863-75.

[16] Ouandaogo CR, Yaméogo TM, Diomandé FVK et al. Adverse events following mass vaccination campaigns during first introduction of a meningococcal A conjugate vaccine in Burkina Faso, 2010. Vaccine 2012; 30 Suppl 2:B46-51.

[14] Voir N° 4, 2015, pp. 18-20.

[15] RTS,S clinical trial partnership. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. *N*ew England Journal of Medicine, 2010, 362: 2360-2369.

[16] Ouandaogo CR, Yaméogo TM, Diomandé FVK et al. Adverse events following mass vaccination campaigns during first introduction of a meningococcal A conjugate vaccine in Burkina Faso, 2010. Vaccine, 2012; 30 Suppl 2:B46-51.

ment of adequate surveillance since there are relatively few diagnosed paediatric autoimmune diseases in sub-Saharan Africa and their epidemiology is largely undetermined. They also noted that data from experimental models show no evidence that AS01 triggers immune reactions away from the injection site. GACVS agreed that initially the guidance document would not address monitoring of autoimmune disorders. This could be revised in case a signal is identified from passive safety surveillance of RTS,S or from the study and monitoring of other vaccines using the same adjuvant.

GACVS recommended that the guidance document be completed with more detailed protocols for studies written later, if RTS, S/AS01 is introduced and suitable study sites identified. ■

de surveillance adéquat, car il y a relativement peu de maladies autoimmunes pédiatriques diagnostiquées en Afrique subsaharienne et leur épidémiologie est en grande partie indéterminée. Ils ont également noté que les données provenant des modèles expérimentaux n'indiquent en rien que l'AS01 puisse déclencher des réactions immunitaires hors du site d'injection. Le GACVS a convenu que le document d'orientation ne traiterait pas, dans un premier temps, de la surveillance des affections autoimmunes. Cette approche pourra être revue si un signal est identifié dans le cadre de la surveillance passive du RTS,S ou d'études et de la surveillance portant sur d'autres vaccins utilisant le même adjuvant.

Le GACVS a recommandé que le document d'orientation soit complété par l'ajout ultérieur de protocoles d'étude détaillés si le RTS,S/AS01 est introduit et des sites d'étude appropriés sont identifiés. ■

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Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC): summary of conclusions and recommendations, 9–11 June 2015 meeting

THEME: Research to minimize barriers and improve coverage of vaccines currently in use

Session 1: Research methods for community vaccine acceptance studies

Study designs are needed for research to assess the impact of community factors affecting vaccine uptake and coverage.

Presentation of an antenatal influenza vaccination study in Pune, India, indicated prospects for developing a generic protocol for community study to discuss issues related to acceptance and demand for this vaccine at other sites. Antenatal immunization, however, has many features that distinguish it from routine infant immunization, requiring additional research for other vaccines.

A comprehensive framework to guide the conduct of research on community uptake of vaccines was recommended to facilitate the design of community studies on a range of vaccines and settings. An IVIR-AC subgroup has been set up to provide leadership capacity to develop such a comprehensive framework.

A plan is needed for validating the impact of community interventions on hesitancy in at risk communities in the general population and decisions to prioritize vaccination in professional communities.

The comprehensive framework should facilitate development of vaccine-specific

Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC): résumé des conclusions et recommandations, réunion du 9 au 11 juin 2015

THÈME: Recherche pour réduire les obstacles à l'utilisation des vaccins actuels et améliorer la couverture vaccinale associée

Session 1: Méthodes de recherche pour étudier l'acceptation des vaccins au niveau communautaire

Des méthodes de recherche doivent être établies pour évaluer l'incidence des facteurs communautaires sur l'adoption des vaccins et la couverture vaccinale.

La présentation d'une étude réalisée à Pune (Inde) sur la vaccination prénatale contre la grippe a mis en évidence la possibilité d'élaborer un protocole générique pour mener des études communautaires susceptibles de permettre de discuter de problèmes liés à l'acceptation et la demande à l'égard de ce vaccin sur d'autres sites. La vaccination prénatale se distingue toutefois par de nombreux aspects de la vaccination systématique des nourrissons, ce qui nécessite de la recherche supplémentaire pour les autres vaccins.

Le Comité a préconisé l'établissement d'un cadre exhaustif destiné à orienter la recherche sur l'adoption des vaccins au niveau communautaire pour faciliter la conception d'études communautaires sur divers vaccins et dans différents contextes. Un sous-groupe de l'IVIR-AC a été créé pour œuvrer à l'élaboration de ce cadre.

Le Comité recommande en outre qu'un plan soit formulé pour valider l'impact des questions de réticence chez les populations à risque et des priorités vaccinales dans la communauté professionnelle.

Le cadre exhaustif doit faciliter l'élaboration de stratégies et de méthodes d'étude propres

strategies and research designs based on an underlying chain-of-causality dynamic model of the processes and behaviours.

Assessment of the effectiveness of community interventions to improve vaccine acceptance is needed to ensure that research outcomes may contribute to programmatic actions.

Session 2: Non-specific immunological effects of vaccines

IVIR-AC appreciates the scope and value of the reviews that have been conducted of non-specific effects of vaccines, and re-affirms the conclusions of the Oxford meeting on this topic.

IVIR-AC reiterates SAGE conclusions that there is insufficient evidence for a schedule change. However, the available findings warrant further research exploration in this area.

There is scepticism about some of the large effect sizes (up to 50%) reported in some studies linking vaccination (by vaccines such as measles and bacille Calmette–Guérin (BCG)) to reductions in all-cause mortality.

The link between immunological readouts and epidemiological endpoints has not been clearly established. The relevance of the work to public health outcomes such as changes to vaccine schedules needs to be highlighted. Immunological studies could be incorporated in clinical trials so that their relevance to clinical/epidemiological endpoints can be understood.

Clinical trials do not need to be delayed until the completion of immunological studies. Rather studies that include evaluation of the non-specific effect of vaccination should be conducted in parallel and where appropriate with the immunological studies nested within the clinical trial. Nevertheless, available data from immunological studies should be used to determine key times for sample collection in clinical trials. IVIR-AC re-iterates SAGE conclusions that further observational studies are not likely to inform public health decision-making and thus emphasizes the importance of randomized trials.

IVIR-AC can be involved in setting research questions and designing the appropriate methodology for clinical trials to investigate epidemiological outcomes. Two IVIR-AC representatives will be included in groups which may be formed in the near future to consider next steps for designing epidemiological studies to explore non-specific clinical effects of vaccines. Others with appropriate expertise should also be identified and engaged in such consultations.

The distinction between a vaccine's specific and non-specific effects needs further delineation as there are different pathways involved, and the latter may not correlate with immunological responses to vaccination.

à chaque vaccin en s'appuyant sur un modèle causal dynamique des processus et des comportements.

L'efficacité des interventions communautaires visant à renforcer l'acceptation des vaccins doit être évaluée, condition nécessaire à l'application des résultats de la recherche au niveau programmatique.

Session 2: Effets immunologiques non spécifiques des vaccins

Le Comité se félicite de la portée et de l'utilité des études menées sur les effets non spécifiques des vaccins et réaffirme les conclusions de la réunion d'Oxford à ce sujet.

Il réitère l'avis du SAGE selon lequel les données disponibles ne justifient pas un changement du calendrier de vaccination. Cependant, les résultats obtenus à ce jour méritent des travaux de recherche approfondis à ce sujet.

Le Comité émet des doutes quant au niveau considérable des effets relevés (jusqu'à 50%) dans certaines études liant la vaccination (par exemple par le vaccin antirougeoleux ou le bacille de Calmette-Guérin (BCG)) à une réduction de la mortalité toutes causes confondues.

Le lien entre les données immunologiques mesurées et les critères d'évaluation épidémiologiques n'a pas été clairement établi. L'intérêt de ce travail en termes de santé publique, notamment pour décider d'une modification éventuelle des calendriers de vaccination, mérite d'être souligné. Des études immunologiques pourraient être intégrées aux essais cliniques pour mieux comprendre la pertinence des données immunologiques vis-à-vis des critères d'évaluation cliniques/épidémiologiques.

Il n'est pas nécessaire de reporter les essais cliniques jusqu'à ce que les études immunologiques soient achevées. L'évaluation des effets non spécifiques de la vaccination devrait plutôt être menée en parallèle, et si possible conjointement, avec les études immunologiques intégrées à l'essai clinique. On utilisera toutefois les données immunologiques disponibles pour fixer les principales dates de prélèvement des échantillons durant les essais cliniques. Le Comité réitère les conclusions du SAGE, estimant que les études d'observation ne suffiront pas à fournir des données à l'appui du processus décisionnaire en matière de santé publique et soulignant à cet égard l'importance des essais randomisés.

Le Comité peut contribuer à définir les questions abordées par la recherche et à concevoir une méthodologie d'essai clinique apte à étudier les issues épidémiologiques. Deux représentants du Comité participeront à certains groupes devant être formés prochainement, dont le rôle sera de réfléchir à la conception d'études épidémiologiques permettant d'explorer les effets non spécifiques des vaccins. D'autres personnes possédant les compétences appropriées seront également identifiées et consultées.

La distinction entre les effets spécifiques et non spécifiques d'un vaccin doit être définie de manière plus précise car différentes voies sont impliquées et les effets non spécifiques peuvent ne pas être liés à la réponse immunologique à la vaccination.

Consideration should be given to developing mechanistic models of non-specific immune response to vaccination, and to link them to between-host epidemiological models.

Failure to collect appropriate samples during ongoing clinical trials of vaccines is problematic, particularly in trials with a randomized design. Consideration is needed on whether the trial design could answer questions around non-specific vaccine effects. If so, collection of the appropriate specimens should be ensured; such specimens could be bio-banked pending available resources and specific study design for future investigation.

There is no a priori reason not to include other vaccines besides diphtheria–tetanus–pertussis (DTP), measles and BCG. Additional vaccines that could be considered for investigation into immunological pathways include other live-virus vaccines, mucosal vaccines, protein-polysaccharide conjugates, or newer vaccines such as those against malaria or dengue. However, such additional study pathways should be driven by clinical, laboratory or epidemiologic evidence for non-specific immunological effects.

THEME: Research to conduct impact evaluation of vaccines in use

Session 3: Polio vaccine modelling

IVIR-AC agreed that models, such as the one presented at the meeting, which explore the long-term implications of current polio vaccination strategies, and considering silent poliovirus transmission, are valuable. IVIR-AC takes note of the work in progress and recommends that the Polio Group continues funding modelling work such as the current model to investigate silent transmission of poliovirus, assuming that the issues highlighted below are incorporated.

The current model is useful but there is a need to explore strengthening some of its simplifying assumptions, particularly concerning waning mucosal immunity and vaccine-derived poliovirus. Also of priority is the incorporation of inactivated polio vaccine (IPV) into the model, alongside oral polio vaccine (OPV) which is already in the model, as IPV is increasingly a part of national EPI programmes around the world, and is scheduled to replace OPV in 2016.

There is a need to explore whether the experience in Israel, demonstrating widespread shedding of poliovirus in a setting where IPV was used routinely (without use of OPV) is relevant for other settings. Prolonged silent circulation of polio in the setting of IPV-only may have very different dynamics from that in settings of OPV-end game eradication.

The model could be used to identify the parameters and assumptions that have the greatest impact on model uncertainty, so that these can be prioritised for future research funding.

On envisagera d'élaborer des modèles mécanistes de la réponse immunitaire non spécifique à la vaccination et d'établir un lien entre ces modèles et les modèles épidémiologiques inter-hôtes.

La collecte insuffisante d'échantillons dans le cadre des essais cliniques en cours pose problème, en particulier pour les essais randomisés. Il importe de déterminer si la conception des essais peut répondre aux questions relatives aux effets non spécifiques des vaccins. Si c'est le cas, il faudra veiller au prélèvement d'échantillons adéquats; ces derniers pourront être stockés dans une biobanque pour analyse future en attendant que les ressources nécessaires soient disponibles et que le schéma précis de l'étude soit fixé.

Il n'y a aucune raison a priori d'exclure les vaccins autres que celui contre la diphtérie, le tétanos, la coqueluche (DTC), le vaccin antirougeoleux et le BCG. Parmi les autres vaccins pouvant être envisagés pour l'étude des voies immunologiques figurent les autres vaccins à virus vivants, les vaccins par voie muqueuse, les conjugués protéine-polyoside ou les nouveaux vaccins comme ceux contre le paludisme ou la dengue. Toutefois, le choix de telles nouvelles voies d'étude doit être motivé par des indices cliniques, épidémiologiques ou de laboratoire de la présence d'effets immunologiques non spécifiques.

THÈME: Recherche pour évaluer l'impact des vaccins actuels

Session 3: Modélisation relative au vaccin antipoliomyélitique

Le Comité a constaté l'utilité des modèles qui explorent les conséquences à long terme des stratégies actuelles de vaccination antipoliomyélitique en tenant compte de la transmission silencieuse du poliovirus, comme celui qui a été présenté lors de la réunion. Le Comité a pris connaissance des travaux en cours et a recommandé que le Groupe Poliomyélite continue de financer les activités de modélisation, telles que celles menées actuellement pour étudier la transmission silencieuse du poliovirus, dans la mesure où elles tiennent compte des points soulevés ci-dessous.

Le modèle actuel est utile, mais un renforcement de certaines de ses hypothèses de simplification devrait être envisagé, en particulier en ce qui concerne le déclin de l'immunité mucosale et les poliovirus dérivés d'une souche vaccinale. Il est également primordial d'incorporer le vaccin antipoliomyélitique inactivé (VPI) à ce modèle, qui couvre déjà le vaccin antipoliomyélitique oral (VPO), car le VPI figure de plus en plus souvent dans les programmes élargis de vaccination de divers pays du monde entier et est appelé à remplacer le VPO en 2016.

Il convient en outre de déterminer si la situation survenue en Israël, où une excrétion à grande échelle du poliovirus a été observée au sein d'une population où le VPI était utilisé de manière systématique (sans administration de VPO), pourrait être pertinente dans d'autres contextes. La circulation silencieuse prolongée de poliovirus dans un contexte où seul le VPI est administré peut présenter une dynamique très différente de celle rencontrée dans un contexte de phase finale d'éradication par le VPO.

Le modèle pourrait être utilisé pour identifier les paramètres et les hypothèses qui ont l'impact le plus important sur l'incertitude afin de leur consacrer en priorité les futurs fonds de recherche.

Further work to understand the kinetics of vaccine waning and its implications on vaccine strategies across different polio models is needed. IVIR-AC members were nominated to represent IVIR-AC in a polio modelling meeting in Seattle on 1 July 2015.

An important outcome from any modelling work is to inform future policy decisions such as the addition of adult boosters to the immunization schedule.

Session 4: Decade of Vaccine Economics (DoVE)

IVIR-AC recognizes the ambitious scope of the present DoVE work, and the limited time and resources still available to investigators to complete it. IVIR-AC also appreciates that the DoVE team returned to update the committee on the status of DoVE and to report their responses to last year's comments.

IVIR-AC members reported continued concern over the internal and external validity, uncertainty, transparency and nature of extrapolation of the work to define the economic impacts of immunization programmes. Many of these concerns have been raised at previous IVIR-AC meetings.

IVIR-AC appreciates that some of these issues are beyond the remit or remaining timelines of the DoVE investigators to address. Hence, it is strongly recommended that any publications of the DoVE work is accompanied by clear statements about the appropriate use of the results at global, regional and country level. Since donors and decision-makers often want country-level and vaccine-specific estimates, a clear statement about aspects for which the model cannot be used needs to be given prominence.

There were concerns about the face validity of some of the grades given to the health impact models that are used as inputs to the DoVE work. It is recommended that these are graded independently of the model developers or the DoVE team. IVIR-AC is willing to assist with this if needed.

IVIR-AC supports efforts by the GAVI Alliance (GAVI) to communicate uncertainty in model outcomes to decision-makers.

For future work of this nature, it is recommended that investigators involve members of IVIR-AC from earliest stages of scoping out and drawing up terms of references of the work to maximize the value of committee recommendations to the ultimate products. Committee recommendations are less useful if the study and report are essentially completed by the time the recommendations can be provided.

Session 5: Impact evaluation of hepatitis B vaccines

IVIR-AC appreciates the value of the new work done in response to last year's recommendations.

Il importe également de mener de nouvelles études pour mieux comprendre la cinétique du déclin de l'immunité vaccinale et ses implications pour les stratégies de vaccination dans les différents modèles sur la poliomyélite. Des membres ont été désignés pour représenter le Comité lors de la réunion sur la modélisation devant se tenir à Seattle le 1er juillet 2015.

L'un des objectifs majeurs de tout travail de modélisation est de fournir les informations nécessaires à la prise de décisions futures, concernant par exemple l'ajout de doses de rappel à l'âge adulte dans le calendrier de vaccination.

Session 4: Décennie sur l'aspect économique des vaccins (DoVE, Decade of Vaccine Economics)

Le Comité a salué le caractère ambitieux du travail actuellement accompli dans le cadre du projet DoVE et a reconnu que le temps et les ressources encore disponibles pour mener ces travaux à bon terme sont limités. Le Comité sait gré à l'équipe DoVe d'être revenue l'informer de l'avancement des activités et donner suite aux commentaires formulés l'an dernier.

Les membres du Comité ont de nouveau fait part de leurs inquiétudes quant à la validité interne et externe, l'incertitude, la transparence et la nature des extrapolations utilisées pour définir l'incidence économique des programmes de vaccination. Nombre de ces inquiétudes avaient déjà été exprimées lors de réunions précédentes du Comité.

Le Comité reconnaît que certaines de ces questions vont au-delà du domaine de compétence des chercheurs DoVE ou ne peuvent être résolues dans les délais dont ils disposent. Il est donc vivement recommandé d'inclure, dans toute publication sur le projet DoVE, une notification énonçant clairement l'usage approprié pouvant être fait des résultats aux niveaux mondial, régional et national. Les donateurs et les décideurs souhaitant généralement disposer d'estimations spécifiques à chaque pays et chaque vaccin, il importe de fournir, de manière bien visible, une explication claire sur les aspects ne se prêtant pas à l'utilisation du modèle.

Le Comité a également émis des doutes sur la validité apparente de certaines notes d'évaluation attribuées aux modèles d'incidence sur la santé utilisés dans le cadre du projet DoVE. Il recommande que ces modèles soient évalués de manière indépendante, par une partie autre que les concepteurs de ces modèles ou l'équipe DoVE. Le Comité est disposé à contribuer à cette initiative le cas échéant.

Le Comité soutient les efforts déployés par l'Alliance GAVI pour communiquer l'incertitude des résultats de modélisation aux décideurs.

Dans les futurs travaux de cette nature, il est recommandé d'impliquer les membres du Comité dès les premiers stades de définition du travail à effectuer pour que le produit final tire le meilleur parti des recommandations du Comité. Ces recommandations sont d'une utilité réduite si elles ne peuvent être fournies que lorsque l'étude et le rapport sont déjà essentiellement terminés.

Session 5: Évaluation de l'impact des vaccins contre l'hépatite B

Le Comité se félicite du travail accompli suite aux recommandations de l'an dernier.

There are 3 important policy questions concerning Expanded Programme on Immunization (EPI) schedules that the model should address:

- Early administration of a birth dose (which the current model addresses)
- Whether or not EPI schedules should include a birth dose at all. The current model does not address this issue, which IVIR-AC considered the key policy question related to infant hepatitis B vaccine schedules. Consequently, the model should be assessed to determine if this question can be addressed.
- The choice of whether a DPT booster dose given from age 9–15 months should be delivered as standard pentavalent (DTP–*Haemophilus influenzae* type b (Hib) – hepatitis B (Hep B)) or as quadrivalent (DTP-Hib)

A question related to presentation is whether there is any advantage to providing single component HepB vaccine at any visit other than a birth visit rather than multivalent (usually pentavalent) vaccines.

Further clarifications of assumptions and findings seem necessary on the following issues:

- Main reasons why the annual rate of hepatitis B virus carrier clearance was estimated (through Markov Chain Monte Carlo) to be substantially different in different countries;
- What would be the potential impact of changes in HepC epidemiology;
- Main reasons for deviations between the modelled post-vaccination anti-HBc estimates and the observed anti-HBc data, especially for children in China.

The cost and benefit of improving the current hepatitis B vaccination programme, i.e. with both the current (imperfect) vaccination schedule and an optimized schedule, could be highlighted in a way that is relevant for decision-makers.

Since the force of infection in the model is unaffected by changing demographics (in the absence of vaccination), it may be possible to reduce model complexity by keeping the population static until disease outcomes are projected.

The next step for IVIR-AC after the model is completed is to consider cost-effectiveness issues around a broader package of maternal and child interventions.

Session 6: Pertussis impact modelling comparison

IVIR-AC appreciates the plan for phase 1 of the comparison of pertussis models from Australia, England & Wales and the United States of America, which is meant to be a rapid assessment on the relative contributions of vaccine formulations, waning immunity, vaccine coverage and schedule to observed pertussis resurgence in these countries. If successful, phase 2 offers further opportunities to test whether existing models are sufficiently robust to changes in factors such as demographics, spatial heterogeneity,

Il estime que le modèle doit aborder les 3 questions politiques suivantes concernant les calendriers des programmes élargis de vaccination:

- l'administration précoce d'une dose à la naissance (prise en compte par le modèle actuel);
- la pertinence de l'inclusion d'une dose à la naissance dans les calendriers des programmes élargis de vaccination. Le modèle actuel n'aborde pas la question, considérée par le Comité comme primordiale dans l'établissement des calendriers de vaccination des nourrissons contre l'hépatite B. Une évaluation du modèle est donc nécessaire pour déterminer si cette question peut être prise en compte;
- le type de vaccin à administrer pour la dose de rappel du DTC à partir de l'âge de 9-15 mois: vaccin pentavalent standard (DTC– *Haemophilus influenzae* type b (Hib) – hépatite B (Hep B)) ou vaccin quadrivalent (DTC-Hib).

Concernant la présentation des vaccins, il serait utile de déterminer si l'administration d'un vaccin HepB à composant unique lors d'une visite autre que la visite à la naissance comporterait des avantages par rapport à l'administration de vaccins multivalents (généralement pentavalents).

Les points suivants semblent exiger des précisions quant aux hypothèses retenues et aux résultats obtenus:

- les principales raisons pour lesquelles l'estimation du taux annuel de clairance des porteurs du virus de l'hépatite B (obtenue par la méthode de Monte Carlo par chaîne de Markov) varie de manière considérable d'un pays à l'autre;
- l'impact potentiel qu'aurait un changement de l'épidémiologie de l'hépatite C;
- les causes principales de la déviation observée entre l'estimation modélisée du taux postvaccinal d'anticorps anti-HBc et les taux d'anti-HBc effectivement observés, en particulier chez les enfants en Chine.

Les coûts et les avantages associés à une amélioration du programme de vaccination contre l'hépatite B, mis en évidence par une comparaison entre le calendrier vaccinal actuel (imparfait) et un calendrier optimisé, pourraient être communiqués sous une forme plus utile pour les décideurs.

Puisque dans le modèle, l'intensité de l'infection n'est pas affectée par les modifications d'ordre démographique (en l'absence de vaccination), la complexité du modèle pourrait être réduite en conservant les données de population à un niveau statique jusqu'à l'établissement de projections sur les issues de la maladie.

Le Comité estime que la prochaine étape, une fois ce modèle achevé, sera d'étudier le rapport coût-efficacité d'un ensemble plus vaste d'interventions chez la mère et l'enfant.

Session 6: Comparaison des modèles sur l'impact de la vaccination contre la coqueluche

Le Comité accueille favorablement le plan de la phase 1 de comparaison des modèles sur la coqueluche utilisés en Angleterre et pays de Galles, en Australie et aux États-Unis d'Amérique. L'objectif de cette phase est de fournir une évaluation rapide des contributions relatives de la formulation vaccinale, du déclin de l'immunité, de la couverture vaccinale et du calendrier de vaccination sur la résurgence de la coqueluche dans ces pays. Si la phase 1 est concluante, la phase 2 permettra de déterminer de manière plus détaillée si les modèles existants sont suffisamment résistants à la modification de certains facteurs, tels que

immunity and contact matrices across multiple settings.

In many countries using whole-cell pertussis vaccine in the national immunization programme, acellular pertussis vaccine is used in the private sector which represents a variable proportion of infant immunizations, so these complexities will need to be reflected when the models are extended to low and middle income settings.

Pertussis surveillance and laboratory capacity are still extremely poor in low income countries (particularly in Africa), and beyond the scope of the model comparison exercise to address. The committee noted that data are expected to be forthcoming through ongoing studies and follow-on analysis of maternal influenza trials, and strongly endorses the identification or further opportunities to add pertussis markers (primarily PCR on respiratory specimens) to studies such as GAVI– or the Bill & Melinda Gates Foundation– supported vaccine impact studies.

There were concerns that the opportunistic process by which the 3 models were identified may not have included all relevant parameters or modelling approaches. The feasibility of taking into account other models and parameters identified through a literature review and/or open call should be assessed, focusing on the main results of the different models for phase 1, and if they are interested to include them in phase 2.

Session 7: Dengue vaccine modelling comparison exercise

IVIR-AC appreciated the process of identifying the participating models (such as having an open call and clear inclusion criteria) and the general plan for the comparison exercise. The participating models were generally appropriate given the policy question involved. Not all the models may eventually be suitable to inform SAGE processes, but their relative strengths and weaknesses will become clear during the process of model comparison.

Data and models relevant to dengue vaccines in Africa are lacking and need to be prioritised in the future.

Considerations about the safety of dengue vaccines need to be addressed in addition to questions about impact or efficiency. The model comparison needs to prioritize exploring whether there is potential for vaccination to increase the risk of disease in subgroups, such as groups defined by age or by prior immunity.

Model outputs need to include infection. The influence of different vaccine coverage levels on infection prevalence should be explored. The infection prevalence at equilibrium should also be identified.

Models should report their level of spatial stratification, incorporation of vectors, as well as temporal changes and assumptions about efficacy of vector control and case management.

la démographie, l'hétérogénéité géographique, l'immunité et les matrices de contact dans plusieurs contextes différents.

Dans les pays où le programme national de vaccination administre le vaccin anticoquelucheux à germes entiers, il arrive souvent que le vaccin anticoquelucheux acellulaire soit utilisé par le secteur privé, couvrant une proportion variable des nourrissons. Cette complexité devra être prise en compte dans les modèles lorsqu'ils seront étendus aux populations à revenu faible ou intermédiaire.

La surveillance de la coqueluche et les capacités des laboratoires demeurent nettement insuffisantes dans les pays à faible revenu (en particulier en Afrique), ces pays ne pouvant de ce fait pas être inclus dans l'exercice de comparaison des modèles. Notant que de nouvelles données sont attendues à l'issue des études en cours et des analyses de suivi des essais portant sur la grippe maternelle, le Comité préconise vivement d'identifier de nouvelles opportunités pour intégrer les marqueurs de la coqueluche (principalement par amplification PCR d'échantillons respiratoires) à certaines études d'impact des vaccins, notamment celles réalisées avec l'appui de l'Alliance GAVI ou de la Fondation Bill & Melinda Gates.

Le Comité craint que le processus opportuniste employé pour identifier les 3 modèles à comparer n'ait pas inclus tous les paramètres appropriés ou toutes les approches de modélisation pertinentes. Il recommande d'envisager la prise en compte d'autres modèles et paramètres, identifiés par un examen de la littérature et/ou un appel ouvert, en mettant l'accent sur les principaux résultats des différents modèles pour la phase 1, à inclure ensuite dans la phase 2 s'ils semblent intéressants.

Session 7: Comparaison des modèles sur les vaccins contre la dengue

Le Comité a apprécié le processus employé pour identifier les modèles à comparer (appel ouvert, critères d'inclusion clairs), ainsi que le plan général de l'exercice de comparaison. Les modèles retenus étaient généralement bien adaptés à la question politique posée. Les modèles ne s'avéreront pas nécessairement tous utiles pour informer les travaux du SAGE, mais leurs forces et leurs faiblesses relatives seront clairement mises en évidence par le processus de comparaison.

Les données et les modèles portant sur les vaccins contre la dengue en Afrique sont insuffisants et doivent se voir accorder la priorité à l'avenir.

Outre l'impact ou l'efficacité, les questions relatives à l'innocuité des vaccins contre la dengue doivent être abordées. La comparaison des modèles devra en priorité déterminer s'il est à craindre que la vaccination augmente le risque de maladie chez certains sous groupes, définis par exemple par leur âge ou leur immunité préalable.

Les modèles doivent fournir des données relatives à l'infection, et notamment étudier l'effet des différentes couvertures vaccinales sur la prévalence de l'infection et déterminer la prévalence à l'équilibre.

Ils doivent également faire état de leur niveau de stratification spatiale, de l'incorporation des vecteurs, ainsi que de l'évolution temporelle et des hypothèses relatives à l'efficacité de la lutte contre les vecteurs et de la prise en charge de la maladie.

Results of both phase 1 and phase 2 of the model comparison process should be reported to prevent over-harmonization in phase 2.

Both the pertussis and dengue model comparison exercises highlight the need for guidelines on best practice for conducting model comparison exercises to guide further work in this field.

THEME: Research to improve methods for monitoring of immunization programmes

Session 8: Development of guidance for the collection, assessment, and use of immunization data

IVIR-AC appreciated this work not only for the value of guidance it may provide for programme management but also for acquiring data that serve the interests of advocacy.

The aims, scope, and anticipated products of the work should be made more explicit and clearer at the outset, indicating the documents, tools for field managers and interactions the work aims to encourage.

Strategic aims may be usefully informed by prior relevant planning documents, e.g. the Global Framework for Immunization Monitoring and Surveillance and the Global Immunization Vision and Strategy.

The committee recognized a danger of overloading field workers with data collection responsibilities. Documentation for field workers on collecting and using their data should be brief, and should include practical advice informed by a bottom-up approach to ensure the relevance of recommendations.

For redesigning Health Management Information Systems (MIS) and for integrating an immunization MIS with a primary health care MIS, the approach should be process-driven and tailored to the particular context and needs of a specific health system.

Use of qualitative methods should be encouraged to explain vaccine acceptance and features of both more and less well-functioning programmes.

Further consideration of enhancing capacity for use of electronic data collection methods is needed. Paper-based tools for acquiring and using data are being replaced by electronic strategies that offer many advantages, such as data cleaning and opportunities to verify data sources and avoid double counting.

A single work plan will not be suitable for application in every country, given financial and infrastructure constraints. It is therefore important to develop a set of options as templates for contexts and settings, and to thereby enable national planning to develop an optimal system in each country.

Il conviendra de rendre compte des résultats obtenus aussi bien en phase 1 qu'en phase 2 de la comparaison pour éviter une harmonisation excessive lors de la phase 2.

Ces exercices de comparaison des modèles, tant pour la coqueluche que pour la dengue, mettent en évidence la nécessité d'élaborer des lignes directrices sur les meilleures pratiques à adopter pour la comparaison des modèles afin d'orienter les futures initiatives en la matière.

THÈME: Recherche pour améliorer les méthodes de suivi des programmes de vaccination

Session 8: Élaboration d'éléments d'orientation sur la collecte, l'évaluation et l'utilisation des données de vaccination

Le Comité a salué cette initiative, non seulement pour l'utilité des éléments d'orientation visant à guider la gestion des programmes, mais aussi pour l'acquisition de données susceptibles d'appuyer les activités de sensibilisation.

Les objectifs, le champ d'application et les produits attendus de ces travaux devraient être définis d'emblée de manière plus explicite et plus claire, indiquant les documents, les outils destinés aux administrateurs sur le terrain et les échanges que l'initiative cherche à encourager.

Pour définir les objectifs stratégiques, il pourra être utile de s'appuyer sur des documents de planification préalables, tels que le Cadre mondial de suivi et de surveillance pour la vaccination et le document « La vaccination dans le monde: vision et stratégie ».

Le Comité estime qu'il serait dangereux de surcharger les agents de terrain en leur confiant des responsabilités excessives de collecte des données. Les documents destinés aux agents de terrain sur la collecte et l'utilisation des données doivent être concis, contenant des conseils pratiques découlant d'une démarche ascendante pour garantir la pertinence des recommandations.

La révision des systèmes d'information pour la gestion sanitaire (MIS) et l'intégration d'un MIS sur la vaccination avec un MIS sur les soins de santé primaires devront reposer sur une approche axée sur les processus et être adaptés au contexte et aux besoins spécifiques du système de santé concerné.

Il est recommandé d'encourager l'utilisation de méthodes qualitatives pour analyser l'acceptation des vaccins et les caractéristiques des programmes dont les performances sont particulièrement faibles ou élevées.

Il importe par ailleurs d'améliorer les capacités d'utilisation des méthodes électroniques de collecte de données. Les outils d'acquisition et d'utilisation des données sur support papier sont en train d'être remplacés par des stratégies électroniques offrant de nombreux avantages, comme le nettoyage des données et la possibilité de vérifier les sources de données et d'éviter le double comptage.

Il ne sera pas possible d'utiliser un plan de travail unique dans tous les pays, compte tenu des contraintes liées à la situation financière et aux infrastructures de chaque pays. Il est donc essentiel de mettre au point un ensemble d'options pouvant servir de modèles pour différents contextes, permettant ainsi aux responsables de la planification nationale d'élaborer un système optimal adapté à leur pays.

Session 9: Proposed analysis of EPI surveys

IVIR-AC appreciated the work done since comments given by the committee last year.

The work was felt to be of value for identifying potential missed opportunities for vaccination, although it was not designed to indicate solutions to missed opportunities. A clear definition and an algorithm for identifying all missed opportunities are needed. It was agreed that early doses are unlikely to be ineffective and considering them invalid for the purpose to identifying missed opportunities is not a useful approach.

Correlation between the proportions of missed, as opposed to utilised, opportunities for vaccination catch-up and vaccination coverage should be explored.

Development of methods for missed opportunities for vaccination should include:

- Assessment of the degree to which decreases in missed opportunities will translate into improvements in vaccination coverage;
- Reasons for missed opportunities;
- The degree to which evaluations need repeated to reflect temporal and geographic variations.

IVIR-AC welcomed the plans of the team working on revising EPI coverage survey methodology to update COSAS, the software designed for analysis of such data, to run on current operating systems and accommodate the new statistical features of the methodology. ■

Session 9: Analyse proposée des enquêtes sur les programmes élargis de vaccination

Le Comité apprécie les progrès accomplis suite aux commentaires qu'il avait émis l'an dernier.

Il juge que le travail réalisé est d'une grande utilité pour identifier les occasions manquées en matière de vaccination, même si le projet n'a pas été conçu pour trouver des solutions à ces occasions manquées. Une définition claire et un algorithme d'identification de toutes les occasions manquées doivent être formulés. Le Comité a convenu que les premières doses ont peu de chances d'être inefficaces et qu'il n'est donc pas judicieux de les considérer comme invalides aux fins d'identification des occasions manquées.

Le Comité estime utile d'étudier la corrélation entre le pourcentage d'occasions manquées, par opposition aux occasions utilisées, pour la vaccination de rattrapage et la couverture vaccinale.

Pour mettre au point des méthodes d'identification des occasions il faudra entre autres:

- évaluer dans quelle mesure la réduction des occasions manquées se traduira par une amélioration de la couverture vaccinale;
- identifier les facteurs responsables des occasions manquées;
- déterminer dans quelle mesure les évaluations doivent être répétées pour tenir compte des variations temporelles et géographiques.

Le Comité note avec satisfaction que l'équipe chargée de réviser la méthodologie des enquêtes sur la couverture des programmes élargis de vaccination a prévu une mise à jour de COSAS, le logiciel destiné à l'analyse de ces données, pour le rendre apte à fonctionner sur les systèmes d'exploitation actuels et à prendre en charge les nouvelles fonctionnalités statistiques de la méthodologie. ■

PERFORMANCE OF ACUTE FLACCID PARALYSIS (AFP) SURVEILLANCE AND INCIDENCE OF POLIOMYELITIS (DATA RECEIVED IN WHO HEADQUARTERS AS OF 25 AUGUST 2015)

FONCTIONNEMENT DE LA SURVEILLANCE DE LA PARALYSIE FLASQUE AIGUË (PFA) ET INCIDENCE DE LA POLIOMYÉLITE (DONNÉES REÇUES PAR LE SIÈGE DE L'OMS AU 25 AOÛT 2015)

Country/area Pays/territoire	Performance of AFP surveillance, 2015 Fonctionnement de la surveillance de la PFA, 2015			Poliomyelitis cases Cas de poliomyélite			
				2015		2014	
	AFP cases reported Cas de PFA signalés	Annualized non-poliomyelitis AFP rate[1] Taux de PFA non poliomyélitique annuel[1]	AFP cases with adequate specimens[2] Cas de PFA avec échantillons conformes[2]	WPV1 PVS1	cVDPV2[3] PVDV2c[3]	WPV1 PVS1	cVDPV2[3] PVDV2c[3]
Regional totals – Totaux régionaux							
AFR	15 977	06.04	94%	0	10	17	33
AMR	981	00.62	73%	0	0	0	0
EMR	7 590	05.36	92%	37	0	342	22
EUR	972	00.93	88%	0	0	0	0
SEAR	28 851	07.96	86%	0	0	0	0
WPR	3 485	01.42	89%	0	0	0	0
Global total – Total mondial	**57 856**	**04.53**	**89%**	**37**	**10**	**359**	**55**
African Region – Région africaine (AFR)							
Algeria – Algérie	65	00.95	58%	0	0	0	0
Angola	275	04.24	95%	0	0	0	0
Benin – Bénin	106	03.32	97%	0	0	0	0

The World Health Organization Product Development for Vaccines Advisory Committee (PDVAC)

7-9 Sep 2015. Initial Summary. Full Meeting Report to follow.

The World Health Organization Product Development for Vaccines Advisory Committee (PDVAC) met from Sep 7 to 9 2015. The committee reviewed 22 pathogens for which specific read-ahead documents had been prepared. Each document provided a global pipeline analysis commissioned by WHO according to a standardised template which included the following sections: the pathogen, disease and unmet public health need focusing on low and middle income countries (LMICs); the status of the vaccine development pipeline; the pathway to licensure; suggested possible roles for WHO to advance the vaccine pipeline towards public health objectives. All of these documents will be made available in a supplement of the journal Vaccine by Q1 2016. WHO thanks the many individuals and organizations that contributed to this community effort to assess the global pipeline for these pathogens.

PDVAC's core role is to consider in which pathogen areas vaccines are likely to emerge in the short to medium term from the pipeline for diseases inflicting a substantial public health burden in LMICs, and in areas where WHO has a key role to play to increase the likelihood that the vaccines are used to reduce the disease burden in LMICs. Thus, PDVAC is not a vaccine prioritization committee, but rather the committee assesses the status of the vaccine pipeline for diseases for which new or improved vaccines are a priority. PDVAC does not generally assess the vaccine landscape for pathogens with licensed vaccines, unless there are major new technologies that could be brought to bear to develop second generation vaccines.

Following consideration of the 22 documents, and presentations by leaders in 13 of the pathogen fields, the following statements were made.

- RSV is highlighted as a pathogen for which there is major vaccine pipeline activity, high technical feasibility, and major disease burden in LMICs. RSV vaccine developments will therefore be reviewed at a specific "For information" SAGE session in April 2016.
- Two major manufacturers are engaged in Group B Streptococcal (GBS) vaccine development, technical feasibility appears good, and GBS is a major disease burden in LMIC,s particularly those in Africa. PDVAC recommends that WHO develops guidance on the testing and development pathway for Group B Streptococcal vaccines. This would include agreement of strategic goals, trial design considerations and development of Preferred Product Characteristics (PPCs) for GBS vaccines.
- With regard to universal influenza vaccines, the committee advised WHO to develop strategic public health goals for improved seasonal influenza vaccines and PPCs for such vaccines to provide guidance on data that would need to be generated to establish improved performance of such vaccines.
- Group A Streptococcal causes a substantial disease burden, particularly in terms of rheumatic heart disease in some regions of the world, and the technical feasibility for developing a vaccine appears high. A WHO PPC, document is in development. It is

recommended that two business/investment cases are developed by the GAS community – these would include a public sector investment case based on prevention of severe outcomes in resource poor settings such as southern Africa, parts of Asia and certain high risk communities, including those in Australasia. In addition, a business case should be developed for a dual market product for the indication of GAS Pharyngitis in high income countries, and for prevention of cardiac outcomes in LMICs. Once such a business case is developed PDVAC would be better able to advise on the next steps.

- PDVAC advised that WHO explore the possibility of addition of Norovirus surveillance to the WHO network for rotavirus surveillance. Norovirus vaccine development is proceeding, and filling in gaps related to disease burden estimation and strain surveillance in all regions of the world may be enabling to decision-making related to Norovirus vaccine development beyond the well-established high income setting indications.
- WHO should expand its capacity to be able to better support pipeline enteric vaccine development, including consensus building on the key design considerations for Phase 3 trials of ETEC and potentially Shigella vaccines. It will be essential that such guidance is available prior to the start of Phase 3 trials.

PDVAC notes the initiation of WHO's Blueprint for Emergency R&D Preparedness and Research Response. PDVAC will review vaccine-related elements that will feed into the Blueprint, understanding the need to ensure complementarity with guidance in development also related to drugs, diagnostics and non product-development related research as part of the emerging pathogen R&D focus of the blueprint. The first of these are the WHO Ebola Vaccine Target Product Profiles under public consultation in September 2015.

Very important and helpful presentations were given on HIV, malaria, tuberculosis, HSV, dengue, chikungunya and MERS. PDVAC endorsed the importance of the major ongoing product development activities in all these areas.

PDVAC noted that many important platform technologies, such as certain viral vectors, novel antigen design and broadly neutralising antibody approaches, are often being tested first in HIV and malaria. It is therefore very important that information on clinical portfolios is shared between communities. WHO will begin to collate summary information on the global portfolios across several pathogen fields, building on the existing experience in malaria vaccines.

PDVAC noted the major progress towards Phase 3 trials in HIV vaccines and will follow developments with great interest. PDVAC requested further information on the potentially promising developments (of interest beyond HIV alone) related to replication competent vectors and broadly neutralising antibody induction. It was noted that it was HIV clinical trial data that was available for a rVSV vector, which proved helpful in planning rVSV ebola vaccine trials.

PDVAC commended the consensus emerging in the TB vaccine field that development of vaccines to prevent pulmonary tuberculosis in adults and adolescents is now a significant focus for the field. Further work on development pathways for this indication was encouraged, noting that the TB vaccine field is at too early a stage to focus too much emphasis on any single approach. Basic and translational research should remain an important focus for TB vaccines, whilst establishing a development pathway towards an adult pulmonary TB vaccine in parallel.

For HSV it was recommended that a systematic review be conducted of age-specific seroprevalence data for HSV-1 and HSV-2 in different LMIC paediatric populations. This will be helpful to guide the important product development activities underway. PD VAC noted that a major incentive for the development of HSV vaccines, in addition to the public health burden directly accountable to these viruses, was their potential to reduce HIV infection rates. PDVAC would like to review the business case and modelling outcomes under development for HSV once they are available, and commends the HSV community for taking up this initiative. Finally, with regard to HSV it was recommended that the HSV data from the minimally invasive autopsy component of the large CHAMPS study is carefully assessed in better understanding the neonatal HSV mortality burden. PDVAC also notes and supports the broader sexually transmitted infection roadmap for vaccine development, and would like to be kept updated on progress.

In the cases of dengue and malaria vaccines, PDVAC noted that vaccine development for both both diseases are entering a critical stage whereby guidance on trial design and endpoints related to second generation vaccines will be needed, and recommended that WHO initiates development of such guidance. The promise of chimeric vaccine vectors has been highlighted from both Dengue and Ebola (yellow fever and VSV backbones respectively).

MERS and chikungunya vaccines will be further assessed as part of the WHO Blueprint discussions.

The next meeting of PDVAC is planned for June 8-10 2016.

A full meeting report will be published in a Vaccine journal supplements which will include each pathogen specific pipeline analysis

List of global pathogen-specific vaccine pipeline analyses developed for PDVAC committee

Viruses

- MERS
- EV71
- RSV
- HSV
- HIV
- Dengue
- Nipah
- Cikungunya
- Universal influenza
- Rotavirus (next gen)
- Norovirus

Bacteria

- Group A Streptococcal
- Group B Streptococcal
- Streptococcus pneumonia (next gen)
- Staph. aureus
- Non-typhoidal salmonella
- Paratyphoid fever
- ETEC
- Shigella
- Campylobacter

Tuberculosis

Parasites

- P. falciparum & P. vivax
- Schistosomiasis
- Leishmaniasis
- Hookworm
- Chagas disease

BACKGROUND PAPER ON THE

RTS,S/AS01 MALARIA VACCINE

SEPTEMBER 2015

PREPARED BY THE JOINT TECHNICAL EXPERT GROUP ON MALARIA VACCINES (JTEG) AND WHO SECRETARIAT

Contents

1. Executive summary of JTEG's assessment and proposed recommendations

WHO provides member states with policy advice regarding introduction and use of new interventions. In developing and formulating policy recommendations, WHO considers factors in addition to the benefit-risk assessment performed by regulators, as well as important contextual elements such as the feasibility of implementation, in this case the effects of the vaccine in different transmission intensity settings, the value of the vaccine in the context of other malaria control measures, and the likely cost-effectiveness of the intervention in different settings.

A malaria vaccine has been evaluated in a large, multicentre Phase 3 trial, and key results from this trial were the basis for the proposed recommendations of JTEG. The trial showed that in both age groups evaluated (infants vaccinated at 6-12 weeks of age (vaccine efficacy (VE) over 18 months post dose 3, 26.6%) and a group vaccinated at 5-17 months of age (VE over 18 months post dose 3, 45.7%) there was moderate but potentially important protection against clinical malaria that declined to a low level by 18 months after the third dose. Protection was partially restored by a fourth dose, given 18 months after the third dose, after which there was also a rapid decline in efficacy (see Table 1.1 below, VEs over full duration of trial in the groups vaccinated at 6-12 weeks and 5-17 months of age were 26.7% and 39.0% respectively). The efficacy was substantially higher in the older age category compared to the younger age category. The public health impact of a malaria vaccine is mainly driven by any reduction in mortality conferred by vaccination. It was not possible to measure a reduction in deaths in the Phase 3 trial because of the sample size and close follow-up of the participants, with consequent earlier treatment of malaria than occurs outside trial settings. The best surrogate measure that could be measured to assess the likely impact on mortality was severe malaria, which was a secondary endpoint in the trial. Among those who received a fourth dose, there was demonstrated efficacy against severe malaria during the approximately 4 years of follow-up (median follow-up 48 months) in the group vaccinated at 5-17 months of age (VE 31.5%). Among those who did not receive a fourth dose, the initial protection against severe malaria was balanced by an excess of severe malaria in the later follow-up period such that overall there was no net reduction in the number of severe cases. In the younger age category protection against severe malaria was not demonstrated in children with or without a fourth dose.

Table 1.1: Vaccine efficacy (95% CIs) against clinical and severe malaria. Per protocol analyses.

Study period*	6-12 weeks		5-17 months	
	VE against clinical malaria	VE against severe malaria	VE against clinical malaria	VE against severe malaria
2.5M-14M	32.9% (26.3, 38.9)	38.5% (7.8, 59.0)	51.3% (47.5, 54.9)	44.5% (23.8, 59.6)
2.5M-20M	26.6% (20.3, 32.4)	17.4% (-16.2, 41.3)	45.7% (41.7, 49.5)	37.7% (18.0, 52.6)
2.5M-SE (3 doses)	18.2% (11.4, 24.5)	16.0% (-14.5, 38.4)	26.2% (20.8, 31.2)	-2.2% (-31.3, 20.4)
2.5M-SE (4 doses)	26.7% (20.5, 32.4)	20.5% (-9.8, 42.5)	39.0% (34.3, 43.3)	31.5% (9.3, 48.3)

*2.5M is 2 weeks after the third dose. Thus 20M is approximately 18 months after the third dose. SE (Study end) 6-12 weeks group: median 38 months after dose 1. SE (Study end) 5-17 months group: median 48 months after dose 1.
ITT results are not notably different to the above per protocol figures (Appendix 2).

In children in the older age category there was an excess risk of febrile seizures within 7 days after any of the vaccine doses. In children in the younger age category this excess risk was only apparent after the fourth dose. There were no long-lasting sequelae due to any of the febrile seizures.

In children in the older age category there was an increased number of meningitis cases in malaria vaccine groups compared to the control group. These meningitis cases were not temporally related to the timing of vaccine doses and there were a range of aetiologies in the cases identified. An excess of meningitis was not seen in children vaccinated in the younger age group. Whether this increase in meningitis was due to chance or represents a true adverse effect of the vaccine is unknown.

In children in the older age category there was an increased number of cerebral malaria cases in malaria vaccine groups compared to the control group. This finding was in a subgroup analysis and its significance in relation to vaccination is unclear. An excess of cerebral malaria was not seen in children vaccinated in the younger age group.

There is a need to evaluate initial introductions before wider scale-up is considered to address a number of issues that remain following the conclusion of the trial. The primary issues are:

- The extent to which the protection demonstrated in the Phase 3 trial could be replicated in the post-licensure phase because of the challenge of implementing four doses at the population level, including the need for new immunization contacts

- The safety signals of most concern (i.e. imbalances in meningitis and cerebral malaria) in the trial may be chance findings, but further evaluation is necessary when the vaccine is given to larger numbers of children

- The impact on mortality could not be assessed in the Phase 3 trial and as this is the main driver of the public health impact and cost-effectiveness of the vaccine, it is important to assess the mortality reduction following large-scale vaccination.

Based on the data from the Phase 3 trial, JTEG does not recommend the use of the malaria vaccine in the younger (6-12 weeks) age group. With respect to the older age group (5-17 months), JTEG recommends the initial introduction of 4 doses of the malaria vaccine in 3-5 distinct epidemiological settings in sub-Saharan Africa, likely at subnational level, to generate critical information on the issues described above (large demonstration projects). These settings should be selected such that

- they cover a range of moderate-to-high transmission settings, with at least one setting with strongly seasonal malaria transmission.

- it is possible to ascertain and diagnose cases of meningitis and severe malaria and record deaths.

- the population vaccinated should be of sufficient size to allow evaluation of the impact on mortality, probably through a phased introduction of the vaccine within the selected settings. It is likely that several hundred thousand vaccinated children will be included in each setting and that phased introduction would need to be randomized to ensure

comparability of vaccinated and unvaccinated groups. Each initial introduction will be a large demonstration project.

- there should be high existing coverage of other proven malaria control measures including LLIN (or IRS), access to RDTs and ACT, and SMC in highly seasonal areas.

JTEG strongly recommends that WHO oversees the design and evaluation of these phased introductions and monitors the emerging findings. If appropriate, SAGE and MPAC may broaden recommendations on the basis of these emerging findings.

JTEG notes that it would be appropriate for WHO to recommend countrywide introduction if concerns about safety have been resolved, and if favourable implementation data become available, including high coverage of the fourth dose.

As JTEG recommends introduction in 3-5 moderate-to-high transmission settings, where there is a significant burden of malaria in the first year of life, it is important to vaccinate at a young age within the 5-17 month age range. There is no evidence that vaccine efficacy varied according to the month of age at which vaccination was started within this age group. In the phased introduction of the vaccine, JTEG recommends a three dose initial series of the malaria vaccine with a minimum interval between doses of four weeks, followed by a fourth dose at 15-18 months following the third dose. It is encouraged that the first dose be initiated as close as possible to age five months and the third dose be completed by nine months of age, if possible. Co-administration has been evaluated with measles and DTP-containing vaccines and is considered acceptable.

Prior to any phased introduction appropriate communication materials should be developed and disseminated with particular emphasis on the partial efficacy of the vaccine and the importance of the fourth dose. Messages should include the importance of maintaining usage of non-vaccine malaria preventive measures and the likelihood that febrile episodes in vaccinated children may still be due to malaria.

Research recommendations

There are currently no data to support a fifth dose. Therefore, evaluation of safety and effectiveness of a fifth dose could be included in the proposed phased introductions.

JTEG recommends monitoring of the emergence of vaccine-resistant strains following widespread use of the vaccine.

JTEG recommends that there is further exploration of alternative schedules, including schedules adapted to highly seasonal settings, and other strategies to improve the efficacy of the vaccine.

JTEG recommends an exploration of how to capitalize upon the new immunization contacts for general improvements in child health, including increasing coverage with other vaccines.

JTEG recommends that there is an evaluation of the malaria vaccine in the context of elimination, including studies evaluating administration and effectiveness against infection over a wide age range. A high priority geographic area for such an evaluation is South-East Asia in areas of artemisinin resistance. ***For overall JTEG assessment, see section 10.***

2. Background

2.1 Epidemiology and disease burden of malaria

Based on 2013 data, WHO estimated that approximately 584 000 deaths per year were attributable to malaria, with over 90% of these deaths occurring in sub-Saharan Africa, and nearly all of the remaining occurring in South-East Asia, the Indian subcontinent and South America[1]. Most malaria deaths in Africa occur in children younger than 5 years. Adults who grew up in malaria endemic areas since childhood and remain resident in such areas are generally not at risk of death from malaria. The number of new episodes of clinical malaria in 2013 was estimated to be 198 million (uncertainty range 124-283 million). Infants and young children in malaria-endemic countries in Africa typically experience several clinical episodes of malaria before they accumulate partial immunity, which protects against severe disease and death from malaria. They accumulate immunity to febrile malaria more gradually during childhood and, generally by adulthood, acute episodes of febrile malaria are infrequent. The economic costs of malaria between 1980-1995 in heavily affected countries have been estimated to have been 74 billion USD, and the disease has been estimated to reduce gross domestic product by several percentage points[2].

In most African countries substantial malaria-control efforts have been implemented, including the widespread deployment of long-lasting insecticide-treated bed-nets (LLIN), the use of indoor residual spraying of insecticide in some settings, prompt diagnosis using quality assured rapid diagnostic tests (RDTs) and by using highly effective artemisinin-combination therapies (ACTs). In many settings, these measures are considered to have reduced the annual incidence rates of new malaria cases and malaria deaths by 50% or more since 2000[1, 3] and the geographic area with very high prevalence of malaria has been substantially reduced (Figure 2.1). While economic development and other factors may also have played a role in reducing the malaria burden, much of the decrease is likely attributable to large scale deployment of highly cost-effective interventions supported by over 10-fold increase in financing for malaria control over the last 10-15 years.

In different areas of Africa, malaria parasite transmission may occur throughout the year or be strongly seasonal, determined largely by rainfall patterns. The intensity of transmission generally varies as a function of vector man biting rate and vector survival, which is strongly influenced by temperature and humidity, as well as vector control measures. Because of variations in climatic factors and the availability of vector breeding sites, malaria parasite transmission may be very heterogeneous within a country. For example in parts of western Kenya malaria parasite transmission is very high, and malaria remains a prominent cause of childhood mortality, whereas in some other parts of Kenya there is currently little or no malaria parasite transmission.

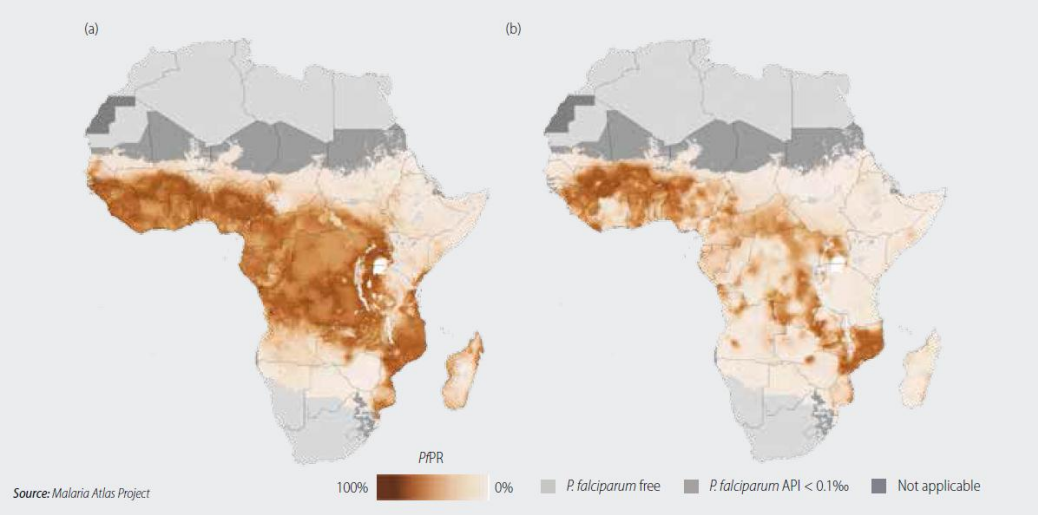


Figure 2.1: Estimated proportion of children aged 2-10 years infected with *P. falciparum* in a) 2000 and b) 2013[1].

A measure of the intensity of malaria parasite transmission is given by the entomological inoculation rate (EIR), which is the estimated number of times that an individual is bitten by an infected mosquito in a year. In different malaria-endemic areas the average EIR may range from in excess of 1000 to less than 1. In areas of very high transmission (i.e. an EIR of 100 or more), most children will have detectable parasites in their blood most of the time. Over the last decade or more the number of such highly infected areas in Africa has reduced substantially due to scaled up malaria control measures.

Acquired immunity to malaria, through repeated infections, may be relatively short-lived in the absence of exposure to natural boosting. Thus persons who leave a malaria endemic area for an extended period (e.g. a year) may be susceptible to severe disease if they are reinfected on return to an endemic area. Similarly, in areas where transmission is irregular and varies greatly from year to year, clinical immunity is difficult to acquire and may be largely lost during a prolonged period when transmission is low, making all age-groups at risk of developing severe malaria.

The frequency of episodes of malaria and the nature of disease due to malaria vary, depending on the age of the individual, and the intensity and seasonality of malaria parasite transmission. Morbidity due to infection with *P. falciparum* can range from a mild febrile illness, which is quite difficult to distinguish from many other similar illnesses, to fulminant and life-threatening disease with severe stupor and coma, or respiratory distress, or severe anaemia or a shock syndrome requiring immediate parenteral treatment, blood transfusions, fluid therapy and supportive measures, often in combination; the distribution of clinical manifestations varies by age as a function of transmission intensity (Figure 2.2). With repeated exposure protection is acquired, first against severe malaria, then against illness with malaria, and, much more slowly, against microscopy-detectable parasitaemia. Some clinical manifestations of malaria, such as cerebral malaria, occur more frequently in older children in both settings when transmission is seasonal or perennial, whereas severe life-threatening anaemia tend to occur in younger age-groups and is more prevalent where malaria parasite transmission is very intense and year-round. Furthermore, especially in

children and non-immune adults the clinical picture can change within 24 hours, from an illness that appears to be relatively mild to a life-threatening disease.

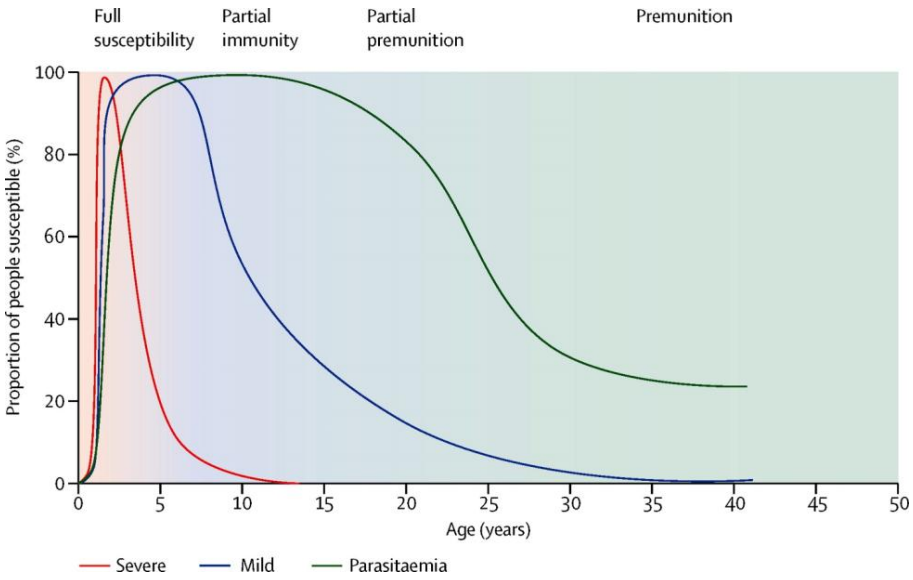


Figure 2.2: Relation between age and malaria severity in an area of moderate transmission intensity. From White *et al.* 2014[4].

2.2 Malaria Parasites and Pathogenesis

Five species of the *Plasmodium* protozoan parasite have been identified which can infect humans (*P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi*). With the exception of *P. knowlesi*, humans are the only known reservoirs of these parasite species (*P. knowlesi* infects long tailed macaques and transmission to humans occurs in some parts of South-east Asia). However, *P. falciparum* accounts for more than 90% of all malaria-attributable deaths. *P. vivax* accounts for much of the remaining disease burden and is the dominant *Plasmodium* species in many areas outside of sub-Saharan Africa. Vaccine development efforts have focused on *P. falciparum* and, to a lesser extent, on *P. vivax*[5]. Human infection with the malaria parasite is established following the injection of the sporozoite form of the parasite by female anopheline mosquitoes; subsequent development occurs over 5-10 days through the liver stage, which is followed by the replication of parasites in red blood cells, causing symptoms, including fever. Morbidity and mortality from malaria may arise from: sequestration of infected red blood cells, severe anaemia due to red blood cell dysregulation and lysis, inflammation-related brain pathology, lactic acidosis, and a general shock-like syndrome with hypotension, hypoglycaemia and poor tissue perfusion.

2.3 Immune response to malaria infection

After repeated exposure to *P. falciparum* malaria infections, individuals develop a significantly reduced risk of developing serious illness or dying from subsequent malaria parasite infections. This acquisition of immunity through natural exposure occurs first to severe malaria and death, and much more slowly to milder clinical features of malaria such as fever. While immunity to patent parasitaemia, as detected by microscopy, does occur by adulthood after many exposures, subpatent

infections, detectable by molecular techniques, may still occur and it is unclear whether or not sterile immunity is acquired by some individuals after repeated infections. In areas of moderate-to-high transmission, malaria mortality begins to drop by around the age of 2 years, with the incidence of acute febrile malaria dropping later in childhood or adolescence. The mechanisms underlying naturally acquired immunity are not fully understood; however, there are two leading hypotheses. One is that the gradual acquisition of strain-specific immunity occurs; the other is that repeated antigenic exposure, perhaps in conjunction with an age-related immune maturation, is necessary for the development of immunity. Additionally, the immunity acquired during childhood does not protect primigravid women, thus accounting for an increased risk in malaria-attributable deaths in these women. Severe malaria in primigravid women is known to be mediated by sequestration based on binding of malaria parasites to placental ligands only present in pregnancy. Naturally acquired immunity is generally believed to wane to a significant degree if an individual migrates out of a malaria-endemic region and ceases to have regular exposure to malaria parasite infection for a number of years. Severe malaria illness can occur in people who have migrated out of, and then have returned to, a malaria-endemic area[6]. It remains a questions for research whether case fatality of severe malaria is as high in the malaria-exposed after a period without ongoing exposure, compared to the truly malaria naïve. Significant roles for both humoral and cell-mediated effectors have been demonstrated in animal models, and both humoral and cell-mediated immune responses have been induced in humans after natural malaria infection and exposure to experimental malaria vaccines. No clear correlates of protection have been established for vaccines, although an accumulating body of evidence indicates that antibodies to circumsporozoite protein (CSP) show some correlation to protection against the pre-erythrocytic stages of the parasite[7].

The development of protection against severe disease after natural malaria infection, and the possible role of identifiable and quantifiable effector mechanisms of protection, both lend a positive perspective to the development of effective malaria vaccines. However, the complexity of the parasite and the highly complex genome with over 5,000 genes pose significant challenges.

2.4 Other malaria control measures

As noted above, there has been a resurgence of funding for malaria vector-control programmes, RDTs and ACTs. On World Malaria Day 2015 WHO drew attention to the major gains associated with the improvements in malaria control with malaria mortality estimated to have reduced by over 50% in WHO AFRO since 2000[1]. At the same time WHO highlighted the ongoing critical gaps in access to preventive, diagnostic and treatment measures. Many individuals and communities still do not have access to LLINs, RDTs and ACTs and WHO has called for an urgent scaling up of existing control measures. LLINs have been shown to cause a reduction in childhood mortality in randomised controlled trials. A Cochrane Review estimated 50% efficacy of ITNs against uncomplicated malaria episodes and 17% efficacy of ITNs against all-cause under five mortality (compared to no nets) in areas of high transmission[8]. Indoor Residual Spraying with insecticide is the predominant vector control method in some settings, and can be associated with marked reductions in malaria parasite transmission. In some countries IRS is deployed together with ITNs for malaria control, and in other countries it is mainly reserved for prevention and control of epidemics. The WHO African Region has the highest proportion of the population at risk protected by IRS: in 2013, 55 million people were protected, representing 7% of the population at risk. To prevent malaria in pregnant women and

newborns, WHO recommends Intermittent Preventive Treatment of malaria in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP), delivered at each scheduled ANC visit after the first trimester. In 2013 among nine reporting countries a median of 17% of all pregnant women received three or more doses of IPTp, in line with WHO recommendations. Seasonal malaria chemoprevention (SMC), previously referred to as Intermittent Preventive Treatment in children (IPTc), is defined as the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season (typically monthly during the transmission season, for a maximum of four doses) to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk. It reduces incidence of malaria (including severe malaria) by 75%. Since 2012, WHO has recommended SMC in areas of highly seasonal malaria parasite transmission across the Sahel sub-region, where an estimated 25 million children aged 3-59 months could benefit from this intervention every year[9].

2.5 Malaria vaccines

2.5.1 Malaria vaccine targets

The pre-erythrocytic stages (stages 1 and 2 in Figure 2.3) encompass the injection of the sporozoite stage of the parasite by the bite of an infected female anopheline mosquito, and the rapid homing of the sporozoite into the liver cells within a matter of minutes to a few hours. Antigens present on the surface of the sporozoite, such as circumsporozoite protein (CSP), or deployed to the surface of the infected hepatocyte, have been used as pre-erythrocytic-stage candidate vaccines. Immune responses directed at either the sporozoite stage or at the infected hepatocyte could, in theory, prevent the blood-stage infection from developing. CSP (the antigen included in RTS,S) is the predominant surface antigen of the sporozoite and antibodies to CSP have been shown to prevent sporozoites migrating to and infecting hepatocytes. The rest of this section is not relevant to RTS,S, but is provided for completion.

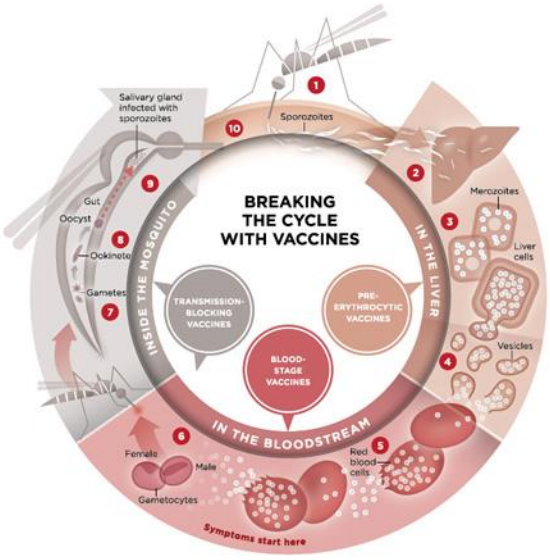


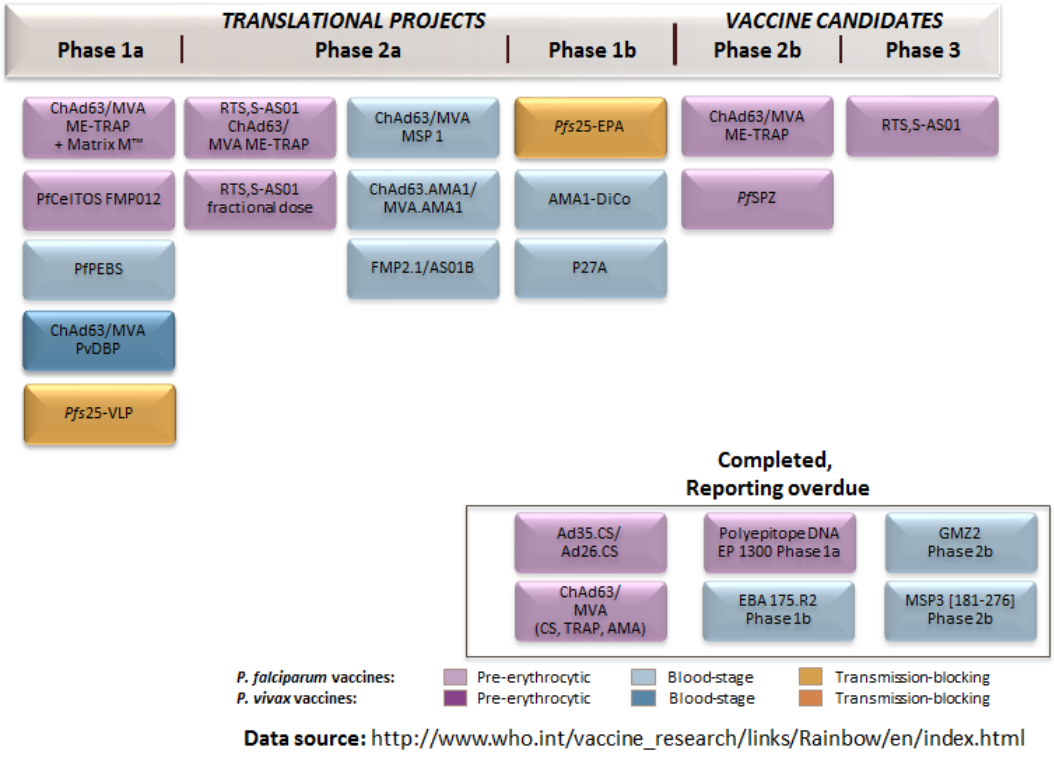
Figure 2.3: Malaria life cycle and associated vaccine targets (Figure by PATH Malaria Vaccine Initiative)[10].

Numerous antigens that are unique to either the merozoite (e.g. the merozoite surface antigens) or to the infected erythrocyte (e.g. erythrocyte-associated surface antigens) are potential erythrocytic-stage vaccine antigens, and such vaccines would either prevent the invasion of the erythrocyte by the merozoite, or would target the infected erythrocyte for destruction by the host's immune system. The net effect of such erythrocyte-stage immune responses could be to limit or ameliorate the blood-stage manifestations of the malaria parasite infection. Small subsets of infected erythrocytes undergo a developmental switch into the sexual stage of the organism, termed gametocytes. Gametocytes develop into extracelluar gametes in the midgut of the mosquito vector when taken in a blood meal

from an infected person to undergo fertilisation and continue development in the mosquito. Although most gametocytes remain within the host erythrocyte until they are taken up during a blood meal ingested by a female anopheline mosquito, some of the infected erythrocytes rupture in the host's reticuloendothelial system and present gametocyte-specific antigens to the host's immune system. Vaccines targeting gametocyte stages of the parasite, or targeting gametes and the post fertilization stage – the zygotes and subsequent ookinetes, which are found only in the mosquito midgut after fertilization occurs, may provide transmission-blocking immune responses that could interrupt transmission of the parasite from an infected person to an uninfected person by preventing development of a mature sporozoite in the mosquito. Combination vaccines containing antigens expressed at different stages of the parasite's life-cycle may induce an immune response with a broad biological effect.

2.5.2 Malaria vaccine pipeline

More than 30 *P. falciparum* malaria-vaccine projects are at either advanced preclinical or clinical stages of evaluation (Figure 2.4)[11]. Approaches that utilize recombinant protein antigens and target blood stages are being developed, but only RTS,S/AS01 (a pre-erythrocytic stage vaccine) has completed pivotal phase III evaluation and reached the regulatory review stage.



Data source: http://www.who.int/vaccine_research/links/Rainbow/en/index.html

Figure 2.4: Global malaria vaccine pipeline Sep 2015.

Four other approaches have been tested in Phase 2b trials with several hundred volunteers each. These are ChAd63/MVA ME-TRAP, MSP3, GMZ2 and PfSPZ. ChAd63/MVA ME-TRAP uses two different recombinant viral vectors to induce T cell responses to the liver stage antigen TRAP. GMZ2 is a recombinant protein approach based on a fusion of two blood stage antigens. Both the ME-TRAP and GMZ2 programmes have enrolled hundreds of volunteers in multiple trials across Africa. MSP3, another blood stage antigen, has mainly been tested in Mali. Efficacy results against clinical malaria

in children have not been reported for any of these trials. Whole parasite vaccines are under development. In one of these vaccines, known as PfSPZ, sporozoites are attenuated by irradiation while still in the mosquito's salivary gland and there is subsequent extraction of irradiated sporozoites by dissection of the salivary glands of these irradiated mosquitoes. Other whole-organism approaches to malaria immunization are being explored using various methods, including genetic attenuation of sporozoites. In addition to the approaches outlined above there are many others in clinical evaluation or at an advanced stage of pre-clinical evaluation[12].

The most advanced candidate is the vaccine against *P. falciparum* malaria disease known as RTS,S/AS01, and is the focus of this background paper. This vaccine, which is based on the *P. falciparum* sporozoite antigen CSP, was developed after a series of clinical trials demonstrated that simpler CSP-based vaccines provided inadequate clinical efficacy. Furthermore, in addition to using a novel delivery system based on the hepatitis B–malaria antigen fusion protein, novel adjuvants have been utilized because RTS,S formulated on aluminium-containing adjuvants alone afforded no protection in human-challenge studies[13]. Various RTS,S/adjuvant formulations have been compared in human-challenge studies, and the formulation designated as RTS,S/AS01 appeared to provide the greatest protection[14].

As RTS,S/AS01 only contains CSP malaria antigen, the only possible biological action of the vaccine is at points 1 and 2 in figure 2.2. This results in either completely preventing an incident liver-stage infection, reducing the numbers of sporozoites infecting hepatocytes after an infective bite, or inhibiting liver-stage development either completely or partially. CSP is not expressed in the blood stage, and so RTS,S/AS01 immune responses do not directly affect the blood stages of the life cycle.

3. RTS,S Overview, including Phase 3 Trial Design

3.1 History of RTS,S Development

Extensive research beginning in the 1960s, indicated that immunization with radiation-attenuated sporozoites could protect animals and human volunteers from malaria parasite infection[15, 16]. The circumsporozoite protein (CSP), a sporozoite surface antigen, was identified as a possible target of protective immune responses, and the gene encoding the CSP of *Plasmodium falciparum* was cloned and sequenced[17].

In early 1984, The US Walter Reed Army Institute of Research (WRAIR) entered into a collaboration with GSK to produce a malaria vaccine using recombinant *E. coli* expression systems. Although efforts to produce a full-length CSP were unsuccessful, a series of alternative constructs were produced. Studies using synthetic peptides had mapped the epitope of protective monoclonal antibodies to the central repeat region of the *P. falciparum* CSP, and several constructs were developed with iterative clinical testing using challenge studies in naive adult volunteers; none proved sufficiently efficacious to take forward.

In 1987, the GSK malaria vaccine program was transferred from its laboratories in Philadelphia, PA, to its vaccine division in Belgium. None of the previous iterations of CSP-based vaccines in the GSK and other malaria vaccine programmes had used a particulate structure. In 1988 details of the first generation particulate CSP-based construct were published[18]. This was followed by the first

publication of a clinical trial using the CSP-Hepatitis B surface antigen fusion particulate structure present in RTS,S[19]. While the particle was a major step forward above the earlier peptide iterations, novel adjuvants were also an important aspect. RTS,S formulated on alum yielded no protection in the human challenge model, whereas formulations using the adjuvant AS02 proved reproducibly efficacious in the challenge model[20]. RTS,S/AS02 was seen as the lead GSK candidate until RTS,S/AS01 was selected for use in the Phase 3 programme in 2009 on the basis of clinical efficacy seen in human challenge trials, together with improved immunogenicity[14]. The RTS,S program has been conducted as a public-private partnership between GSK and the Malaria Vaccine Initiative at PATH since 2001, and is a leading example of this type of public-private partnership approach.

On July 23, 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive scientific opinion under Article 58 of Regulation (EC) No 726/2004[21].

3.2 Technical specifications

RTS,S is a pre-erythrocytic stage hybrid recombinant protein vaccine. It is comprised of the central tandem repeat and carboxyl terminal portion of the *P. falciparum* circumsporozoite protein fused to the hepatitis B surface antigen, co-expressed in yeast with non-fused hepatitis B surface antigen. RTS,S virus-like particles form when the RTS malaria–hepatitis B fusion protein is co-expressed with S antigen alone in *Saccharomyces cerevisiae* yeast cells. The formulation given a positive scientific opinion by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) is 25µg of RTS,S with AS01 as adjuvant, composed of liposomes and the immunomodulatory molecules 3-O-desacyl-f4-monophosphoryl lipid A (MPL) and QS-21. The adjuvant is specifically $AS01_E$ (in contrast to $AS01_B$, which is the formulation used in GSK's Herpes Zoster vaccine that has recently completely Phase 3 trials and contains two times more MPL & QS-21 immunoenhancers in the same liposomal suspension). The reconstituted 0.5mL vaccine is administered by intramuscular injection into the antero-lateral thigh in the 6-12 weeks age group, and the left deltoid in the 5-17 months age group. It has been evaluated most on a 0/1/2 month schedule (including Phase 3 trial). In the pivotal Phase 3 trial, the fourth RTS,S dose was given 18 months after the 3rd dose in the left deltoid. The WHO Programmatic Suitability for Prequalification (PSPQ) Standing Committee confirmed the suitability of the proposed 2-dose vial presentation.

3.3 Available data on RTS,S/AS01 and RTS,S/AS02

Prior to launching the Phase 3 efficacy trial, numerous studies were undertaken using RTS,S/AS02 or RTS,S/AS01 in different age groups, including adults (Appendix 1). Excluding the pivotal Phase 3 trial (Mal-055), RTS,S/AS01 has been given to 1,581 children aged 6 weeks to 17 months, including with various schedule and co-administration regimens, as well as HIV-infected children (Table 3.1).

Table 3.1: Overview of studies with RTS,S/AS01E in the target population of children 6 weeks-17 months at first dose. Provided by PATH-MVI on request.

Trial *Status year*	Objective(s)	Trial Design *Schedule*	Trial population Age *Country*	Trial groups	TVC N	Publication(s)
Malaria-047 *Completed* *2008*	1°: Safety of two vaccine formulations according to various immunisation schedules 2°: Safety and immunogenicity	Phase II, partially blind (blind to vaccine administration, open to vaccination schedule), randomized (1: 1: 1: 1: 1: 1), controlled, multi-centre trial with six groups *0-1 months* *0-1-2 months* *0-1-7 months*	Healthy male and female children 5 - 17 months *Ghana*	RTS,S/AS01$_E$, 0-1, 25µg/0.5ml RTS,S/AS02$_D$, 0-1, 25µg/0.5ml RTS,S/AS01$_E$, 0-1-2, 25µg/0.5ml Rabies vaccine, 0-1-2[a] RTS,S/AS02$_D$, 0-1-2, 25µg/0.5ml [b] RTS,S/AS01$_E$, 0-1-7, 25µg/0.5ml RTS,S/AS02$_D$, 0-1-7, 25µg/0.5ml	90 90 90 45 45 90 90 **540**	Owusu-Agyei 2009 Ansong 2011
Malaria-049 *Completed* *2008*	1°: Efficacy against clinical disease 2°: Safety and immunogenicity	Phase IIb, double-blind, randomized (1:1), controlled, multi-centre, multi-country trial with two groups *0-1-2 months*	Healthy male and female children 5 - 17 months *Tanzania, Kenya*	RTS,S/AS01$_E$, 25µg/0.5ml Rabies vaccine	447 447 **894**	Bejon 2008 Lusingu 2010 Bejon 2011 Olotu 2011a Olotu 2011b Ndungu 2012
Malaria-050 *Completed* *2009*	1°: Safety 2°: Safety and immunogenicity Expl.: Efficacy against clinical disease	Phase II, open, randomized (1:1:1), controlled, multi-centre, multi-country trial with three groups *0-1-2 months* *0-1-7 months*	Healthy male and female infants 6 - 10 weeks *Gabon, Ghana, Tanzania*	RTS,S/AS01$_E$, 0-1-2, 25µg/0.5ml RTS,S/AS01$_E$, 0-1-7, 25µg/0.5ml Control* * *Tritanrix-HepB*™/Hib (DTPw-HepB/Hib), either given alone (control) or co-administered to all groups at 6, 10, 14 weeks of age and measles and yellow fever at 9 months of age	170 170 171 **511**	Agnandji 2010 Asante 2011
Malaria-055 *Completed* *2013*	1°: Efficacy against clinical disease 2°: Efficacy against severe disease; Role of booster; Efficacy against hospitalization and mortality	Phase III, double-blind, randomized (1:1:1), controlled, multi-centre, multi-country trial with three groups in two cohorts *0-1-2-20 months*	Healthy male and female infants and children 6 - 12 weeks and 5 - 17 months *Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, Tanzania*	<u>children 5-17 months of age:</u> RTS,S/AS01$_E$(R3R), 25µg/0.5ml RTS,S/AS01$_E$(R3C), 25µg/0.5ml Rabies vaccine(C3C)	 2976 2972 2974 **8922**	Leach 2011 Vekemans 2011b Lievens 2011 Swysen 2011 The RTS,S Clinical Trials Partnership 2011

				<u>infants 6-12 weeks of age*:</u> RTS,S/AS01$_E$(R3R), 25μg/0.5ml RTS,S/AS01$_E$(R3C), 25μg/0.5ml MCC (C3C) * *Tritanrix-HepB*™/Hib (DTPw-HepB/Hib) + OPV to all groups at 6, 10, 14 weeks of age	2180 2178 2179 **6537**	The RTS,S Clinical Trials Partnership 2012 The RTS,S Clinical Trials Partnership 2014
Malaria-057	1°: Safety and immunogenicity of 7 schedules integrated with an EPI regimen	Phase II, open, randomized, controlled, single-centre, trial with seven groups *Birth-10 weeks-14 weeks* *Birth-10 weeks-26 weeks* *6weeks-10weeks-14weeks* *6weeks-10weeks-26weeks* *Engerix-B at birth-Birth-10 weeks-26 weeks* *10weeks-14weeks-26 weeks* *14weeks-26weeks-9months*	Healthy male and female infants *Malawi*	All received three doses of RTS,S/AS01$_E$, 25μg/0.5ml according to schedules listed. Recruited at 0-7 days of age.	**480**	
Malaria-058 *Completed 2013*	1°: Safety in HIV+ infants and children 2°: Safety and immunogenicity	Phase III, double-blind, randomized (1:1), controlled, multi-centre trial with two groups *0-1-2 months*	HIV infected male and female infants and children 6 weeks - 17 months *Kenya*	RTS,S/AS01$_E$, 25μg/0.5ml Rabies vaccine	99 101 **200**	Otieno 2014
Malaria-063 *Ongoing (estimated completion 2018)*	1°: Non-inferiority of anti-HBs immune response induced by RTS,S/AS01$_E$ compared to licensed *Engerix-B* 2°: Safety; Non-inferiority of vaccine response induced by pneumococcal conjugate or rotavirus vaccines when co-administered with or without RTS,S/AS01$_E$ in an EPI regimen; Lot-to-lot consistency of the anti-HBs immune response	Phase III, open, randomized (1:1:1:1:1:1:1:1:1:3:3), controlled, multi-centre, multi-country trial with eleven trial groups (five treatment groups) *0-1-2 months*	Healthy male and female infants 8 - 12 weeks *Burkina Faso, Ghana*	3 study groups with 3 lots of RTS,S/AS01$_E$, 25μg/0.5ml + CoAd (*Infanrix/Hib* + OPV + *Synflorix*) + *Rotarix* staggered 3 study groups with 3 lots of RTS,S/AS01$_E$, 25μg/0.5ml + CoAd (Infanrix /Hib + OPV + *Rotarix*) + *Synflorix* staggered 3 study groups with 3 lots of RTS,S/AS01$_E$, 25μg/0.5ml + CoAd (*Infanrix /Hib* + OPV) + staggered (Synflorix + *Rotarix*) 1 study group with *Engerix-B* + CoAd (*Infanrix /Hib* + OPV + Synflorix) + *Rotarix* staggered 1 study group with *Engerix-B* + CoAd (*Infanrix /Hib* + OPV + *Rotarix*) + *Synflorix* staggered	142 142 141 141 139 **705**	-
Malaria-061 *Completed 2012*	1°: Lot-to-lot consistency and non-inferiority of the anti-CS immune response induced by	Phase III, double-blind, randomized (1:1:1:1), multi-centre study with four groups *0-1-2 months*	Healthy male and female children 5 - 17 months *Nigeria*	RTS,S/AS01$_E$, lot 1, 25μg/0.5ml RTS,S/AS01$_E$, lot 2, 25μg/0.5ml	81 79 80	Umeh 2014

	RTS,S/AS01$_E$ (3 commercial scale lots pooled) compared to pilot scale lot of RTS,S/AS01$_E$ 2°: Safety and immunogenicity			RTS,S/AS01$_E$, lot 3, 25µg/0.5ml Control RTS,S/AS01$_E$, 25µg/0.5ml	80 **320**	

N= number of subjects
a The PCEC rabies vaccine was only used in one study centre, at Kintampo – KHRC, Ghana
b Enrolment occurred only at Kumasi – KCCR/SMS, Ghana
R3R: Children and infants to receive 3 doses of RTS,S/AS01$_E$ on a 0-1-2-month schedule + a fourth dose of RTS,S/AS01$_E$ at study month 20.
R3C: Children and infants to receive 3 doses of RTS,S/AS01$_E$ on a 0-1-2-month schedule + a dose of a meningococcal C conjugate vaccine (*Menjugate* [Novartis]) at study month 20.
C3C: Children and infants to receive 3 doses of a control vaccine** on a 0-1-2-month schedule + a dose of a control vaccine** at study month 20.
** Control vaccine for children 5-17 months of age: rabies vaccine (VeroRab™ [Sanofi Pasteur]) on a 0-1-2-month schedule + *Menjugate* at study month 20.
** Control vaccine for infants 6-12 weeks of age: *Menjugate* on a 0-1-2-month schedule + *Menjugate* at study month 20.

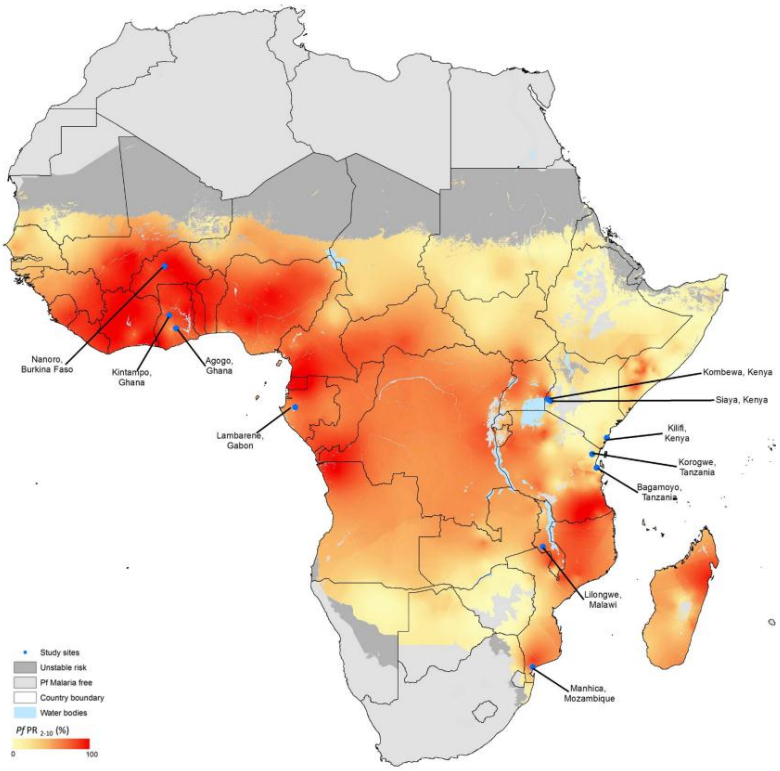


Figure 3.1: Trial sites and malaria endemicity - Adapted from Hay et al[22]. The location of each participating study site is shown on the spatial distribution of *P. falciparum* (Pf) malaria endemicity, modelled to reflect 2007 estimates. Malaria endemicity has changed since this time.

The Phase 3 efficacy trial was a randomized, controlled, multicentre, participant and observer-blinded trial (intervention and control vaccines differ in appearance, so study personnel who administered vaccines were aware of the treatment allocation; the unblinded vaccinators played no other part in the study)(NCT00866619)[23]. Participants in two age categories (5-17 months and 6-12 weeks at first vaccination) were enrolled between May 2009 and February 2011. A total of 6,537 6-12 week olds and 8,922 5-17 month-olds were randomized in the trial. The trial population was selected to represent the target population as much as possible, and low-birth-weight infants, malnourished children, and HIV-infected children who were not clinically unwell were included (participants were not systematically screened for HIV infection but some of the trial sites were in areas of high HIV prevalence). Participants were randomized 1:1:1 to receive control vaccine (C3C), three doses of RTS,S plus control vaccine at 18 months (R3C), or three doses of RTS,S plus a fourth dose of RTS,S at 18 months (R3R) (Figure 3.3). Control vaccines were the cell culture rabies vaccine (given to the 5-17 month age group for the first three doses) and meningococcal serogroup C conjugate vaccine (given to the 6-12 week age group for the first three doses, and to both age groups for the fourth dose). The 6-12 week age category received RTS,S/control co-administered with DTPwHepB/Hib + OPV for the first three doses, and OPV in addition to RTS,S or control vaccine as the fourth dose. The trial was designed to follow up participants for 32 months but was later amended to follow all participants until December 31, 2013, for a median follow up time of 48 months for 5-17 month olds and 38 months for 6-12 week olds. Seventy-eight percent of participants first vaccinated at age 5 – 17 months, and 92% of participants first vaccinated at age 6 – 12 weeks, were included in the per protocol populations[24].

Eleven sites in seven countries participated in the trial, representing different transmission settings (Table 3.2, Figure 3.1, Figure 3.2). These sites were selected to represent variable transmission intensities and seasonality patterns.

Details of the number of children included at different stages of the trial are shown in Figures 3.4 and 3.5.

Table 3.2: Overview of pivotal Phase III trial (MAL-055)

Ages included in trial	Two age categories: children at the age of 6-12 weeks (infants) and 5-17 months (children) at first vaccination.
Trial sites	11 centres in Burkina Faso (Nanoro), Gabon (Lambarene), Ghana (Kintampo and Agogo), Kenya (Kilifi, Kombewa and Siaya), Malawi (Lilongwe), Mozambique (Manhica) and Tanzania (Bagamoyo and Korogwe).
Treatment groups	Three treatment groups per age (1:1:1 randomization): • **R3R** received RTS,S/AS01$_E$ for four vaccinations • **R3C** received RTS,S/AS01$_E$ for three vaccinations and the control (MCC) for fourth vaccination • **C3C** received the control (Rabies for 5-17 month children and MCC for 6-12 week infants) for the first three vaccinations and the fourth (MCC for both age groups) vaccination
Dosing schedule	Doses are given on a 0, 1 and 2 months schedule, the fourth dose at 18 months after the 3rd dose.
Other vaccines administered	Infants receive Tritanrix HepB/Hib + OPV concomitantly with the first three doses and OPV concomitantly with the fourth dose. Additional vaccination with BCG, OPV birth dose, measles and Yellow Fever were given according to local EPI practice.
Follow up time	Vaccine efficacy and immunogenicity are measured over a median of 38 (6-12 week younger age category) or 48 (5-17 month older age category) months after the 3rd dose.
Primary objectives	Efficacy co-primary objectives: • To evaluate the protective efficacy of RTS,S/AS01$_E$ against clinical malaria disease caused by *Plasmodium falciparum* in African children whose age at first dose will be from 5-17 months. • To evaluate the protective efficacy of RTS,S/AS01$_E$ against clinical malaria disease caused by *Plasmodium falciparum* in African children whose age at first dose will be from 6-12 weeks and will receive vaccine in co-administration with DTPwHepB/Hib antigens (Tritanrix HepB/Hib) and OPV. For the co-primary objectives, duration of follow-up was 12 months after completion of the first three doses.

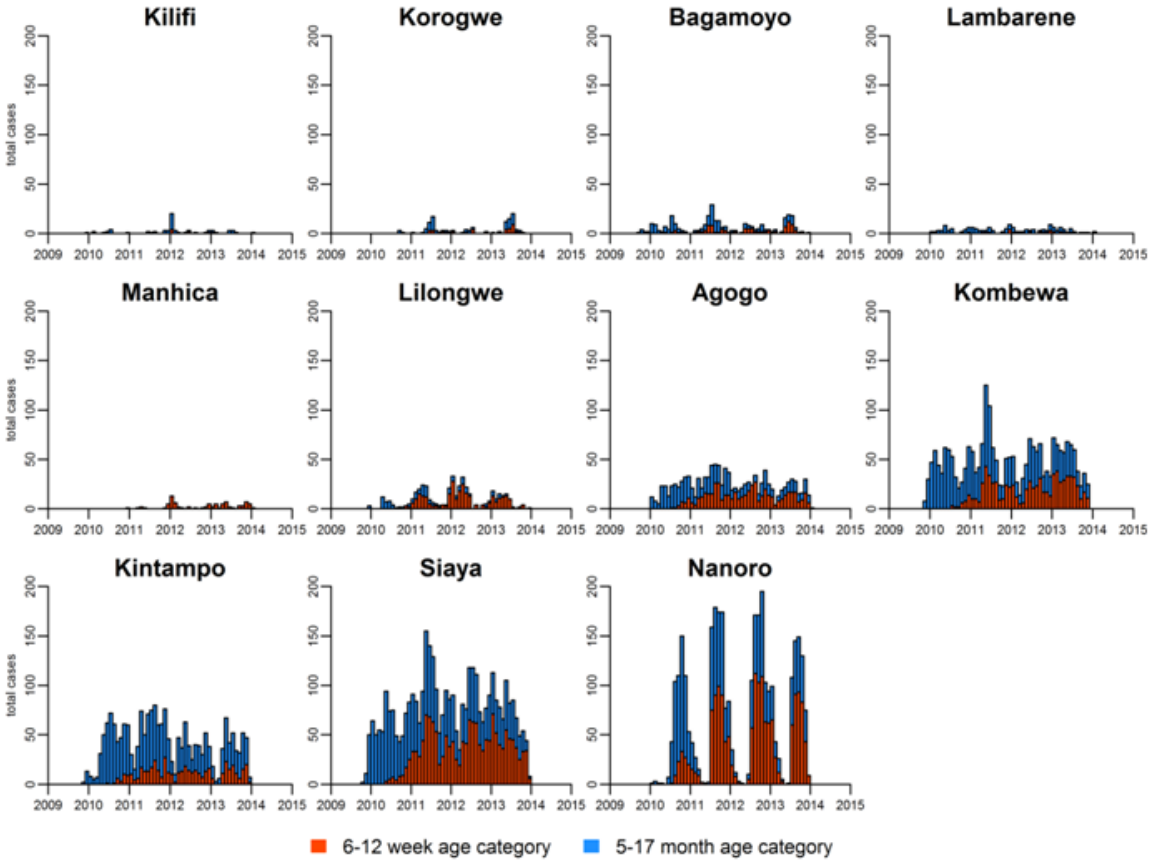


Figure 3.2: Total number of clinical malaria episodes in the control group at Phase 3 trial sites, indicating variation in incidence rate and seasonality profiles. Provided by GSK on request.

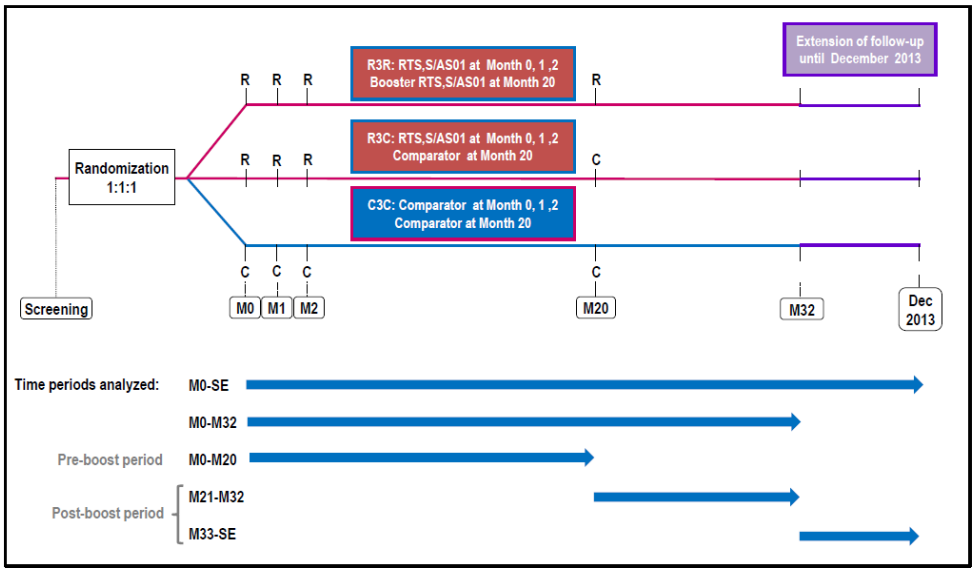


Figure 3.3: Phase III trial design[24].

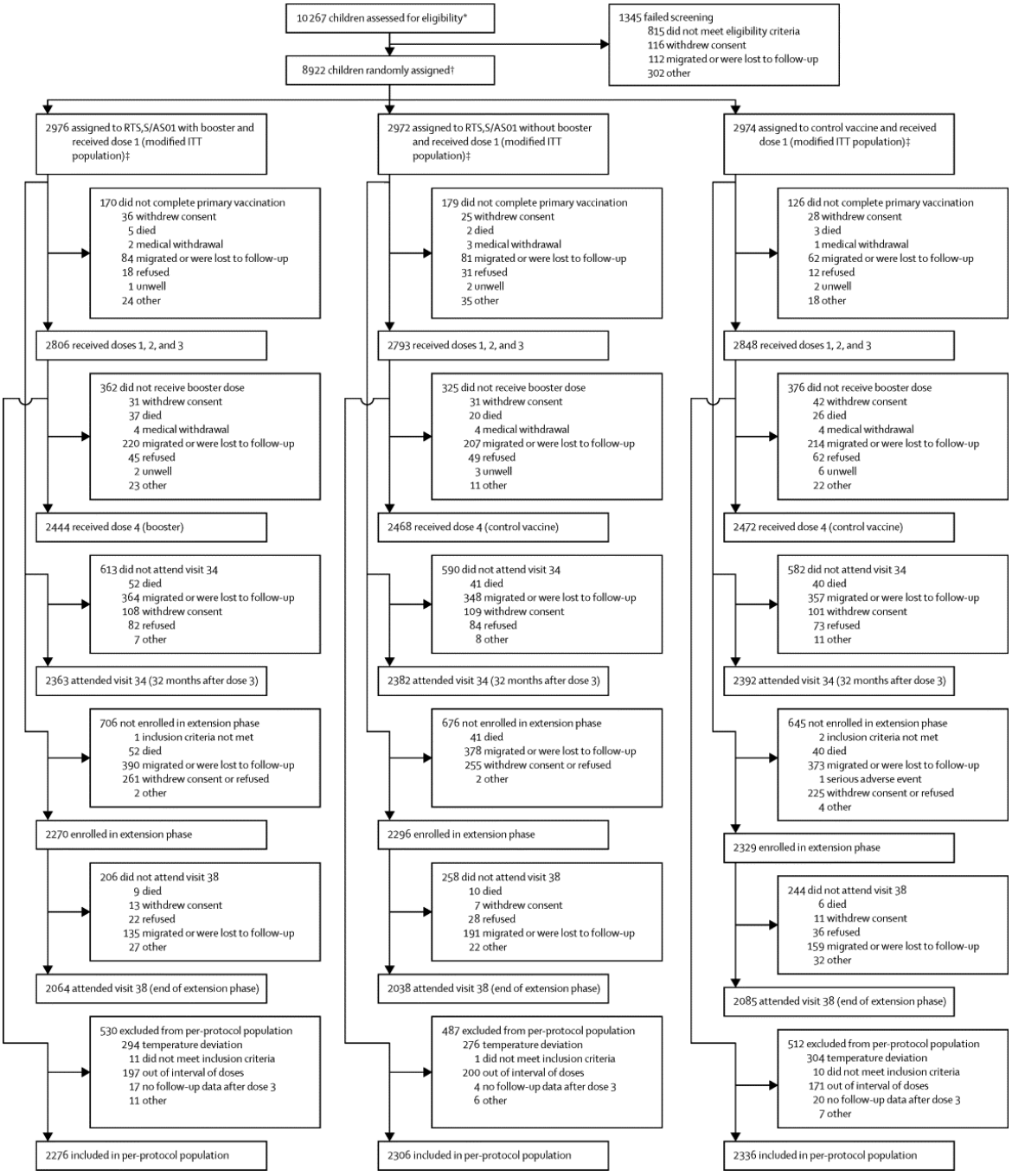


Figure 3.4: Consort diagram for 5-17 months age category[24].

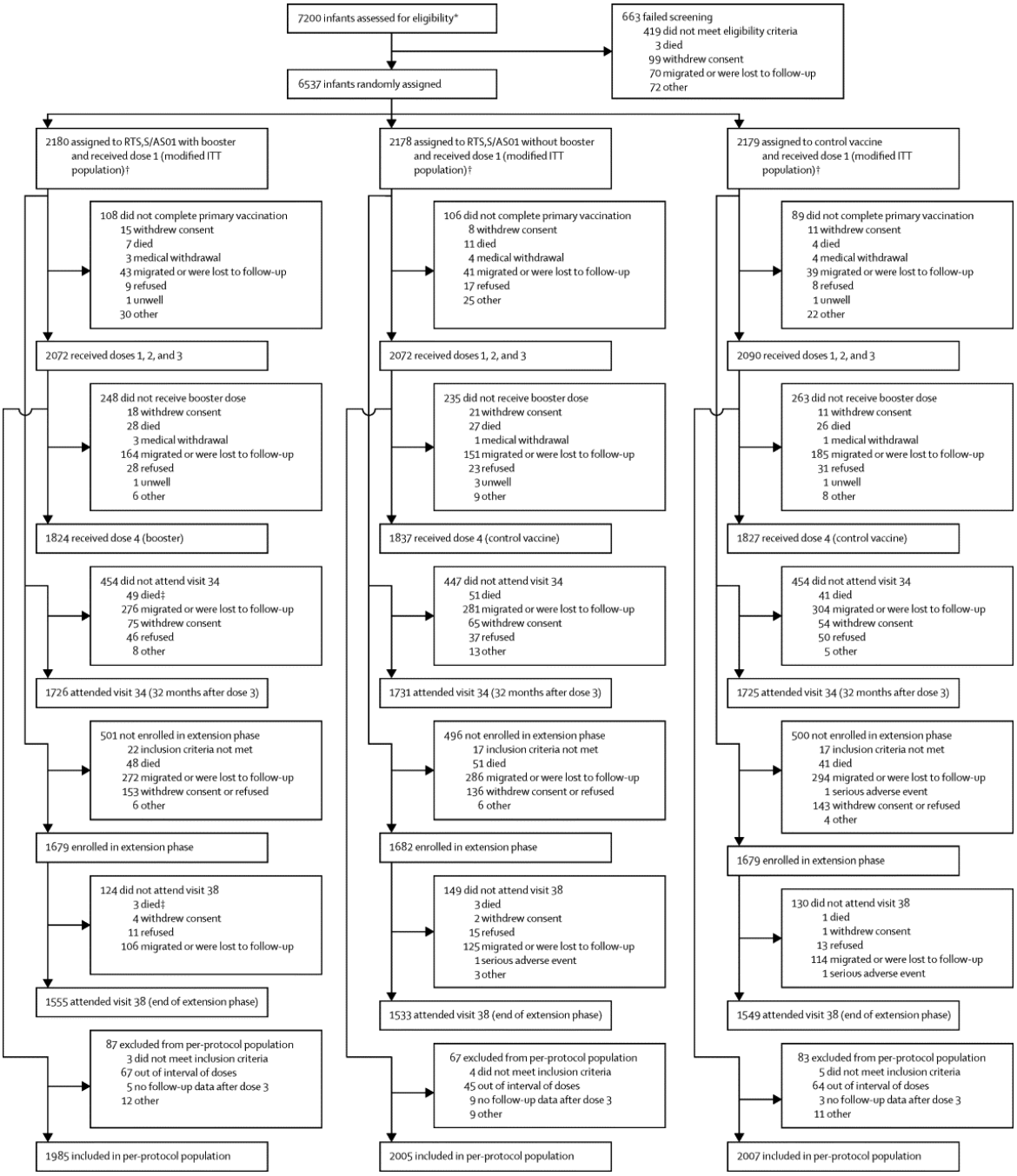


Figure 3.5: Consort diagram for 6-12 weeks age category[24].

4. RTS,S Vaccine Efficacy

4.1 Phase 3 trial efficacy objectives and case definitions

The co-primary objectives of the Phase 3 trial were efficacy over one year post-dose 3 against clinical malaria when administered in each of the two age categories. Clinical malaria cases were identified through passive surveillance at local health facilities. All participants were judged to have adequate access to health care, and health care costs were reimbursed by the trial. Among these children presenting at a health facility, the primary case definition for clinical malaria was >5,000 parasites/uL with an axillary temperature of $\geq$37.5^{o}C or a case that met the primary case definition for severe malaria. Reported efficacy estimates below are against all episodes of malaria, accounting for the fact that individual participants may have multiple episodes over the course of the trial. Vaccine efficacy against all episodes of malaria was assessed using a negative binomial regression with follow-up time as offset. Overall efficacy estimates were adjusted for site as a fixed effect; site-specific efficacy estimates were unadjusted. All vaccine efficacy estimates for Phase 2 and Phase 3 studies are according-to-protocol (ATP) unless otherwise specified. Representative intention-to-treat (ITT) analyses of vaccine efficacy may be found in Appendix 2. Safety analyses are always presented as ITT analyses.

Secondary objectives included vaccine efficacy against severe malaria, anaemia, malaria hospitalization, fatal malaria, all-cause mortality, and other serious illnesses. The 11 sites participating in the trial encompassed a range of malaria parasite transmission settings and there was also evaluation of efficacy by transmission setting and over time, and the effect of a fourth dose given at 18 months.

4.2 Vaccine efficacy against all episodes of clinical malaria

WHO/JTEG specifically requested all vaccine efficacies to be reported against all episodes of the outcome, not the first or only episode as is frequently presented in publications. The rationale for this approach is to better reflect the public health relevance of the vaccine. Readers should note that the estimates and figures presented in this background paper do not always match with cited figures from publications for this reason.

Tables 4.1 and 4.2 are summary tables of vaccine efficacy by age category and treatment group to different time points over the course of the trial. Figures 4.1 and 4.2 show the changing incidence by time, by treatment group. These represent important data that will be revisited throughout the background paper.

Table 4.1: Summary table of vaccine efficacy (95%CI) in the 5-17 month age category for all episodes of clinical malaria and severe malaria from Month 2.5 to selected time points (primary case definitions, ATP population).

Clinical Malaria	RTS,S Group				Control Group				VE
	N	n	T	n/T	N	n	T	n/T	(95%CI)
M2.5-M14	4553	2558	4035.9	0.63	2327	2489	2024.6	1.23	51.3% (47.5, 54.9)
M2.5-M20	4557	4257	6186.0	0.69	2328	3639	3100.4	1.17	45.7% (41.7, 49.5)
M2.5-SE 3-dose schedule	2306	6597	7335.8	0.9	2336	8352	7352.4	1.14	26.2% (20.8, 31.2)
M2.5-SE 4-dose schedule	2276	5691	7247.4	0.79					39.0% (34.3, 43.3)
Severe Malaria	**RTS,S Group**				**Control Group**				**VE**
	N	**n**	**T**	**n/T**	**N**	**n**	**T**	**n/T**	**(95%CI)**
M2.5-M14	4582	87	4358.3	0.020	2336	80	2219.3	0.036	44.5% (23.8, 59.6)
M2.5-M20	4582	129	6379.0	0.020	2336	105	3243.5	0.032	37.7% (18.0, 52.6)
M2.5-SE 3-dose schedule	2306	159	7600.5	0.021	2336	157	7664.8	0.020	-2.2% (-31.3, 20.4)
M2.5-SE 4-dose schedule	2276	101	7459.6	0.014					31.5% (9.3, 48.3)

N = number of subjects included in each group
n = number of episodes included in each group
T = person years at risk
n/T = Incidence = person year rate in each group
SE = Study end (variable follow up period for each participant with a median of 48 months)
VE (%) = Vaccine efficacy (Negative binomial random-effects model)
Sources for clinical malaria: M2.5-M14 and M2.5-M20, Table 1 and Suppl Table 15 in [25]; M2.5-SE, Suppl Table S7 in [24].
Sources for severe malaria: Provided by GSK on request.

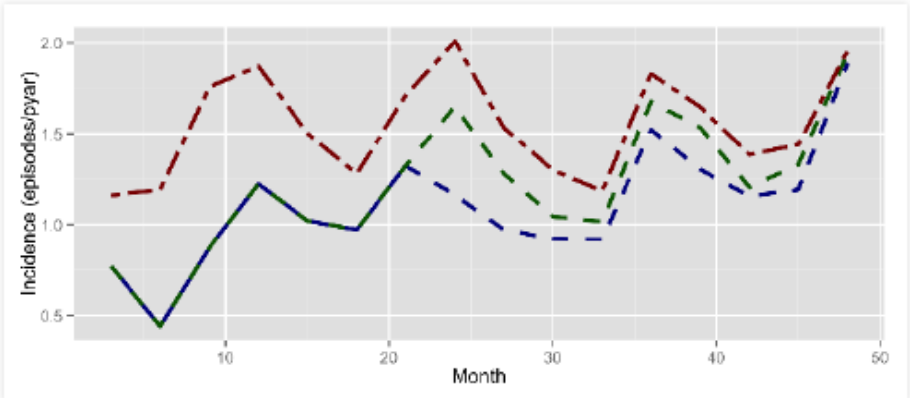


Figure 4.1: Incidence per year at risk (pyar) of clinical malaria after vaccination with three doses by study 3-month periods in 5-17 month age category. Red=C3C, Green=R3C, and Blue=R3R. Provided by J. Aponte.

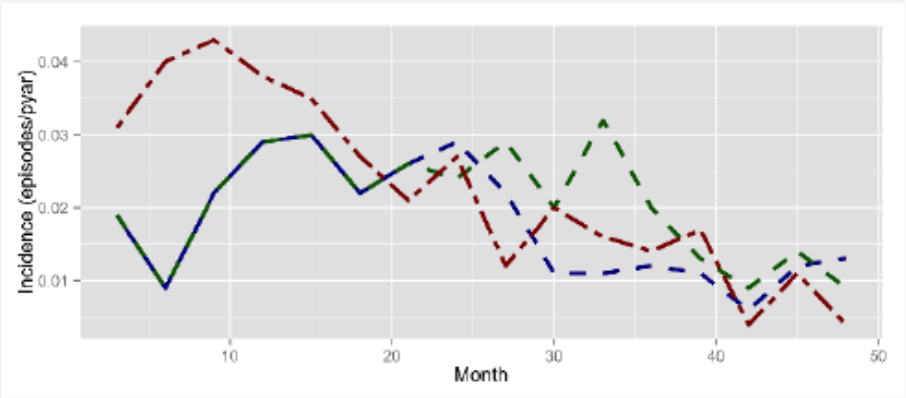


Figure 4.2: Incidence per year at risk (pyar) of severe malaria after vaccination with three doses by study 3-month periods in 5-17 month age category. Red=C3C, Green=R3C, and Blue=R3R. Provided by J. Aponte.

Table 4.2: Summary table of vaccine efficacy (95%CI) in the 6-12 weeks age category for all episodes of clinical malaria and severe malaria from Month 2.5 to selected time points (primary case definitions, ATP population).

Clinical Malaria	RTS,S Group				Control Group				VE
	N	n	T	n/T	N	n	T	n/T	(95%CI)
M2.5-M14	3995	2301	3604	0.64	2008	1626	1790	0.91	32.9% (26.3, 38.9)
M2.5-M20	3996	3848	5396.8	0.71	2007	2464	2674.0	0.92	26.6% (20.3, 32.4)
M2.5-SE 3-dose schedule	2005	5072	5322.9	0.95	2007	5666	5264.6	1.08	18.2% (11.4, 24.5)
M2.5-SE 4-dose schedule	1985	4532	5245.2	0.86					26.7% (20.5, 32.4)
Severe Malaria	**RTS,S Group**				**Control Group**				**VE**
	N	**n**	**T**	**n/T**	**N**	**n**	**T**	**n/T**	**(95%CI)**
M2.5-M14	3990	62	3791.8	0.016	2007	50	1895.7	0.026	38.5% (7.8, 59.0)
M2.5-M20	3990	112	5529.7	0.020	2007	68	2764.2	0.025	17.4% (-16.2, 41.3)
M2.5-SE 3-dose schedule	2005	103	5512.0	0.019	2007	121	5475.7	0.022	16.0% (-14.5, 38.4)
M2.5-SE 4-dose schedule	1985	96	5413.5	0.018					20.5% (-9.8, 42.5)

N = number of subjects included in each group
n = number of episodes included in each group
T = person years at risk
n/T = Incidence = person year rate in each group
SE = Study end (variable follow up period for each participant with a median of 38 months)
VE (%) = Vaccine efficacy (Negative binomial random-effects model)
Sources for clinical malaria: M2.5-M14, Table 1 in [26]; M2.5-M20, Table 2 in [25]; M2.5-SE, Suppl Table S17 in [24].
Sources for severe malaria: Provided by GSK on request.

4.2.1 VE against all episodes of clinical malaria: 5-17 months age category

Vaccine efficacy against all episodes of clinical malaria 12 months following the first three doses was 51.3% (95%CI 47.5, 54.9) across all sites (Table 4.1). Overall efficacy declined to 45.7% (95%CI 41.7, 49.5) by 18 months following the first three doses and to 26.2% (95%CI 20.8, 31.2) by the end of the trial, amongst participants who did not receive a fourth dose. The addition of a fourth dose 18 months following the first three doses increased the overall efficacy to 39.0% (95%CI 34.3, 43.3). The results did not substantially change with vaccine efficacy estimates based on secondary case definitions or with the ITT population (Appendix 2).

When vaccine efficacy was broken down by time interval[1], vaccine efficacy of three doses alone declined in successive six-month periods from 67.6% (95%CI 63.8, 71.0) initially, to 38.9% (95%CI 33.2, 44.0), 27.9% (20.2, 34.9), 13.9% (95%CI 4.7, 22.1), 12.5% (95%CI 1.1, 22.6), and finally to 0.1% (95%CI -9.9, 9.1) between 30 months following the first three doses and the end of the trial (Figure 4.3).

In the six months following the RTS,S/AS01 fourth dose in the R3R group, vaccine efficacy was estimated to be 42.9% (95%CI 36.4, 48.7). Thus efficacy is clearly increased when comparing R3R vs R3C in the period after the fourth dose, although not to the same level reported following the first three doses. Efficacy declines after the fourth dose with a similar timecourse to that seen after the third dose (Figure 4.3).

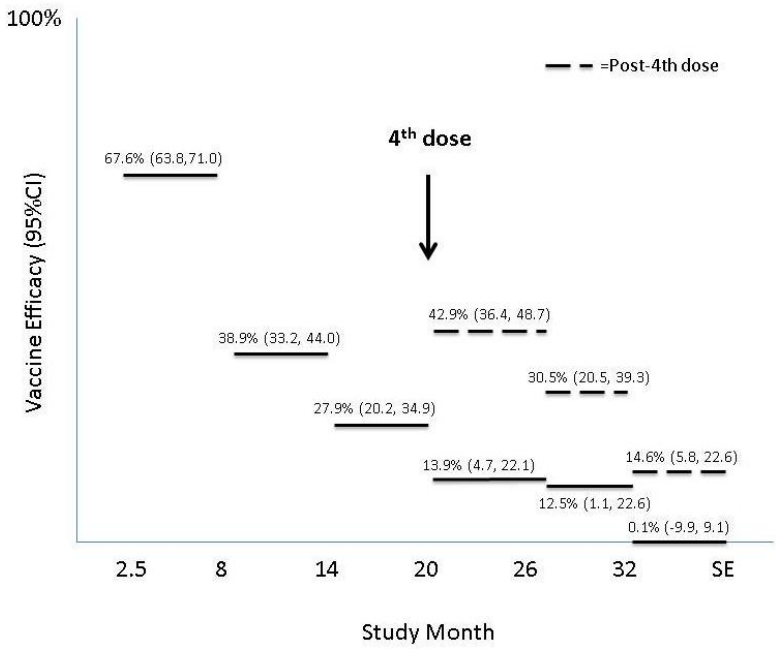


Figure 4.3: Vaccine efficacy against clinical malaria stratified by time period in the 5-17 month age category in the Phase 3 trial (primary case definition, ATP population). Data provided by GSK on request. Case counts available in Appendix 3.

Figure 4.1 shows the time-dependent incidence of clinical malaria among participants in the 5-17 month age category over the course of the trial. The variation in the difference between RTS,S and control groups remains throughout the course of the trial, with similar incidence rates in the three

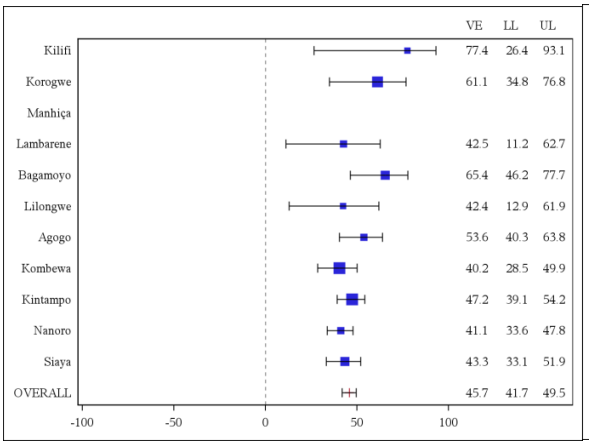
[1] It is important to note the limitation that the groups have different histories of malaria disease at the start of the time intervals after the first, so some prefer to term these estimates comparative incidence rather than vaccine efficacy. We have used vaccine efficacy throughout this document for consistency with terminology in the final Phase 3 publication.

groups in the last period. The estimates of incidence in the RTS,S-vaccinated group remains favourable over the study period, both among those receiving and not receiving a fourth dose (Table 4.1).

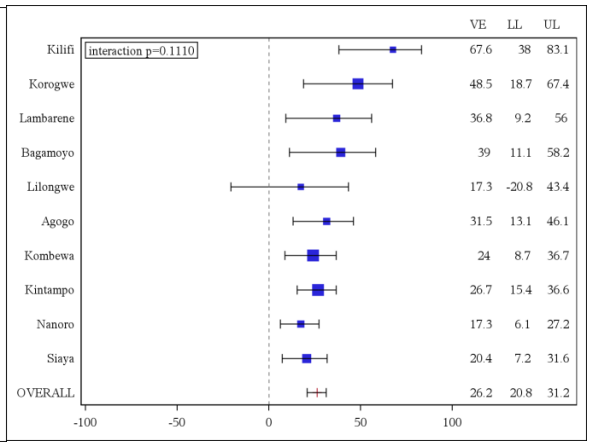
By trial site, vaccine efficacy estimates 18 months following the first three doses ranged from 40.2% (95%CI 28.5, 49.9) in Kombewa, a high transmission setting, to 77.4% (95%CI 26.4, 93.1) in Kilifi, a low transmission setting (Figure 4.4). Up to the end of the study, vaccine efficacy at each study site was higher among those who received a fourth dose, although the confidence intervals are wide. There were not markedly different estimates for vaccines efficacy by site. Still, in the 5-17 months group, the trend test (for higher VE as transmission decreases) was significant without and with the fourth dose (p=0.0095 and p=0.0157, respectively). At each time point the lower limit of the 95% confidence interval for the site-specific efficacy estimate was above 0, with one exception (Figure 4.4b). Vaccine efficacy declined similarly across transmission sites over time.

Of note, Nanoro was a strongly annual seasonal site (Figure 3.2). Trial participants in the 5-17 month age category were recruited to the trial more quickly than the infant group, and in the case of Nanoro, just after the transmission season. In the context of rapidly waning immunity, vaccine efficacy may not have optimally protected Nanoro participants and underestimated potential protection from vaccination.

a) FU: M2.5-20



b) FU: M2.5-SE, 3-dose schedule



c) FU: M2.5-SE, 4-dose schedule

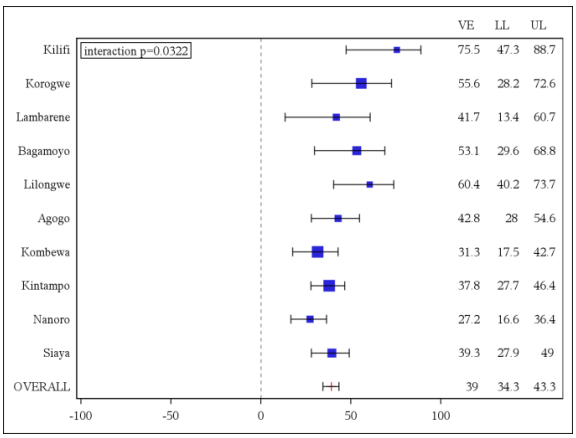


Figure 4.4 a-c Forest plots: Vaccine efficacy against all episodes of clinical malaria (primary case definition) (5-17 month age category) (ATP population). Sites are ordered based on incidence of clinical malaria (secondary case definition) measured in control infants 6-12 weeks of age at enrolment during 12 months of follow up. Provided by GSK on request.

Vaccine efficacy over 18 month follow-up after third dose of RTS,S was also analysed by age in months at first vaccination in the 5-17 month age category (Figure 4.5). No difference in vaccine efficacy by age at administration of the first dose was detected (trend test: p=0.1795), suggesting that vaccine efficacy does not improve with immune maturation in this age category.

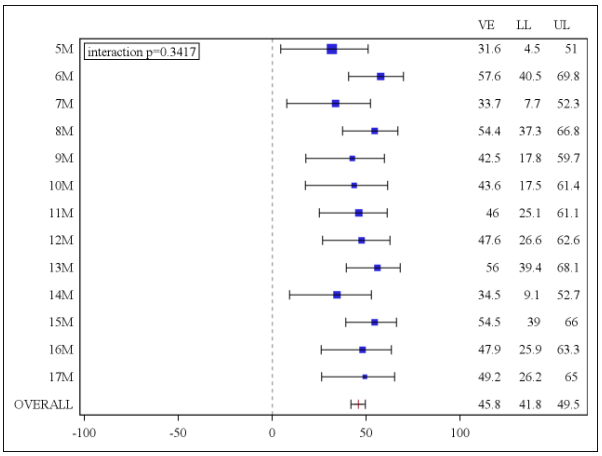


Figure 4.5: Vaccine efficacy against all episodes of clinical malaria by age in month at the time of first vaccination in the 5-17 month age category (primary case definition by age) (FU: M2.5-M20) (ATP population). Provided by GSK on request.

4.2.2 VE against all episodes of clinical malaria: 6-12 weeks age category

Vaccine efficacy against all episodes of clinical malaria 12 months following the first three doses was 32.9% (95%CI 26.3, 38.9) across all sites (Table 4.2). For the period 18 months, efficacy declined to 26.6% (95%CI 20.3, 32.4) and for the whole trial period to 18.2% (95%CI 11.4, 24.5) (median 38 months follow up post dose 3) amongst participants who did not receive a fourth dose of RTS,S. The addition of a fourth dose 18 months following the first three doses increased overall efficacy to 26.7% (95%CI 20.5, 32.4) from the first three doses to the trial end. The results did not substantially change with vaccine efficacy estimates based on secondary case definitions or with the ITT population.

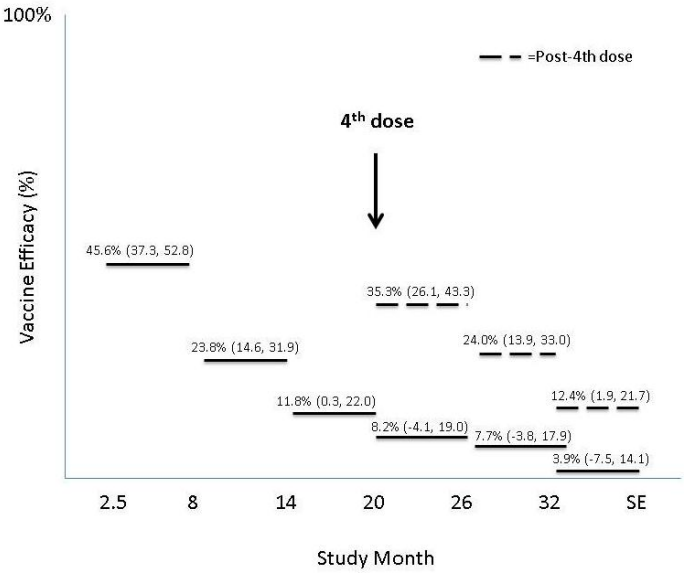
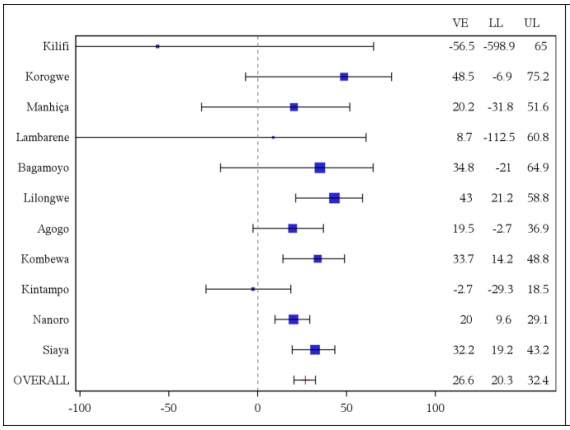


Figure 4.6: Vaccine efficacy stratified by time period in the 6-12 week age category in the Phase 3 trial (primary case definition, ATP population). Data provided by GSK on request.

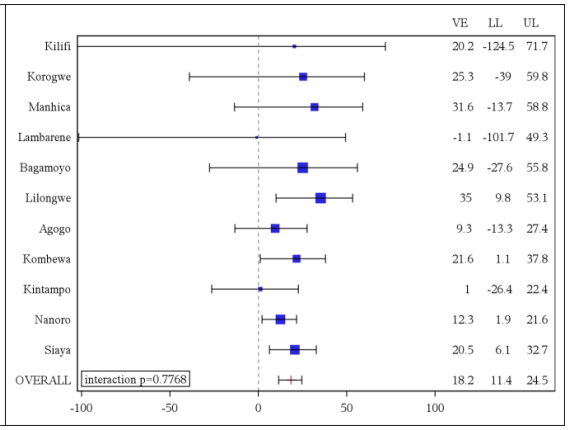
When vaccine efficacy was broken down by time interval (noting the limitation pointed out for the older age group above), the efficacy following three doses alone declined in successive six-month periods from 45.6% (95%CI 37.3, 52.8) in the first six months to 23.8% (95%CI 14.6, 31.9), 11.8% (95%CI 0.3, 22.0), 8.2% (-4.1, 19.0), 7.7% (95%CI -3.8, 17.9), and finally to 3.9% (95%CI -7.5, 14.1) (Figure 4.6). For the first six months that followed receipt of the fourth dose, vaccine efficacy was estimated

to be 35.3% (95%CI 26.1, 43.3), which then decreased to 24.0% (95%CI 13.9, 33.0) over the subsequent six months. From 12 months after the fourth dose to the trial end, efficacy was estimated at 12.4% (95%CI 1.9, 21.7). Administration of a fourth dose did not increase efficacy to the level obtained by the first three doses.

a) FU: M2.5-20



b) FU: M2.5-SE 3 dose schedule



c) FU: M2.5-SE 4 dose schedule

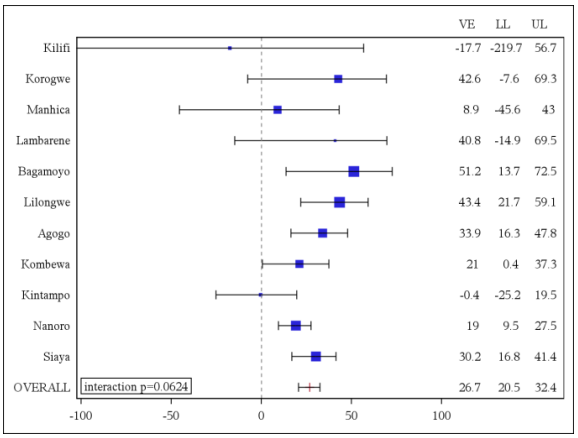


Figure 4.7 a-c Forest plots: Vaccine efficacy against all episodes of clinical malaria (primary case definition) (6-12 week age category) (ATP population). Sites are ordered based on incidence of clinical malaria (secondary case definition) measured in control infants 6-12 weeks of age at enrolment during 12 months of follow up. Provided by GSK on request.

There was not a clear correlation between vaccine efficacy in the 18 months following the vaccination by site and transmission intensity in the 6-12 week age group (Figure 4.7). A trend test of efficacy by site was not significant, without or with the fourth dose (p=0.4835 and p=0.6971, respectively).

4.3 Vaccine efficacy against severe malaria

4.3.1 VE against severe malaria: 5-17 months age category

Vaccine efficacy against all episodes of severe malaria in the first 12 months was 44.5% (95%CI 23.8, 59.6) (Table 4.1). Up to 18 months, the efficacy was estimated at 37.7% (95%CI 18.0, 52.6), and by the trial end (in the group without a fourth dose of RTS,S), the overall efficacy was estimated at -2.2% (95%CI -31.3, 20.4), suggesting that three doses alone had no effect on the overall incidence of

severe malaria, the apparent protective effect in the first 18 months being balanced by a rebound of cases in the period from 18 months to the end of the trial. Among trial participants who received a fourth dose, the vaccine efficacy against severe malaria up to the end of the trial was 31.5% (95%CI 9.3, 48.3).

When vaccine efficacy was analysed by time interval (again with the limitation noted above), efficacy against severe malaria was high in the first 6 months of follow up at 70.1% (95%CI 49.0, 82.5), but steadily declined to -47.9% (95%CI -134.6, 6.8) between 19-30 months after the first three doses were given, and to -74.2% (95%CI -220.0, 5.2) between 31 months and the end of the observation period (Table 4.4). Amongst participations who received a fourth dose of RTS,S at 18 months, efficacy against severe malaria was -6.0 (95%CI -75.2, 35.9) between 19-30 months after the first three doses, and to -22.7% (95%CI -137.9, 36.8) between 31 months and the end of the observation period. Given the positive efficacy over the full observation period in the group that received the fourth dose (31.5%, 95%CI 9.3, 48.3), there was an overall beneficial effect against severe malaria in those who received a fourth dose during the full observation period.

Study Month	Pooled RTS,S groups (R3C + R3R)	
M2.5-M8	70.1 (49.0, 82.5)	
M9-M14	20.5 (-17.8, 46.4)	
M15-M20	14.6 (-41.0, 48.2)	
Study Month	**3-dose schedule (R3C)**	**4-dose schedule (R3R)**
M21-M32	-47.9 (-134.6, 6.8)	-6.0 (-75.2, 35.9)
M33-SE	-74.2 (-220.0, 5.2)	-22.7 (-137.9, 36.8)
M2.5-SE	**-2.2 (-31.3, 20.4)**	**31.5 (9.3, 48.3)**

Table 4.4: Vaccine efficacy VE% (95%CI) against all episodes of severe malaria in 5-17 months age category by study months – primary case definition, ATP population. Provided by GSK on request. Case counts available in Appendix 3.

Many sites experienced too few cases to generate a reliable site-specific estimates for vaccine efficacy against severe malaria. In nearly all sites, even across the full study period, confidence intervals were wide and crossed zero (Figure 4.8). Given the small numbers it is difficult to draw any firm conclusions about variations in efficacy between sites.

a) M0-SE: 3 dose schedule **b) M0-SE: 4 dose schedule**

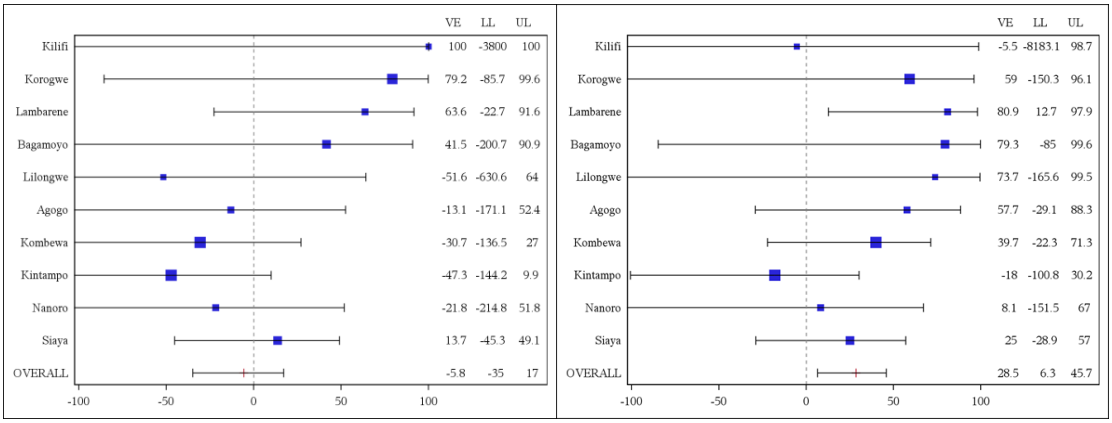


Figure 4.8 a-b Forest plots: Vaccine efficacy in 5-17 month age category against severe malaria by site (primary case definition) (ATP population). Sites are ordered based on incidence of clinical malaria (secondary case definition) measured in control infants 6-12 weeks of age at enrolment during 12 months of follow up. Provided by GSK on request.

Figure 4.2 shows the incidence of severe malaria among participants in the 5-17 month age category over the course of the trial. The difference between the RTS,S and control groups is evident at the beginning of the trial; however, by study month 25 (23 months after vaccination), the incidence of severe malaria in group that received three doses of RTS,S without a fourth dose is generally higher than in the control group. Across all treatment groups, the incidence of severe malaria decreases by study month to a low level by the end of the trial. There is an indication that the overall incidence of severe malaria is declining in all groups, suggesting that any late rebound beyond the period of follow-up in the participants who received a fourth dose may not cancel out the overall protective effect in this group.

Importantly, a similar shift in cases of severe malaria towards older children was seen in the 6-12 week age group, but with a shorter timeframe, consistent with the overall lower efficacy in this age group. Thus the period of negative vaccine efficacy occurs at the 12-18 month time period following the third dose, and further follow-up shows no excess of severe malaria cases thereafter (see Table 4.7). If the same pattern followed in the 5-17 month age group, one would expect to see no excess of cases beyond the end of the trial, with low incidence of severe malaria regardless of randomization group.

From the time when the fourth dose was administered to the trial end, there were 103 cases of severe malaria in the RTS,S group that received a control vaccine at 18 months (R3C), compared to 76 cases in the RTS,S group that did receive a fourth dose of RTS,S (R3R) and 76 cases in the control group (C3C). The majority of cases classified as severe malaria, and most of the excess cases, were associated with other severe disease markers (prostration, respiratory distress, seizures, hypoglycaemia, etc.) rather than cerebral malaria or anaemia. The case fatality rate of these "other" cases is low. Of those severe cases who received RTS,S (R3R and R3C), there appeared to be a tendency for severe malaria to manifest as cerebral malaria (Table 4.5), although the absolute numbers of cerebral malaria cases remain low. The case fatality rate in the trial was lower than usually seen outside a trial setting. Over the first 20 months of the trial, 6 cases who received RTS,S died, and 2 cases in the control group died (2:1 randomization). From month 21 to the study end, six

cases died in the R3C group, three cases died in the R3R group, and two died in the C3C group. A review of the cerebral malaria cases by site showed a distribution consistent with the transmission settings of each site (Table 4.6).

Table 4.5: Cases of severe malaria disease (secondary case definition 1) classified by syndrome, group and time period including fatal cases by syndrome (ITT population; 5-17 month age category). Provided by GSK on request.

Time Period	Syndrome	RTS,S group (R3C + R3R) N=5948		Control group (C3C) N=2974	
		N	Died	N	Died
M0-M20	All Cases	205	6	158	2
	Cerebral	16	3	5	1
	Cerebral + Anaemia	6	1	1	0
	Anaemia	25	0	29	1
	Other	157	2	123	0
	Missing	1	0	0	0

Time period	Syndrome	3-dose schedule (R3C) N=2719		4-dose schedule (R3R) N=2681		Control (C3C) N=2702	
		N	Died	N	Died	N	Died
M21-SE	All Cases	103	6	76	3	76	2
	Cerebral	9	4	11	2	2	0
	Cerebral + Anaemia	0	0	1	0	2	1
	Anaemia	18	1	11	0	17	0
	Other	75	1	53	1	54	1

All cases: Secondary case definition 1 (more than 5000 parasites and at least 1 marker, including comorbidities)
Cerebral: more than 5000 parasites and BCS <= 2 and Hb >= 5 g/dl
Anaemia: more than 5000 parasites and BCS > 2 and Hb < 5 g/dl
Cerebral+Anaemia: 5000 parasites and BCS <= 2 and Hb < 5 g/dl
Other: 5000 parasites and other severe disease marker (prostration, respiratory distress, seizures, hypoglycemia < 2.2 mmol/L, acidosis BE ≤-10.0 mmol/L, lactate ≥ 5.0 mmol/L) excluding BCS and Hb

Table 4.6: Cerebral malaria cases in the 5-17 month age category by site. Provided by GSK on request.

Site	Number of subjects by site 5-17 months	Number of cases of cerebral malaria 5-17 months
Siaya	799	9
Kintampo	1002	14
Nanoro	600	8
Agogo	600	8
Manhica	1002	3
Lambarene	704	3
Kombewa	1000	4
Lilongwe	800	2
Bagamoyo	903	2
Korogwe	912	0
Kilifi	600	0
Total	**8922**	**53**

4.3.2 VE against severe malaria 6-12 weeks age category

Vaccine efficacy against severe malaria in the first 12 months was 38.5% (95%CI 7.8, 59.0) (Table 4.2). At 18 months, the efficacy was estimated at 17.4% (95%CI -16.2, 41.3), and by the trial end (in the group without a fourth dose of RTS,S), the efficacy was estimated at 16.0% (95%CI -14.5, 38.4). Among 6-12 week trial participants who received a fourth dose, the vaccine efficacy to the end of the trial was 20.5% (95%CI -9.8, 42.5).

When this was broken down by time interval, efficacy against severe malaria was 53.7% (95%CI 18.7, 73.6) in the first 6 months, after which the confidence intervals are wide and cross zero, although the point estimate is negative for the 12-18 month follow-up period, with no excess of severe malaria cases in those vaccinated beyond this initial period of rebound. Efficacy against severe malaria was 4.7% (-52.8, 40.6) between 19-30 months after the 3 doses, and 7.3% (95%CI -113.0, 59.9) between 31 months and the end of the observation period without a fourth dose (Table 4.7).

Study Month	Pooled RTS,S groups (R3C + R3R)	
M2.5-M8	53.7 (18.7, 73.6)	
M9-M14	18.2 (-43.8, 53.5)	
M15-M20	-38.9 (-143.2, 20.6)	
Study Month	**3-dose schedule (R3C)**	**4-dose schedule (R3R)**
M21-M32	4.7 (-52.8, 40.6)	37.7 (-4.8, 63.0)
M33-SE	7.3 (-113.0, 59.9)	13.8 (-91.6, 61.2)
M2.5-SE	**16.0 (-14.5, 38.4)**	**20.5 (-9.8, 42.5)**

Table 4.7: Vaccine efficacy against all episodes of severe malaria in 6-12 week age category by study months – primary case definition, ATP population. Provided by GSK on request. Case counts available in Appendix 3.

Stratification by site in this age group shows a wide variation in point-estimates and very wide confidence intervals due to the rarity of the outcome (Figure 4.9).

a) M2.5-SE: 3 doses of RTS,S **b) M2.5-SE: 4 doses of RTS,S**

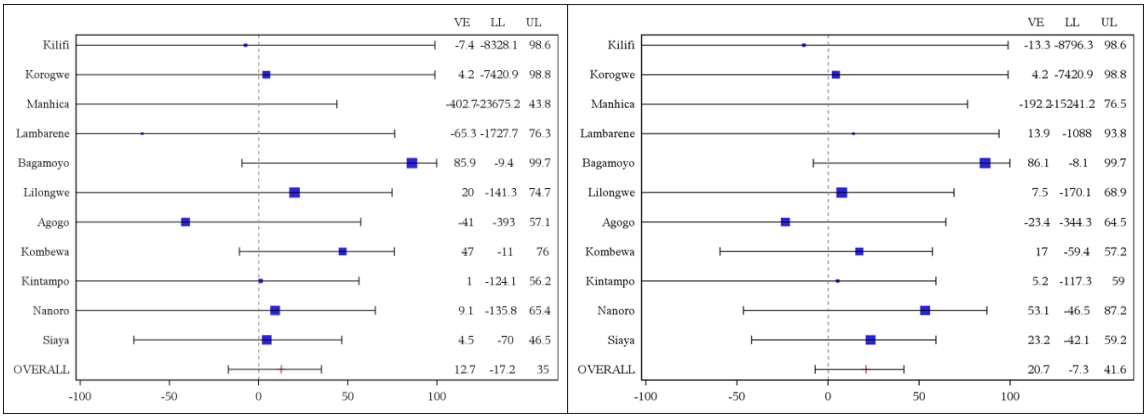


Figure 4.9: Vaccine efficacy in 6-12 week category against severe malaria by site (primary case definition) (ATP population). Sites are ordered based on incidence of clinical malaria (secondary case definition) measured in control infants 6-12 weeks of age at enrolment during 12 months of follow up. Provided by GSK on request.

Cases of severe malaria were also broken down by syndrome for the 6-12 week age category (Table 4.8). In contrast to the 5-17 month category, there was no imbalance between the RTS,S group and the control group in cerebral malaria cases.

Table 4.8: Cases of severe malaria disease (secondary case definition 1) classified by syndrome, group and time period including fatal cases by syndrome (ITT population; 6-12 week age category). Provided by GSK on request.

Time Period	Syndrome	RTS,S group (R3C + R3R) N=4358		Control group (C3C) N=2179	
		N	Died	N	Died
M0-M20	All Cases	148	1	86	2
	Cerebral	2	0	3	0
	Cerebral + Anaemia	3	0	1	0
	Anaemia	30	0	17	0
	Other	111	1	65	2
	Missing	2	0	0	0

Time period	Syndrome	3-dose schedule (R3C) N=1996		4-dose schedule (R3R) N=1966		Control (C3C) N=1976	
		N	Died	N	Died	N	Died
M21-SE	All Cases	63	2	53	3	68	0
	Cerebral	4	1	4	2	2	0
	Cerebral + Anaemia	0	0	0	0	1	0
	Anaemia	15	0	15	0	19	0
	Other	42	0	34	1	45	0
	Missing	2	1	0	0	1	0

All cases: Secondary case definition 1 (more than 5000 parasites and at least 1 marker, including comorbidities)
Cerebral: more than 5000 parasites and BCS <= 2 and Hb >= 5 g/dl
Anaemia: more than 5000 parasites and BCS > 2 and Hb < 5 g/dl
Cerebral+Anaemia: 5000 parasites and BCS <= 2 and Hb < 5 g/dl
Other: 5000 parasites and other severe disease marker (prostration, respiratory distress, seizures, hypoglycemia < 2.2 mmol/L, acidosis BE ≤-10.0 mmol/L, lactate ≥ 5.0 mmol/L) excluding BCS and Hb

4.4 VE against malaria hospitalization and mortality

Table 4.9: Vaccine efficacy (95%CI) against additional outcomes (primary case definitions or case definition 1; ATP population). Provided by GSK on request.

Outcome	5-17 months			6-12 weeks		
	M2.5-20 Pooled RTS,S (R3R + R3R)	M2.5-SE 3-dose schedule (R3C)	M2.5-SE 4-dose schedule (R3R)	M2.5-20 Pooled RTS,S (R3R + R3R)	M2.5-SE 3-dose schedule (R3C)	M2.5-SE 4-dose schedule (R3R)
Malaria hospitalization	41.7 (29.4-51.8)	12.1 (-5.0-26.4)	37.2 (23.6-48.5)	17.8 (-6.3-36.2)	13.2 (-9.2-31.1)	27.1 (7.1-42.9)
Incident Severe anaemia	56.6 (21.3-76.2)	20.6 (-32.7-52.9)	61.2 (26.5-80.6)	3.0 (-100-50.9)	12.8 (-50.9-49.9)	31.5 (-23.1-62.6)
All-cause hospitalization	19.1 (8.7-28.2)	8.8 (-2.9-19.3)	14.9 (3.6-24.8)	6.5 (-6.2-17.5)	4.8 (-8.3-16.4)	7.0 (-6.0-18.4)
All-cause hospitalization excluding malaria	6.0 (-9.1-18.8)	6.6 (-8.5-19.6)	3.2 (-12.4-16.5)	2.0 (-12.9-14.8)	1.8 (-13.8-15.2)	-0.3 (-16.2-13.4)
All-cause mortality	7.3 (-63.8-46.2)	-1.3 (-79.5-42.8)	-17.8 (-105-31.9)	-9.0 (-84.9-43.0)	-21.5 (-108-28.5)	-15.6 (-99.2-32.6)
Bacteraemia	15.8 (-26.0-43.2)	22.3 (-16.0-48.3)	12.8 (-28.9-41.1)	-21.9 (-101-23.9)	-19.6 (-85.8-22.6)	-8.5 (-70.3-30.7)
Pneumonia	6.4 (-28.0-31.0)	21.2 (-10.9-44.2)	-3.9 (-43.0-24.5)	10.5 (-17.9-31.7)	16.4 (-11.4-37.4)	11.0 (-18.2-33.0)

4.4.1 VE against malaria-related hospitalization, mortality and severe anaemia: 5-17 months age category

In the 5-17 month age category, vaccine efficacy against malaria-related hospitalization (defined as a medical hospitalization with confirmed *P. falciparum* >5000 parasites/µL) was 41.7% (95%CI 29.4, 51.8) up to study month 20 (Table 4.9). Among participants who did not receive the fourth dose (R3C), efficacy against malaria-related hospitalization was 12.1% (95%CI -5.0, 26.4) by the trial end. Among participants who did receive the fourth dose (R3R), vaccine efficacy against malaria-related hospitalization was 37.2% (95%CI 23.6, 48.5) during the full observation period.

Vaccine efficacy against malaria-related mortality based on the primary case definition (defined as a case of severe malaria meeting the primary case definition of severe malaria with a fatal outcome) could generally not be assessed due to the lack of cases. During the first 20 months of the study,

there were 12 malaria-related deaths in the RTS,S group and 7 malaria-related deaths in the control group (2:1 randomization) (Table 4.10). From 21 months to the study end, there were 11 malaria-related deaths in the RTS,S group that did not receive a fourth dose (R3C), 7 malaria-related deaths in the group that did receive a fourth dose (R3R), and 5 malaria-related deaths in the control group.

During the full study period, vaccine efficacy against incident severe anaemia (defined as a documented haemoglobin < 5.0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a *P. falciparum* parasitaemia at a density of > 5000 parasites per cubic millimetre) was 20.6% (95%CI -32.7, 52.9) in the group that did not receive a fourth dose (R3C), and it was 61.2% (95%CI 26.5, 80.6) in the group that did receive a fourth dose (R3R).

4.4.2 VE against malaria-related hospitalization, mortality and severe anaemia: 6-12 weeks age category

In the 6-12 week age category, vaccine efficacy against malaria-related hospitalization was 17.8% (95%CI -6.3, 36.2) up to study month 20 (Table 4.9). Among participants who did not receive the fourth dose (R3C), efficacy was against malaria-related hospitalization was 13.2% (95%CI -9.2, 31.1) to the trial end. Among participants who did receive the fourth dose (R3R), vaccine efficacy against malaria-related hospitalization was 27.1% (95%CI 7.1, 42.9) during the full observation period.

Table 4.10: Number of fatalities due to malaria or all-causes by treatment group and time period (ITT population; Fatal malaria based on ICD10 code (B50, B53, B54) case review). Provided by GSK on request.

5-17 Months age category		Pooled RTS,S (R3R + R3R) (N=5948)	3-dose schedule (R3C) (N=2719)	4-dose schedule (R3R) (N=2681)	Control (C3C) (N=2702)
Fatal malaria cases (N)	M0-M20	12	-	-	7
	M21-SE	-	11	7	5
All-cause mortality (N)	M0-M20	74	-	-	33
	M21-SE	-	23	15	13
6-12 Week age category		**Pooled RTS,S (R3R + R3R) (N=4385)**	**3-dose schedule (R3C) (N=2178)**	**4-dose schedule (R3R) (N=2180)**	**Control (C3C) (N=2179)**
Fatal malaria cases (N)	M0-M20	9	-	-	4
	M21-SE	-	6	5	2
All-cause mortality (N)	M0-M20	83	-	-	34
	M21-SE	-	11	11	8

Vaccine efficacy against malaria-related mortality based on the primary case definition could generally not be assessed due to the lack of cases. During the first 20 months of the study, there were 9 malaria-related deaths in the RTS,S group and 4 malaria-related deaths in the control group (2:1 randomization) (Table 4.10). From 21 months to the study end, there were 6 malaria-related deaths in the RTS,S group that did not receive a fourth dose (R3C), 5 malaria-related deaths in the group that did receive a fourth dose (R3R), and 2 malaria-related deaths in the control group.

During the full study period, vaccine efficacy against incident severe anaemia was 12.8% (95%CI -50.9, 49.9) in the group that did not receive a fourth dose (R3C), and it was 31.5% (95%CI -23.1, 62.6) in the group that did receive a fourth dose (R3R).

4.5 VE against other outcomes

4.5.1 VE against other outcomes: 5-17 months age category

Vaccine efficacy was assessed also against all-cause hospitalization, all-cause mortality, bacteraemia, and pneumonia (Table 4.9). Among these, the only significant protection demonstrated was in the 5-17 month category against all-cause hospitalization (including malaria-related hospitalizations) in the first 18 months after third vaccination (R3C + R3R) and in the full study period among those who received a fourth dose (R3R). The efficacy estimates were 19.1% (95%CI 8.7, 28.2) and 14.9% (95%CI 3.6, 24.8), respectively. When malaria was excluded as a cause of hospitalization, the vaccine efficacy estimates were no longer significant.

During the first 20 months of the study (M0-M20), there were 74 deaths from any cause in the RTS,S groups and 33 deaths in the control group (2:1 randomization) (Table 4.10). From 21 months to the study end (M21-SE), there were 23 deaths in the RTS,S group that did not receive a fourth dose (R3C), 15 deaths in the group that did receive a fourth dose (R3R), and 13 deaths in the control group. The efficacy against all-cause mortality (defined as a fatality of any cause that occurs in the community or in hospital) up to study month 20 was 7.3% (95%CI -63.8, 46.2) in 5-17 month old participants. Across the entire study period, the vaccine efficacy against all-cause mortality was –1.3% (95%CI -79.5, 42.8) in those without a fourth dose (R3C), and -17.8% (95%CI -105, 31.9) among those who did receive a fourth dose of RTS,S (R3R). Mortality overall was low in the follow-up period across all groups (1.8%).

4.5.2 VE against other outcomes: 6-12 weeks age category

In the 6-12 weeks age category, vaccine efficacy was not significant in any group for the outcomes reviewed: all-cause hospitalization, all-cause mortality, bacteraemia, and pneumonia (Table 4.9)

During the first 20 months of the study (M0-M20), there were 83 deaths from any cause in the RTS,S group and 34 deaths in the control group (2:1 randomization) (Table 4.10). From 21 months to the study end (M21-SE), there were 11 deaths in the RTS,S group that did not receive a fourth dose (R3C), 11 deaths in the group that did receive a fourth dose (R3R), and 8 deaths in the control group. The efficacy against all-cause mortality up to study month 20 was -9.0% (95%CI -84.9, 43.0) in 6-12 week old participants. Across the entire study period, vaccine efficacy against all-cause mortality was -21.5% (95%CI -108, 28.5) in those without a fourth dose (R3C), and -15.6% (95%CI -99.2, 32.6) among those who did receive a fourth dose (R3R). Mortality was also low (2.3%) in young infants across all groups.

The efficacy against all-cause hospitalizations was 6.5% at study month 20 (95%CI –6.2, 17.5). By the trial end, vaccine efficacy was estimated at 4.8% (95%CI -8.3, 16.4) in the group that did not receive a fourth dose (R3C) and 7.0% (95%CI -6.0, 18.4) in the group that did receive a fourth dose (R3R).

4.5.3 Mortality among participants in the RTS,S clinical trial

As remarked above, this trial did not identify an effect of vaccination on mortality. There were relatively few deaths in the trial (Table 4.10), far less that would have been expected in the absence of the trial. A case-control analysis at the KEMRI/CDC RTS,S trial site (also a DSS site) in Kisumu Kenya identified a 70% reduction in mortality among children who participated in the control arm of the trial compared to those who live in the DSS catchment area but did not participate in the trial[27]. This trial was not powered to detect a possible reduction in mortality due to vaccination in either the 5-17 month age category or 6-12 week age category, and it remains an open question as to whether the vaccine will produce a mortality reduction if deployed in populations in which the standard of care may be less than experienced by children in the Phase 3 trial.

4.6 Summary of VE profile of RTS,S/AS01 & RTS,S/AS02 in Phase 2 trials

Table 4.11 summarises results from Phase 2 trials. All paediatric trials show significant protection against clinical malaria.

Table 4.11: Overview of vaccine efficacy estimates from Phase 2 trials of AS01- and AS02-containing RTS,S vaccine (adapted from Bejon et al 2013)[28].

Country	Subjects (n)	Active vaccine(s)	Control vaccine	Surveillance	Median age at enrolment (IQR)	Local parasite prevalence (%)	Duration of follow up post-dose 3	Vaccine Efficacy (95%CI)
Gambia	250	RTS,S/AS02	Rabies	ACDi, weekly blood films	24 years (19-34)	70%	15 weeks	34 % (8, 53)
Kenya	250	RTS,S/AS02 RTS,S/AS01	Rabies	ACDi, weekly blood films	25 years (21-29)	60%	14 weeks	30% (-15, 57)
Mozambique	411	RTS,S/AS02	HepB or PCV/Hib	ACDi, blood films every 3 weeks	36 months (24-45)	70%	6 months	45% (31, 56)
Mozambique	214	RTS,S/AS02	HepB	ACDi, blood films every 2 weeks	1.8 months (1.8-2.1)	45%	3 months	66% (43, 80)
Tanzania	340	RTS,S/AS02	HepB	ACDi, blood films every 2 weeks	1.9 months (1.8-2)	30%	6 months	65% (21, 85)
Kenya	447	RTS,S/AS01	Rabies	ACDc, weekly visits	11 months (8-14)	35%	Variable (mean of 7.9 months)	53% (28, 69)
Tanzania	447				12 months (9-15)	15%		
Mozambique	1589	RTS,S/AS02	HepB or PCV/Hib	PCD	35 months (24-48)	40%	6 months	30% (11, 45)
Tanzania	209	RTS,S/AS01	None	PCD	1.8 months (1.7-1.9)	30%	16.5 months	53% (26, 70)
Gabon	215				1.5 months (1.4-1.7)	5%		
Ghana	81				1.6 months (1.5-1.8)	80%		

ACDi=active case detection for infection. ACDc=active case detection for clinical malaria. PCD=passive case detection for clinical malaria. Active case detection includes a passive component.

5. RTS,S Immunogenicity

5.1 Theoretical mechanism of action

It has been established that RTS,S/AS reduces the rate of acquisition of new blood stage infections[29], reduces the initial inoculum of each blood stage infection[30] and reduces the multiplicity of infections in vaccinees[31]. This might result from the induction of CS-specific antibodies and/or $CD4^+$ T cells and to date there are no accepted correlates of protection for RTS,S/AS[32].

The available evidence about the protective mechanism of RTS,S/AS, however, supports a critical role for IgG against the CS repeat sequence in the protection seen against infection, whether in multiple clinical challenge trials in USA, adult or paediatric field trials in different age groups and across the distinct transmission settings of The Gambia, Kenya, Tanzania and Mozambique[7]. When a mosquito probes for a blood meal, sporozoites are deposited intradermally and migrate for several hours before entering skin microvasculature or entering lymphatics[33, 34], although some sporozoites may perhaps entering directly into vessels during mosquito probing. Anti-CS antibodies have been shown to reduce the numbers of sporozoites that enter skin blood vessels to begin the journey to the liver[35]. No anti-CS antibody threshold level has been found as indicative of full protection against infection: the data are consistent with a dose response such that at higher IgG concentrations a reduced risk of infection is seen. Importantly, antibody titres after the fourth dose do not reach levels seen after the first three doses, which is consistent with efficacy also not being as high. The reasons for this are not fully understood. One hypothesis is that high titre hepatitis B antibodies induced by first three doses would interfere with subsequent induction of anti-CS immunogenicity. A more likely hypothesis, supported by the lower anti-CS titers elicited in malaria-immune than naïve adults[14], is that increasing exposure to CS – whether through repeated malaria infection or vaccination - leads to B cell hyporesponsiveness. This phenomenon, first described for meningococcal and pneumococcal polysaccharide vaccines[36], reflects the recruitment and differentiation of fewer antigen-specific B cells into successive responses, the B cell reservoir being exhausted by repeat and/or high-dose antigen exposure. This has two implications: 1) the booster dose is a fourth dose; 2) the capacity of subsequent doses to “reactivate” immunity and protection is unknown and difficult to predict.

Cell-mediated immunity (CMI) indicators were used as a down-selection criterion for adjuvant choice in the RTS,S development programme[37]. Both CS-specific γ-interferon secreting $CD4^+$ T cell responses (as enumerated by *ex vivo* ELISPOT) and multifunctional CS-specific $CD4^+$ T cells (defined as expressing two or more of γ-interferon, TNF, IL-2 and CD40 ligand using an intracellular cytokine staining assay) were greater in protected than in unprotected vaccinees in an RTS,S clinical challenge trial[14]. Multifunctional $CD4^+$ T cell responses were reported not to be correlated with anti-NANP IgG responses. Some data on CMI responses to RTS,S is available in African children[38], although none from the pivotal Phase 3 trial. Most RTS,S studies performing CMI studies have reported an absence of substantial CS-specific $CD8^+$ T cell responses[14, 39]. Weak CS-specific $CD8^+$ T cell responses were reported in a trial, with a highly sensitive ELISPOT assay performed on cultured cells[40]. $CD8^+$ T cells are thus not thought to be an important mediator of protection for RTS,S/AS01.

Prior to the pivotal Phase 3 study, there was a consistently reported association between IgG that bind CS and protection from infection, but not from disease. This is consistent with the pre-erythrocytic biological target of the vaccine. It is possible that complete protection occurs in some volunteers, but in high transmission settings most vaccinees do eventually develop malaria, suggesting that the proportion completely protected is, at most, small. This needs to be taken into account in interpreting associations of immune responses and efficacy, as partial protection from infection might be expected in most individuals. This also implies that vaccinated individuals, during the initial period when protected against malaria, also experience less exposure to blood-stage parasites and therefore may have a deferred development of naturally acquired immunity, which may render them later on more susceptible to adverse effects of malaria infection as vaccine efficacy wanes than persons who have not been vaccinated.

5.2 Summary of immunogenicity of RTS,S/AS in Phase 2 and Phase 3 studies, other than the Pivotal Phase 3 study

In the paediatric population, after 3 doses of RTS,S/AS01 vaccine given according to the 0, 1, 2-month schedule, over 98% of subjects were seropositive for anti-CS antibody response. Seropositivity was defined as 0.5 EU/ml. Immunogenicity tends to increase with decreasing age from adulthood to a peak at median age of 11-12 months (Table 5.1). From the age of 11-12 months, a decrease in immunogenicity with age de-escalation to infants vaccinated at 1-2 months of age is seen.

Table 5.1: Peak anti-CSP titre by Phase 2 clinical trial site[41]

Site	Participants (RTS,S)	Active vaccine	Median age (IQR)	Parasite prevalence[a]	Schedule	Peak anti-CSP titre (95% range)
Gambia [12]	250 (136)	RTS,S/AS02A	24 (19 to 34) years	70%	0,1,5,14 months	25 (13 to 43) µg/mL
Kisumu, Kenya [13]	250 (159)	RTS,S/AS02A and RTS,S/AS01B	25 (21 to 29) years	60%	0,1,2 months	34 (2 to 210) EU/mL
Manhica, Mozambique (cohort 1) [7,14]	1,589 (768)	RTS,S/AS02A	35 (24 to 48) months	40%	0,1,2 months	191 (9 to 916) EU/mL
Ilha Josina, Mozambique (cohort 2) [7,14]	411 (196)	RTS,S/AS02A	36 (24 to 45) months	45%	0,1,2 months	266 (16 to 1,390) EU/mL
Kilifi, Kenya [6,15]	447 (209)	RTS,S/AS01E	11 (8 to 14) months	35%	0,1,2 months	580 (104 to 1,922) EU/mL
Korogwe, Tanzania [6]	447 (224)	RTS,S/AS01E	12 (9 to 15) months	15%	0,1,2 months	493 (138 to 1,768) EU/mL
Kintampo, Ghana [10]	180 (180)	RTS,S/AS02D and RTS,S/AS01E	11 (8 to 14) months	80%	0,1,2 and 0,1,7 months	465 (73 to 2,632)[b] EU/mL
Kumasi, Ghana [10]	270 (270)	RTS,S/AS02D and RTS,S/AS01E	11 (7 to 13) months	35%	0,1,2 and 0,1,7 months	460 (84 to 1,785)[b] EU/mL
Lambaréné, Gabon [9]	180 (180)	RTS,S/AS02D and RTS,S/AS01E	38 (31 to 48) months	5%	0,1,2 months	198 (32 to 888) EU/mL
Bagamoyo, Tanzania [8]	209 (136)	RTS,S/AS01E	1.8 (1.7 to 1.9) months	30%	0,1,2 and 0,1,7 months[c]	167 (14 to 934)[b] EU/mL
Lambaréné, Gabon [8]	215 (139)	RTS,S/AS01E	1.5 (1.4 to 1.7) months	5%	0,1,2 and 0,1,7 months[c]	337 (97 to 1,836)[b]EU/mL
Kintampo, Ghana [8]	81 (52)	RTS,S/AS01E	1.6 (1.5 to 1.8) months	80%	0,1,2 and 0,1,7 months[c]	70 (11 to 455)[b] EU/mL
Mozambique infants [16]	214 (98)	RTS,S/AS02D	1.8 (1.8 to 2.1) months	45%	0,1,2 months	211 (6 to 1,008) EU/mL
Bagamoyo, Tanzania [11]	340 (157)	RTS,S/AS02D	1.9 (1.8 to 2) months	30%	0,1,2 months[c]	87 (1 to 572)[b] EU/mL

For participants receiving at least one dose of RTS,S the peak anti-CSP antibody titre following vaccination is presented as the median and 95% range within the cohort at each trial site. [a]Age-corrected parasite prevalence in 2- to 10-year olds taken from Malaria Atlas Project [17]; [b]indicates peak anti-CSP antibody titre in the cohort vaccinated through a 0, 1, 2 month schedule; [c]indicates co-administration with the EPI vaccines (diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenza* type b). CSP, circumsporozoite protein; EPI, expanded programme on immunization; EU, ELISA units; IQR, interquartile range.

Table 5.1 shows peak anti-CS responses, generally measured 4 weeks after the final dose of RTS,S/AS01. The anti-CS antibody GMCs one month after the third dose tended to be higher in the

malaria-naïve adults (160.3 EU/ml in US adults, RTS,S/AS01 group) than in adults living in malaria-endemic areas (see first 2 rows in the table). In the first Phase 2b field efficacy trial, which involved 306 Gambian adults, 34% efficacy was reported against the incidence rate of first blood stage infections over a 15-week period[42]. In this study a linear relationship was found between IgG concentration post dose 3 and protection from blood stage infection, such that the odds ratio for a ten-fold increase in IgG concentration and infection with malaria was 0.21 (p = 0.023). After correction for age and pre-vaccination titre the odds ratio was 0.27 (p = 0.07).

The largest Phase 2b field efficacy trial of RTS,S/AS02 to date reported data on 2,022 Mozambican children, first vaccinated aged 1-4 years, and an association was found between anti-NANP IgG concentration and efficacy against malaria infection[43, 44]. A similar association was reported in a trial in infants in Mozambique[45]. In contrast, in paediatric trials there has generally been a lack of association between the anti-NANP IgG concentration and protection against clinical disease[29, 46].

The kinetics of the antibody response over time are shown in the Figure 5.1, from several Phase 2 studies in young children.

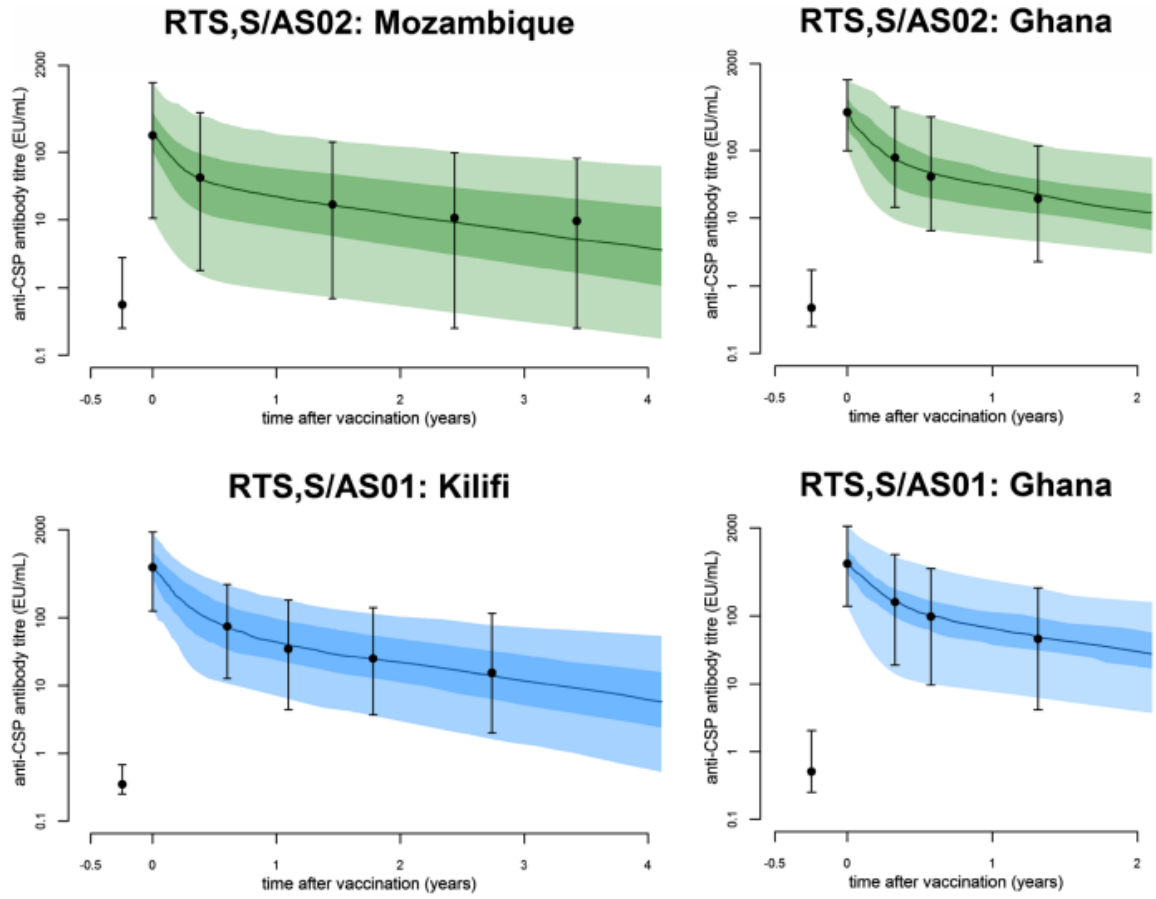


Figure 5.1: Decay of IgG titres from Phase 2 trials of RTS,S/AS02 and RTS,S/AS01[41].

Figure 5.1 highlights the biphasic decay of IgG titres, with a steeper decline in the six months following vaccination and a slower decline thereafter.

5.3 Summary of immunogenicity findings in the RTS,S/AS01 Phase 3 trial

RTS,S/AS01 was immunogenic in both age groups. There were very few non-responders to RTS,S. Anti-CS antibody geometric mean titres (GMTs) were highest at the measurement 1 month post-vaccination and did not return to the original level with a fourth dose (Figure 5.2). The absolute GMT value was higher in the 5-17 month age group compared to the 6-12 week age group at each time point following vaccination, as previously seen in Phase 2 studies. There was site-to-site variation in GMTs (Figures 5.4 and 5.5) and the reasons for this are not understood. Lot-to-lot consistency of immunogenicity has been demonstrated comparing three lots of vaccine formulated from commercial scale bulk material. These lots were shown to be at least as immunogenic (non-inferiority demonstrated for both anti-CS and anti-HBs immune response) as the vaccine lots used in the pivotal Phase 3 trial.

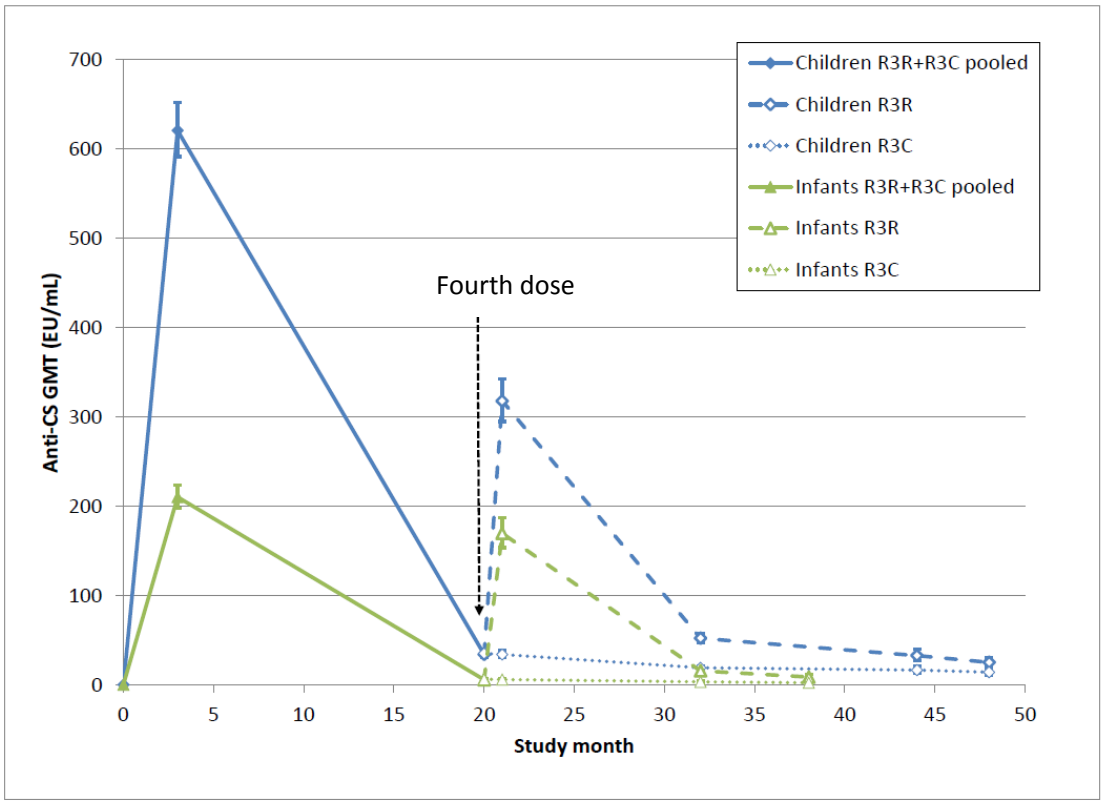
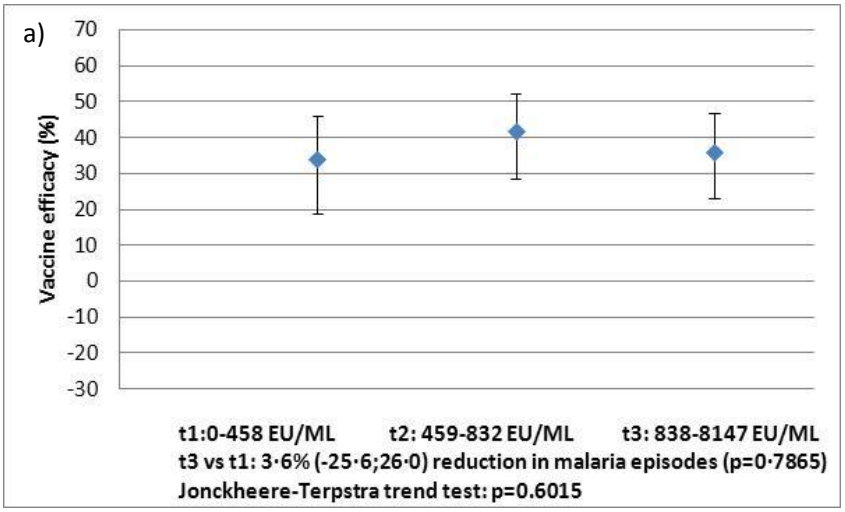


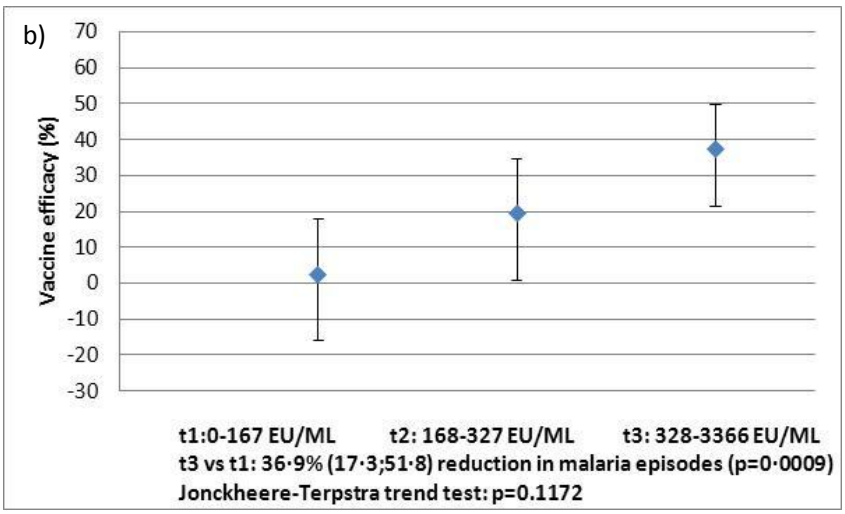
Figure 5.2: Anti-CS geometric mean titres in 5-17 month age category (labelled as "children") and 6-12 week old age category ("infants") in pivotal Phase 3 trial (per-protocol population for immunogenicity). Provided by GSK.

In order to interpret the immunogenicity data from the Phase 3 trial, it is necessary to consider the differences in pre-existing immunity between those in the 6-12 week and the 5-17 month age categories. The 6-12 week olds would have had variable quantities of pre-existing maternally acquired passive anti-CS IgG that may have interfered with vaccine immunogenicity, but they have little or no pre-existing naturally acquired immunity to CS antigen through prior exposure to malaria infection. In this group, an inverse association between anti-CS antibody pre-vaccination and

induction of anti-CS through vaccination was expected and confirmed through analyses of Phase 3 data: there was an association between higher post vaccination anti-CS IgG and reduced incidence of clinical malaria (p=0.0003). Infants who were seropositive for anti-CS at baseline (maternal antibodies) had lower post vaccination anti-CS IgG GMT (and a higher clinical malaria incidence (p=0.0001)), consistent with interference between maternally acquired CS antibodies, immunogenicity and protection.

By contrast, in the 5-17 month age category, maternally acquired anti-CS IgG will have decayed, and pre-existing naturally acquired immunity to malaria will have begun to develop. Further, as a result of immune maturation RTS,S/AS01 induces 3-fold higher IgG GMTs in the 5-17 month age category than in 6-12 week age category. In the 5-17 month age category there is no clear correlation between anti-CS IgG and protection against disease. Anti-CS antibody titers at one month post dose 3 were not associated with the incidence of clinical malaria (p=0.2426). Children who were seropositive for anti-CS at baseline experienced a higher incidence of clinical malaria (p=0.0042), perhaps indicating residence in a higher exposure setting. When participants in the 5-17 month age category were grouped by tertile of their vaccine induced anti-CS responses, there was no clear association with efficacy (Figure 5.3), whereas there was some evidence of an association for the 6-12 week age category, although the trend test was not significant.





Taking these findings together, one possible interpretation is that there is an association between anti-CS IgG and protection against disease in the range of GMTs seen at 1 month post dose 3 in the 6-12 week age category, but that at the higher immunogenicity levels seen in 5-17 month age category this association is no longer seen.

Figure 5.3 a-b: Vaccine efficacy by tertile of anti-CS antibody concentration (ATP population) a) 5-17 month age category (R3C, 3-dose schedule), and b) 6-12 week age category (R3C, 3-dose schedule). Error bars represent 95% confidence interval. t1-3: tertile 1-3 of anti-cs titer post vaccination. Provided by GSK on request.

As noted above, immunogenicity is not as high after the fourth dose, as after the third dose. There is no immunogenicity data on a fifth dose.

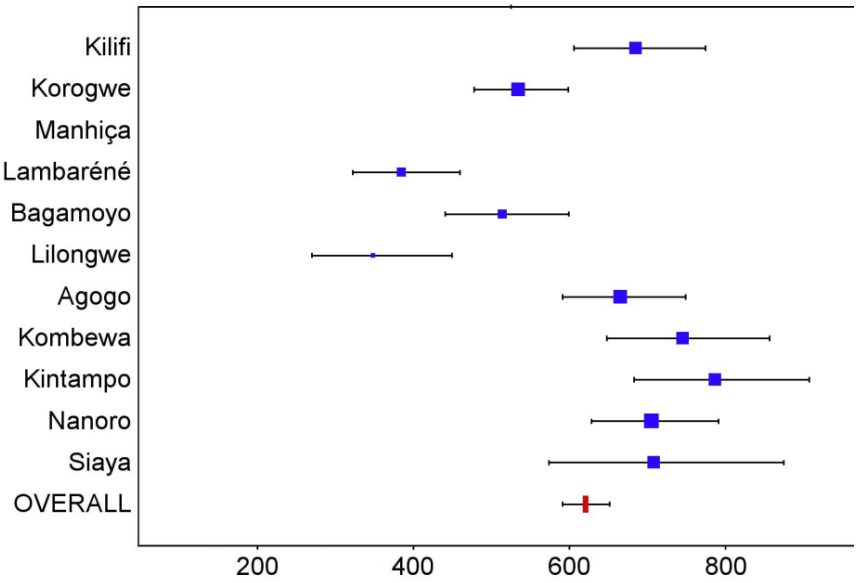


Figure 5.4: Anti-CS antibody geometric mean titres (EU/ml) in RTS,S/AS01 recipients 1 month after dose 3 in children 5-17 months of age at enrolment, ordered by increasing malaria incidence at each trial site (ATP population)[25].

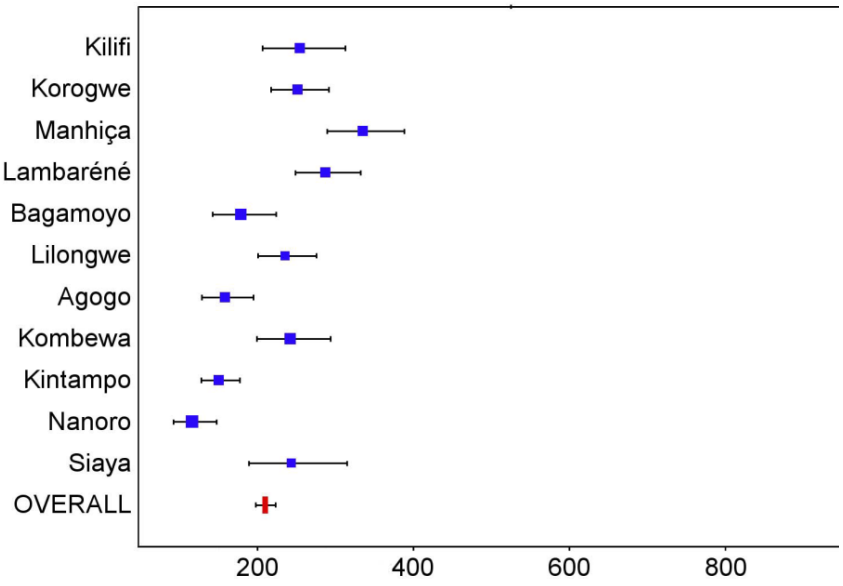


Figure 5.5: Anti-CS antibody geometric mean titres (EU/ml) in RTS,S/AS01 recipients 1 month after dose 3 in children 6-12 weeks of age at enrolment, ordered by increasing malaria incidence at each trial site (ATP population)[25].

Table 5.2: Anti-CS antibody GMT and VE in the 5-17 month age category at 12 months post dose 3 by site, ordered by increasing GMT[25].

Trial site	GMT (LL, UL)	$VE_{2.5\text{-}14M}$ (95%CI)
Lilongwe	348.4 (270.2, 449.2)	53.2 (17.6, 73.4)
Lambaréné	385.0 (322.6, 459.5)	61.7 (28.5, 79.5)
Bagamoyo	514.0 (441.0, 599.0)	73.9 (57.7, 83.9)
Korogwe	534.7 (477.6, 598.5)	62 (23.6, 81.1)
Agogo	665.5 (591.4, 749.0)	60.5 (48.1, 70)
Kilifi	685.2 (606.1, 774.6)	83 (37.2, 95.4)
Nanoro	705.1 (628.6, 791.0)	44 (36.9, 50.4)
Siaya	708.6 (573.8, 875.0)	50 (40.1, 58.2)
Kombewa	745.1 (648.1, 856.6)	46.1 (34.8, 55.4)
Kintampo	787.1 (682.6, 907.6)	50.7 (42.5, 57.7)
OVERALL	**621.0 (591.5, 651.9)**	**51.3 (47.5, 54.9)**

Table 5.3: Anti-CS antibody GMT and VE in the 6-12 week age category at 12 months post dose 3 by site, ordered by increasing GMT[25].

Trial site	GMT (LL, UL)	$VE_{2.5\text{-}14M}$ (95%CI)
Nanoro	116.9 (92.5, 147.9)	27.5 (17.1, 36.5)
Kintampo	151.0 (128.5, 177.4)	-12.1 (-47.9, 15.1)
Agogo	158.6 (129.1, 194.8)	23.7 (0, 41.8)
Bagamoyo	179.1 (143.1, 224.0)	44.7 (-11.2, 72.5)
Lilongwe	235.5 (200.9, 276.0)	55.4 (31.4, 71)
Kombewa	242.3 (199.7, 294.1)	44.4 (25.5, 58.5)
Siaya	244.1 (189.2, 315.0)	38.5 (25.2, 49.5)
Korogwe	252.1 (217.7, 292.0)	46.6 (-26.1, 77.3)
Kilifi	254.4 (206.8, 313.2)	-11.9 (-1146.5, 90)
Lambaréné	287.6 (248.8, 322.3)	13.9 (-209.2, 76)
Manhiça	335.3 (289.5, 388.5)	8.9 (-95.8, 57.6)
OVERALL	**210.5 (198.2, 223.6)**	**32.9 (26.4, 38.9)**

6. RTS,S/AS01 Vaccine Safety

RTS,S/AS01 is a new vaccine, and AS01 has not yet been used in other licensed vaccines. There is clinical experience with AS01 in a number of other non-malaria experimental products, including in over 7,000 adults in a Phase III trial of varicella–zoster virus glycoprotein E and AS01[47]. Nearly 12,500 infants and children have received the RTS,S/AS01 vaccine in clinical trials. The WHO Global Advisory Committee on Vaccine Safety (GACVS) reviewed the safety data for RTS,S/AS01 in 2009, 2014 and 2015 and determined RTS,S/AS01 has an acceptable safety profile[48-50].

The following sections cover the safety results generated from the Phase 3 trial of RTS,S/AS01. Among the first 200 participants enrolled at each trial site for both age categories, unsolicited adverse events within 30 days after vaccination and local and systemic reactogenicity within 7 days after vaccination were collected. Serious adverse events were identified for all participants by

passive surveillance throughout the observation period (48 months in 5-17 month age category, 38 months in 6-12 week age category).

6.1 Reactogenicity

Safety parameters evaluated included reactogenicity observed during the 7 days following vaccination and unsolicited symptoms recorded during 30 days after vaccination with doses 1, 2 and 3 (first 200 subjects enrolled at each site, for each age group).

In the 5-17 month age category, the proportion of unsolicited reports within 30 days of any of the first three vaccine doses were similar between the RTS,S and control groups: 86.1% (95%CI 84.2, 87.8) and 86.8% (95%CI 84.1, 89.2), respectively[51]. Pain, drowsiness, irritability, loss of appetite, and fever (≥37.5°C) were reported more frequently in the seven days following RTS,S compared to control vaccine (Figure 6.1). Fever occurred most frequently and was reported after 31.1% of doses in the RTS,S group (95%CI 29.7, 32.5) compared with 13.4% of doses in the control group (95%CI 12.0, 14.9). Grade 3 fever (>39°C) occurred in 2.5% of participants in the RTS,S group (95%CI 2.1, 3.1) compared to 1.1% in the control group (95%CI 0.7, 1.7).

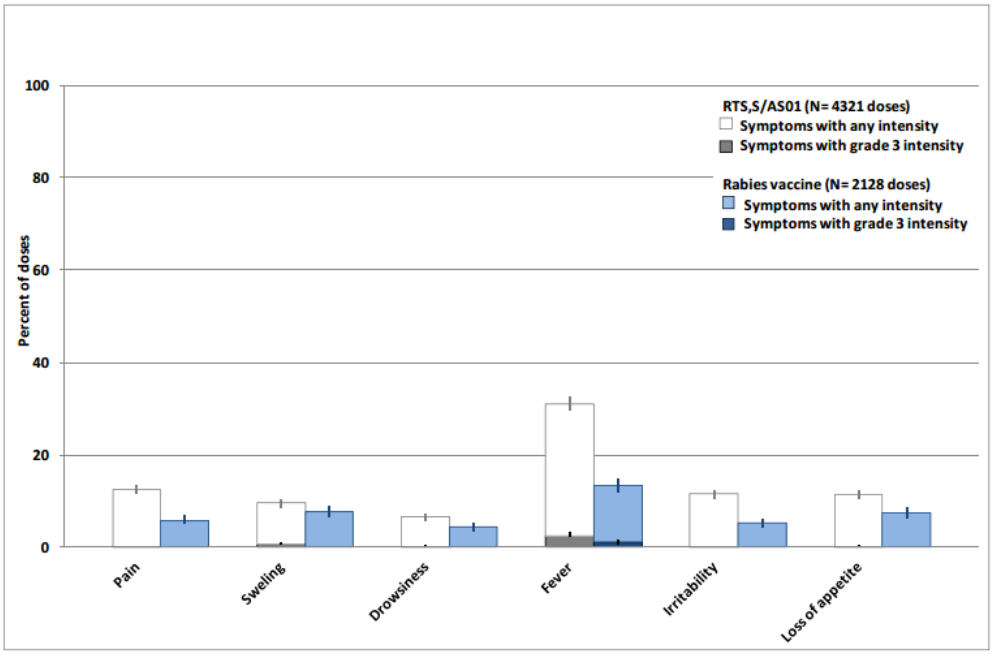


Figure 6.1: Incidence of solicited local and general adverse events reported during the 7-day post vaccination period following each dose in children 5-17 months of age at enrolment (ITT Population, Malaria-055)[51].

In the 6-12 week age category, the proportion of unsolicited reports within 30 days of any of the first three doses co-administered with DTPwHepB/Hib and OPV were similar between the RTS,S and control groups: 79.4% (95%CI 77.2, 81.5) and 81.3% (95%CI 78.3, 84.1), respectively. The proportion of solicited local symptoms (pain, redness, and swelling) was also similar between the RTS,S and control groups (Figure 6.2). The rates of systemic reactions (specifically drowsiness, irritability, and fever) were higher for participants in the RTS,S group compared to the control group. Fever again

occurred most frequently and was reported after 30.6% of doses in the RTS,S group (95%CI 29.2, 32.0) compared with 21.1% of doses in the control group (19.4, 22.8)[26].

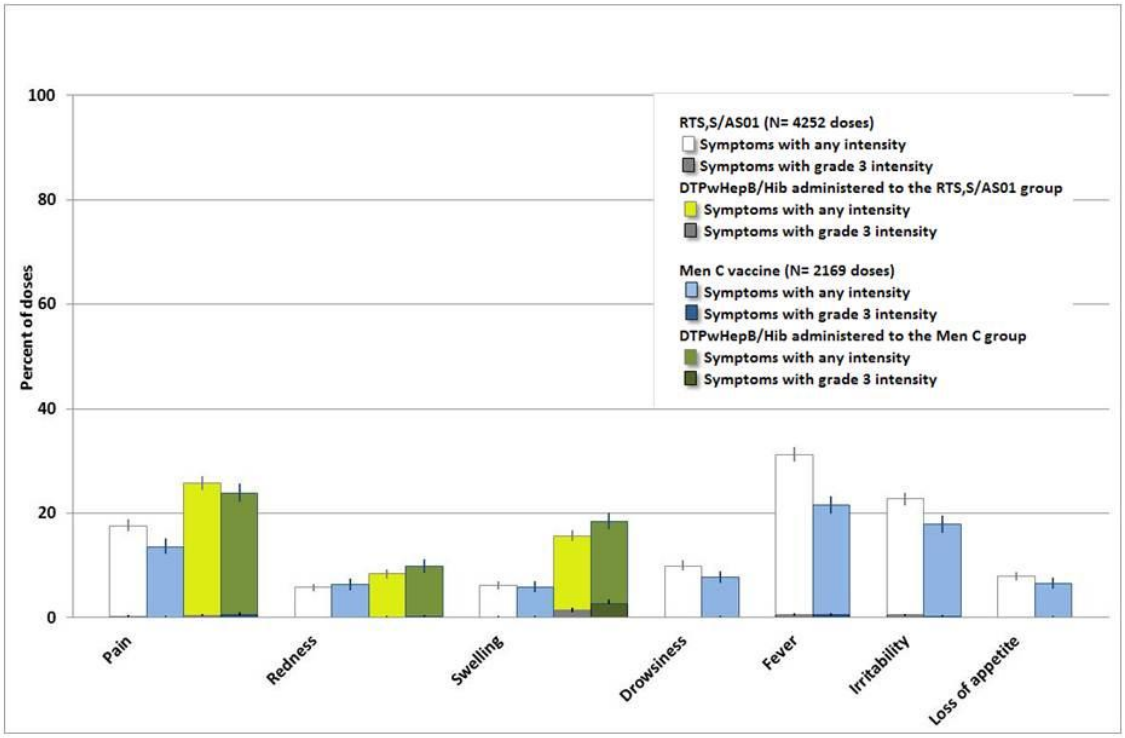


Figure 6.2: Incidence of solicited local and general adverse events reported during the 7-day post vaccination period following each dose in infants 6-12 weeks of age at enrolment (ITT, Malaria-055). Provided by GSK on request.

6.2 Serious adverse events

In the 5-17 month age category, from the first dose to the trial end (M0-SE), Serious Adverse Events (based on MEDRA preferred terms) were slightly less frequent in the RTS,S groups compared to the control group (R3R-24.2%, R3C-25.3%, C3C- 28.4%)(Table 6.1) and this remained so when malaria was excluded as an SAE (R3R-22.6%, R3C-23.7%, C3C- 26.4%). A similar number of deaths occurred in the RTS,S/AS01 groups compared with the control group (R3R-2.0%, R3C-1.7%, C3C- 1.5%). Of the 1472 reported SAEs in the RTS,S/AS01 groups (with and without the fourth dose), 12 were considered related to the vaccine by the investigator (7 seizures, 3 episodes of pyrexia, one episode of myositis, and one injection-site reaction); of the 846 SAEs in the control group, 1 was considered related to the vaccine by the investigator (seizure).

In the 6-12 week age category, from the first dose to the trial end (M0-SE), the frequency of SAEs reported in RTS,S/AS01 groups and the control group were similar (R3R-26.6%, R3C-27.6%, C3C-28.4%) (Table 6.1) and this remained so when malaria was excluded (R3R-25.8%, R3C-26.7%, C3C-27.1%). A similar number of deaths occurred in the RTS,S groups compared with the control group (proportion by group: R3R-2.3%, R3C-2.5%, C3C- 1.9%). Of the 1182 reported SAEs in the RTS,S groups, seven were considered related to the vaccine by the investigator (one injection site reaction,

two episodes of pyrexia, and four episodes febrile convulsions); of the 619 SAEs in the control group, three were considered related to the vaccine by the investigator (two episodes pyrexia and one anaphylactic reaction). The most common SAEs reported in both age categories (>1% of participants) were pneumonia, gastroenteritis, malaria, anaemia, febrile convulsion, and bronchiolitis: the frequency of none of these were statistically significantly different between the RTS,S/AS01 and control groups[26].

Table 6.1: SAEs from first vaccine dose to trial end[24].

5-17 Month Age Category	4-dose schedule (R3R) N=2976		3-dose schedule (R3C) N=2972		Control group (C3C) N=2974	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
At least one SAE	720	24.2 (22.7, 25.8)	752	25.3 (23.7, 26.9)	846	28.4 (27, 30.1)
At least one SAE excluding malaria	673	22.6 (21, 24.2)	704	23.7 (22, 25.3)	784	26.4 (25, 28.0)
At least one fatal SAE	61	2.0 (2, 2.6)	51	1.7 (1, 2.3)	46	1.5 (1, 2.1)
At least one related SAE	8	0.3 (0, 0.5)	4	0.1 (0, 0.3)	1	0.0 (0, 0.2)
Meningitis (any pathogen)	11	0.4 (0, 0.7)	10	0.3 (0, 0.6)	1	0.0 (0, 0.2)
6-12 Week Age Category	**4-dose schedule (R3R) N=2180**		**3-dose schedule (R3C) N=2178**		**Control group (C3C) N=2179**	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
At least one SAE	580	26.6 (25, 28.5)	602	27.6 (26, 29.6)	619	28.4 (27, 30.4)
At least one SAE excluding malaria	562	25.8 (24, 27.7)	582	26.7 (25, 28.6)	591	27.1 (25, 29.0)
At least one fatal SAE	51	2.3 (2, 3.1)	55	2.5 (2, 3.3)	42	1.9 (1, 2.6)
At least one related SAE	6	0.3 (0, 0.6)	1	0.0 (0, 0.3)	3	0.1 (0, 0.4)
Meningitis (any pathogen)	5	0.2 (0.1, 0.5)	7	0.3 (0.1, 0.7)	6	0.3 (0.1, 0.6)

6.3 Adverse events of specific interest

Febrile convulsion had been identified as an adverse event of specific interest in Phase 2 trials. Therefore the Phase 3 trial was designed with proactive collection of data to assess incidence of febrile convulsion within 7 days of vaccination according to the Brighton Collaboration Working Group consensus case definition.

An additional numerical imbalance was identified in the Phase 3 trials of RTS,S/AS01: an excess number of meningitis cases in participants in the 5-17 month age category and an increased risk of febrile seizures in the seven days following vaccination in the same age category. Excess of

meningitis events were not identified during Phase 2 studies. Note that 18 cases of meningitis occurred in the 6-12 week age category, evenly distributed between RTS,S and control groups. Twenty-two cases of meningitis were seen in the 5-17 month age category with an imbalance between RTS,S and control groups.

A list of potential immune mediated disorders were assessed and no imbalance was seen. Given the theoretical concerns associated with a new adjuvant, GACVS consulted with several African experts in autoimmunity, and given the lack of any concerning data from experimental models as well as the infeasibility of surveillance for paediatric autoimmune disorders, for which the epidemiology is largely undetermined, GACVS made no specific recommendation for post-licensure surveillance of auto-immune disorders[50] .

6.3.1 Febrile Seizures

In the 5-17 month age category, the incidence of generalized convulsions (Brighton Collaboration diagnostic certainty level of 1 to 3) within the seven days following any of the first three vaccinations was 1.04 per 1000 doses (95%CI 0.62, 1.64) in the RTS,S/AS01 groups (R3R + R3C) and 0.57 per 1000 doses (95%CI 0.19, 1.34) in the control group (C3C) (Table 6.2), a risk ratio of 1.8 (95%CI 0.6, 4.9). All children who experienced a convulsion reported a history of fever. Twelve of the 18 convulsions in the RTS,S/AS01 groups occurred within 3 days of vaccination; two of the five convulsions in the control group occurred within 3 days of vaccination. Febrile convulsions post-vaccination were not defined as a contraindication per protocol but it was left to the judgment of the investigator to withdraw a subject from further doses if it was considered that remaining in the study would be a risk for the subject.

Following a fourth dose of RTS,S, the incidence of generalized convulsions increased to 2.5 per 1000 doses (95%CI 0.9, 5.3) in the R3R group (Table 6.3). The incidence in the RTS,S group without a fourth dose of RTS,S/AS01 (R3C – received rabies vaccine as control vaccine at 18 months) was still 1.2 per 1000 doses (95%CI 0.3, 3.5), while the incidence in the control group (C3C) was 0.4 (95%CI 0.0, 2.3).

In the 6-12 week age category, the incidence of generalized convulsions within seven days following any of the first three doses was 0.16 per 1000 doses (95%CI 0.02, 0.57) in the RTS,S groups (R3R + R3C) and 0.47 per 1000 doses (95%CI 0.10, 1.37) in the control group (C3C) (Table 6.2), a risk ratio of 0.3 (95%CI 0.1, 2.0). Similarly to the 5-17 month age category, following a fourth dose of RTS,S (R3R group), the incidence was 2.2 per 1000 doses (95%CI 0.6, 5.6); the incidence rates in the R3C and C3C group remained low (Table 6.3).

Table 6.2: Rate of febrile seizures within seven days following any of the first three vaccinations (ITT population). Provided by GSK.

R3R+R3C			C3C			Relative Risk (95%CI)	Risk Difference (95%CI)
N	n	Rate/1000 doses (95%CI)	N	n	Rate/1000 doses (95%CI)		
5 – 17 month age category							
17306	18	1.04 (0.62,1.64)	8728	5	0.57 (0.19,1.34)	1.8 (0.7,4.9)	0.5 (-0.4,1.2)
6 – 12 week age category							
12739	2	0.16 (0.02, 0.57)	6403	3	0.47 (0.10,1.37)	0.3 (0.1, 2.0)	-0.3 (-1.2,0.2)

N: Number of doses; n: number of febrile seizures within 7 days post vaccination;

Table 6.3: Rate of febrile seizures within seven days following the fourth vaccination (ITT population). Provided by GSK and[24].

R3R			R3C			C3C				
N	n	Rate/1000 doses (95%CI)	N	n	Rate/1000 doses (95%CI)	N	n	Rate/1000 doses (95%CI)	Relative Risk (95%CI)	Risk Difference (95%CI)
5 – 17 month age category										
2447	6	2.5 (0.9,5.3)	2472	3	1.2 (0.3,3.5)	2473	1	0.4 (0.0,2.3)	6.1 (0.7,50.3)	2.0 (-0.3,5.0)
6 – 12 week age category										
1825	4	2.2 (0.6,5.6)	1837	0	0.0 (0.0,0.2)	1827	1	0.5 (0.0,3.0)	4.0 (0.5,35.8)	1.6 (-1.2,5.1)

N: Number of doses; n: number of febrile seizures within 7 days post vaccination; Relative Risk and Risk Difference are R3R vs C3C

6.3.2 Meningitis

In the 20 months following the first dose (M0-M20), meningitis was reported as an SAE in 16 of the 5949 5-17 month old participants in the RTS,S groups, and in 1 of the 2974 5-17 month old participants in the control group, a relative risk of 8.0 (95%CI 1.1, 60.3)[25]. In 11 of the meningitis cases (10 in the RTS,S groups and the only case in the control group), no pathogen was identified. Of those cases in the RTS,S groups in which a pathogen could be identified, four were meningococcus, one pneumococcus, and one *Haemophilus influenzae* (Table 6.4). There were six deaths among the meningitis cases (five in RTS,S groups and one in the control group). In the period after the fourth dose until the end of the trial (M21-SE), 2 additional cases occurred in the RTS,S group that received the fourth dose, 3 cases occurred in the RTS,S group that did not receive the fourth dose, and no additional cases occurred in the control group. Of these five cases in the RTS,S groups, two were *Haemophilus influenzae*, one was meningococcus, and one was tuberculosis (no pathogen was identified in one).

Table 6.4: Identified pathogen in the 22 meningitis cases through the duration of the trial in 5-17 month age category (ITT population). Provided by GSK.

Months 0-20	4-dose schedule (R3R) N=2976	3-dose schedule (R3C) N=2972	Control (C3C) N=2974
Meningitis	4	5	1
Meningitis haemophilus	1	0	0
Meningitis meningococcal	3	1	0
Meningitis pneumococcal	0	1	0
Meningitis viral	1	0	0
Meningitis total (17 cases)	**9**	**7**	**1**
Months 21- SE	**4-dose schedule (R3R) N=2681**	**3-dose schedule (R3C) N=2719**	**Control (C3C) N=2702**
Meningitis	1*	0	0
Meningitis haemophilus	0	2	0
Meningitis meningococcal	0	1	0
Meningitis tuberculous	1	0	0
Meningitis total (5 cases)	**2**	**3**	**0**

*1 subject reported the occurrence of meningitis after month 21 in the R3R group but did not receive the fourth dose.

Most sites reported only one or two cases of meningitis during the 48 month follow up period in this age group (Figure 6.3). However, two sites outside of the Meningitis Belt (Lilongwe, Malawi, and Kombewa, Kenya) reported nine and five cases, respectively (64% of total reported in the 5-17 month age category).

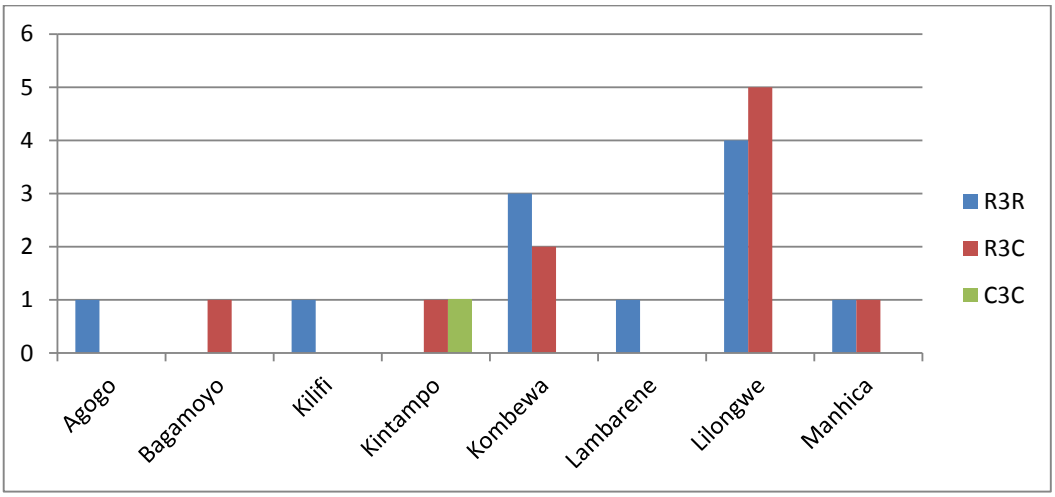
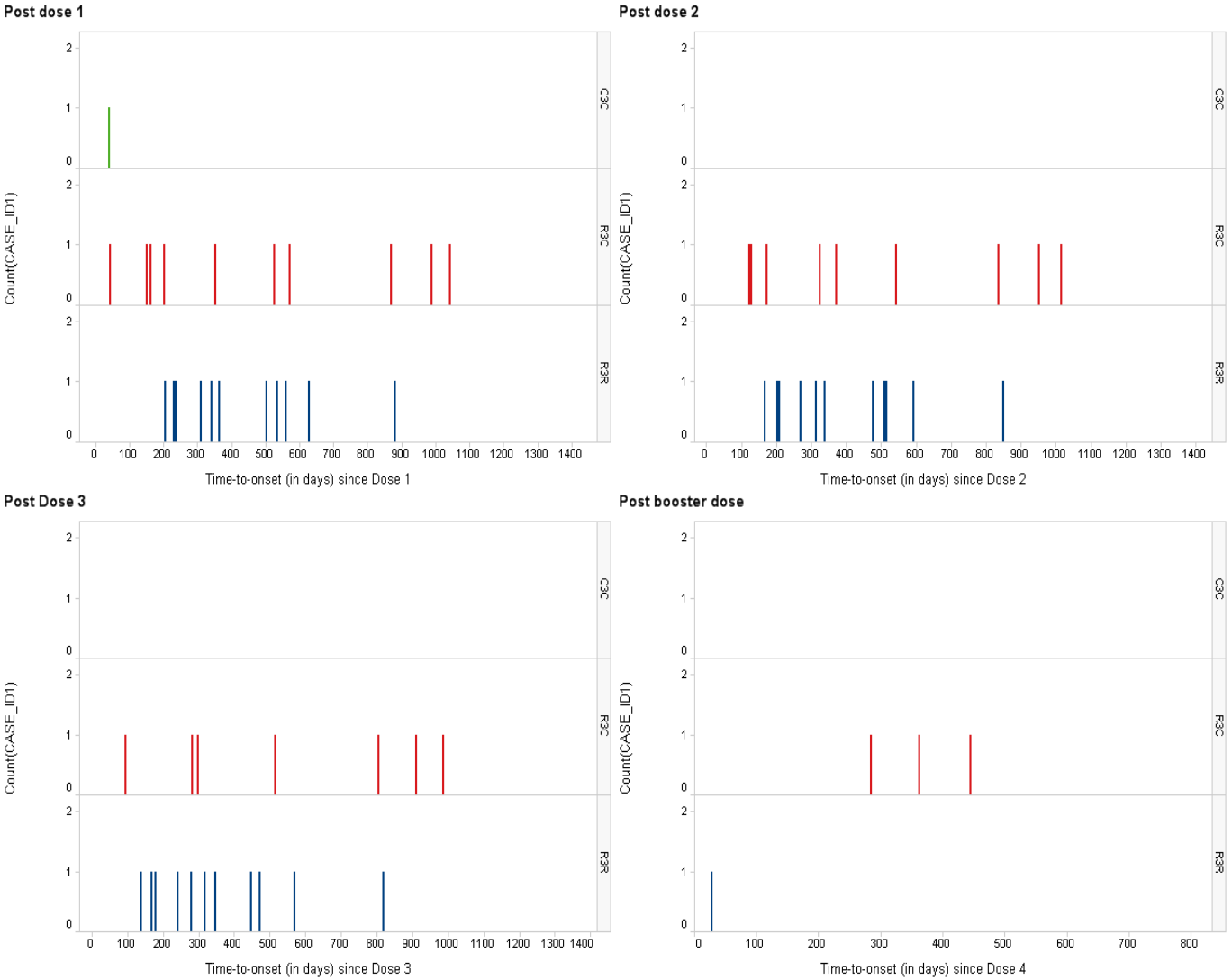


Figure 6.3: Distribution of the 22 meningitis cases in the 5-17 month age category by trial site throughout the complete study period (median 48 months follow-up from dose 1). Provided by GSK.

a) 5-17 months age category (M0-SE; median 48 months follow-up from dose 1)



b) 6-12 weeks age category (M0-SE; median 38 months follow-up from dose 1)

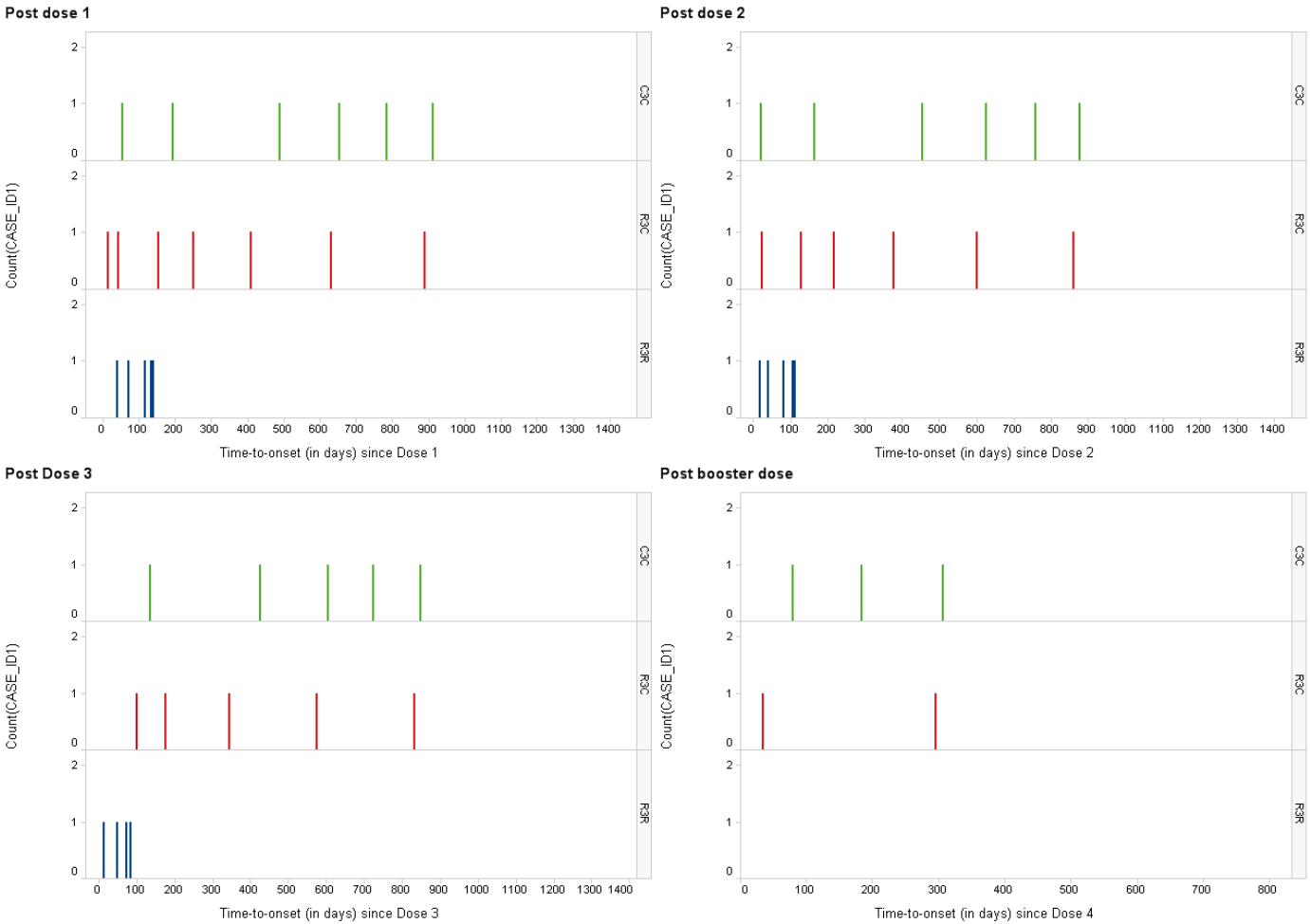


Figure 6.4: Time to onset distribution of meningitis cases following vaccination (any dose), by study group (ITT population). a) 5-17 month age category, b) 6-12 week age category[24].

GACVS reviewed the possible association and determined there was no evidence of temporal clustering in relation to the time of vaccination (Figure 6.4). GACVS ultimately determined meningitis should therefore be regarded as a potential signal which requires further assessment post-licensure[50].

Among participants in the 6-12 week age category, in the 20 months following the first dose (M0-M20), meningitis was reported as an SAE in nine of the 4358 participants in the RTS,S groups, and in three of the 2179 participants in the control group, a relative risk of 1.50 (95%CI 0.41, 5.55). In five of the meningitis cases (three in the RTS,S groups and two in the control group), no pathogen could be identified. Of the remaining seven cases for which a pathogen could be identified, four were pneumococcus and three were salmonella. There were four deaths among the meningitis cases (two in the RTS,S groups and two in the control group). From months 21 to the trial end (M21-SE; median 18 months of follow-up from fourth dose to study end), two additional cases occurred in the RTS,S group that did not receive the fourth dose (one without a pathogen identified, one *Haemophilus influenzae*), three additional cases occurred in the control group (one without a pathogen identified, one *Haemophilus influenzae* and one pneumococcus), and no additional cases occurred in the RTS,S group that received the fourth dose. Of the three *Haemophilus influenzae* cases in the RTS,S group, one participant had documented Hib vaccination, one had no documentation of Hib vaccination, and for one Hib vaccine status could not be determined. In the totality of the trial (M0-SE), the number of meningitis cases in the RTS,S/AS01 groups were similar to those in the control group (R3R: 5, R3C: 7, C3C: 6).

The sponsor coordinated an expert chart review of the meningitis cases. Based on this review, the number of confirmed meningitis cases was reduced (Table 6.5); however, the imbalance between the RTS,S groups and the control group remained in the 5-17 month age group.

Table 6.5: Determination of meningitis cases following expert review in the 5-17 month and 6-12 week age groups. Provided by GSK on request.

5-17 month age group				6-12 weeks age group			
After 3 doses	**R3R**	**R3C**	**C3C**	**After 3 doses**	**R3R**	**R3C**	**C3C**
Confirmed meningitis	5	4	0	Confirmed meningitis	3	4	1
No meningitis	4	2	2	No meningitis	2	2	3
Undetermined	4	2	3	Undetermined	2	0	0
After fourth dose	**R3R**	**R3C**	**C3C**	**After fourth dose**	**R3R**	**R3C**	**C3C**
Confirmed meningitis	1	2	0	Confirmed meningitis	0	1	2
No meningitis	1	2	0	No meningitis	0	0	1
Undetermined	1	0	0	Undetermined	0	1	0

6.4 Summary of safety profile of RTS,S/AS vaccines from Phase 2 studies

Phase 2 studies in children did not identify any concerning safety signals, either for AS01-adjuvanted vaccines[52-55] or for AS02-adjuvanted vaccines[45, 52, 53, 56-59], including when co-administered with EPI vaccines. In a pooled analysis of Phase 2 studies of AS01 and AS02-adjuvanted vaccines, including data on 2,981 infants and children, a similar proportion of participants in the RTS,S/AS and control groups experienced at least one adverse event within 30 days of vaccination (75.0% and 70.2%, respectively)[60]. Upper respiratory tract infections, malaria, pneumonia, and gastroenteritis were reported most frequently. Fewer non-malaria serious adverse events (SAEs) were reported in the RTS,S group (14.9%) compared to the control group (17.7%)(RR=0.81, 95%CI 0.69, 0.95). Five recipients in the Phase 2 trials experienced a seizure within 7 days after RTS,S, which was a similar proportion to that of controls (0.3% of participants). In this pooled analysis, no one SAE occurred at a significantly higher frequency in RTS,S-recipients compared to control vaccine-recipients, including febrile convulsions. Fatal SAEs occurred in 0.7% of RTS,S-recipients, compared to 1.5% of control participants (RR=0.49, 95%CI 0.24, 0.94).

Table 6.6: Meningitis cases reported in Phase II or Phase III studies (excluding Malaria-055). Provided by GSK on request.

Study	Site	Age of case	Gender	Treatment group	Meddra term	Last dose	Time since last dose
Mal-026	Mozambique	3Y	Male	RTS,S/AS02	Meningitis, pyrexia, musculoskeletal stiffness, excoriation	3	299 days
Mal-040	Tanzania	4M	Male	RTS,S/AS02, Tetract-hib	Meningitis viral, pyrexia, fontanelle bulging	2	17 days
Mal-040	Tanzania	4M	Male	Control	Pneumonia, meningitis viral, pyrexia, vomiting, decreased appetite, diarrhoea, crying, dyspnoea, irritability, crepitations, wheezing	2	25 days
		7M*			Pneumonia, meningitis viral, pyrexia, rhinorrhoea, cough, fontanelle bulging, crepitations*	3*	79 days*
Mal-044	Kenya	35Y	Male	Control	Meningitis cryptococcal, HIV infection, headache, photophobia, neck pain, oral candidiasis, asthenia, pulmonary tuberculosis	3	149 days
Mal-044	Kenya	36Y	Male	RTS,S/AS01	Meningitis, HIV infection, hallucination, pyrexia	3	150 days
Mal-044	Kenya	27Y	Female	Control	Meningitis, HIV infection, headache, neck pain, photophobia, pyrexia, cough, oropharyngeal pain, malaise, pallor, lymphadenopathy, pelvic inflammatory disease	3	196 days
Mal-057	Malawi	1M	Male	Control	Pneumococcal sepsis, meningitis pneumococcal	1	8 days
Mal-057	Malawi	7D	Male	RTS,S/AS01, BCG, OPV	Meningitis neonatal, pneumonia	1	7 days
Mal-058	Kenya	3M	Male	Control	Pneumonia, febrile convulsion, sepsis, meningitis haemophilus	1	28 days
Mal-063	Burkina Faso	28M	Female	RTS,S/AS01, OPV, Rotavirus, DTPa+Hib, PCV	Sepsis, anaemia, meningitis streptococcal	2	763 days

*Same patient as preceding row

7. Vaccine Impact

7.1 Estimated cases averted due to RTS,S/AS01

The estimated number of cases averted by RTS,S/AS01 in the trial was the sum of differences in the number of cases between the control and the RTS,S/AS01 groups, expressed per 1000 participants vaccinated.

7.1.1 Cases of clinical malaria averted

In the 18 months following the first three doses (M2.5-M20), 721 cases of clinical malaria were estimated to be averted per 1000 vaccinees (95%CI 591, 847) in the 5-17 month age category compared to 296 (95%CI 179, 413) in the 6-12 week age category (Table 7.1). Among 5-17 month old participants who did receive a fourth dose of RTS,S (R3R), the estimated number of cases of clinical malaria averted by study month 33 (M2.5-M32) and by study end (M2.5-SE) were 1097 (95%CI 894, 1295) and 1239 (95%CI 908, 1552) per 1000 vaccinees. In this same group (R3R) in the 6-12 month age category, the estimated number of cases of clinical malaria averted by study month 33 (M2.5-M32) and by study end (M2.5-SE) were 583 (95%CI 374, 798) and 665 (95%CI 407, 922) per 1000 vaccinees, respectively.

Table 7.1: Cumulative cases of clinical malaria averted per 1000 vaccinees and 95% confidence interval (primary case definition) at months 21, 33, and 48 (ATP population). Provided by GSK on request.

Study month	5-17 month age category		6-12 week age category	
	3-dose schedule (R3C)	4-dose schedule (R3R)	3-dose schedule (R3C)	4-dose schedule (R3R)
M2.5-M20	721 (591, 847)		296 (179, 413)	
M2.5-M32	855 (653, 1053)	1097 (894, 1295)	336 (103, 558)	583 (374, 798)
M2.5-SE	860 (534, 1166)	1239 (908, 1552)	368 (73, 638)	665 (407, 922)

The greatest number of cases averted per 1000 vaccinees were at sites with the highest level of transmission (Figure 7.1). The impact of a fourth dose of RTS,S was largest in these sites as well.

a) 5-17 month age categories **b) 6-12 week age category**

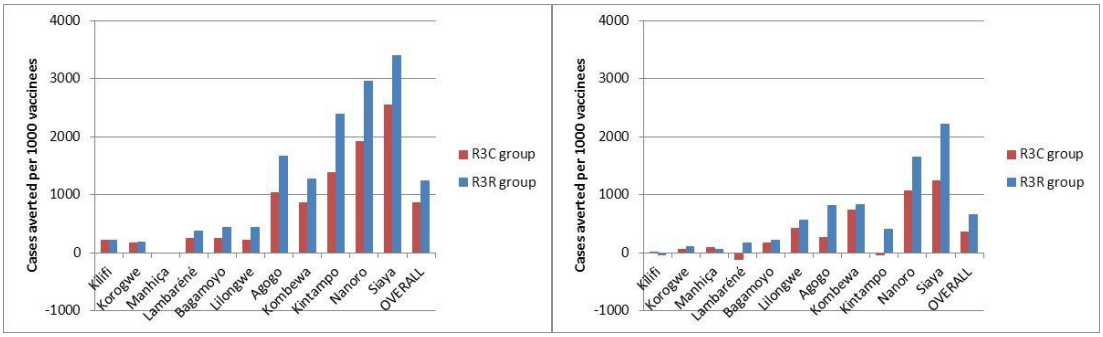


Figure 7.1: Cases of clinical malaria averted per 1000 vaccinees at each site for M2.5-SE (ATP population, primary case definition). Sites are ordered based on incidence of clinical malaria (secondary case definition) measured in control infants 6-12 weeks of age at enrolment during 12 months of follow up. Provided by GSK on request.

7.1.2 Cases of severe malaria averted

At 18 months following the first three doses (study month 21), 16 cases of severe malaria were estimated to be averted per 1000 vaccinees (95%CI 5, 27) in the 5-17 months group compared to 4 (95%CI -8, 16) in the 6-12 weeks age group (Table 7.2). Among 5-17 month old participants who did receive a fourth dose of RTS,S (R3R), the estimated number of cases of severe malaria averted at study month 33 and at study end were 15 (95%CI 1, 29) and 13 (95%CI -3, 29) per 1000 vaccinees. In this same group (R3R) in the 6-12 months group, the estimated number of cases of severe malaria averted at study month 33 and at study end were 12 (95%CI -4, 28) and 13 (95%CI -4, 30) per 1000 vaccinees.

Table 7.2: Cumulative cases of severe malaria averted per 1000 vaccinees and 95% confidence interval (primary case definition) at months 21, 33, and study end (ATP population). Provided by GSK on request.

Study month	5-17 month age category		6-12 week age category	
	3-dose schedule (R3C)	4-dose schedule (R3R)	3-dose schedule (R3C)	4-dose schedule (R3R)
M2.5-M20	16 (5, 27)		4 (-8, 16)	
M2.5-M32	7 (-9, 23)	15 (1, 29)	4 (-13, 22)	12 (-4, 28)
M2.5-SE	0 (-18, 17)	13 (-3, 29)	6 (-12, 26)	13 (-4, 30)

7.2 Estimated vaccine impact using mathematical modelling

In 2010, WHO initiated an extensive comparison exercise of four mathematical models (Imperial College, Swiss Tropical and Public Health Institute, Institute for Disease Modelling and GlaxoSmithKline) to estimate the public health impact and cost-effectiveness of RTS,S/AS01 in a range of scenarios. The current status of this work and outcomes so far are reported here. Aggregate site-specific clinical efficacy and disease incidence data from the phase III trial were made available to the modelling groups before publication. This data was used for parameterising

the vaccine impact component of the models. Additionally, Imperial College had access to individual participant data including antibody levels from the trial to inform their models. For population predictions, the modelling groups were asked to consider a 6, 7.5, 9 months schedule with and without a fourth dose at 27 months (18 months after dose 3). Following a recommendation from the WHO JTEG/IVIR-AC subgroup overseeing the process, the time horizon for impact evaluation was set at 15 years. The models explore RTS,S/AS01 impact under a set of harmonised assumptions, including demography, access to effective malaria treatment, and a range of transmission intensities (described by Plasmodium falciparum parasite prevalence in 2-10 year olds, $PfPR_{2-10}$). Incremental cost-effectiveness ratios (ICERs) were calculated using a single set of agreed costs and a harmonised methodology to enable comparative outputs from the four models. As a further step, the impact of RTS,S/AS01 in six African countries, with varied malaria transmission intensity and seasonality, was assessed under largely non-harmonised conditions (except for costing, vaccine coverage, demographics and and $PfPR_{2-10}$ estimates provided by the Malaria Atlas Project).

Although not assessed directly in the trial, RTS,S mode of action is protection against malaria infection and vaccine impact is therefore modelled as efficacy against infection in all the models (the proportion of blood-stage infections prevented). All four models demonstrated good fits to the clinical efficacy and consistently estimated RTS,S/AS01 to have high initial efficacy against infection in children vaccinated between 5 and 17 months of age immediately following the third dose, with initial efficacy ranging from 75% to 95% against infection. This efficacy is estimated to wane rapidly in the first 12 months. All models predict low efficacy beyond 12 months but with variation in the rate of decline over time due to different assumptions regarding the shape of the waning profile and different assumptions in translating efficacy against infection into protection against clinical malaria. In all four models the fourth dose is found to increase protection against infection to a level that is lower than the initial protection. All four models predict a faster decay in vaccine efficacy against clinical disease at higher transmission levels due to the combined effects of waning of vaccine efficacy against infection and different rates of acquisition of natural immunity in the vaccine and control arms.

A comparison of the models in the absence of vaccination showed some differences in baseline disease burden which are largely attributable to differences in case definition and assumptions underlying immunity acquisition. Although largely consistent in age patterns of underlying burden with transmission intensity, with differences in magnitudes related to case definitions and data used to a parameterise the models, at very high transmission settings (> 65% prevalence) there is divergence between the models in the predicted pattern of burden. This divergence impacts the estimate of cases and deaths available for a vaccine to avert. In very high transmission settings some modelling groups predict that a reduction in transmission may temporarily and marginally increase the number of cases and subsequent deaths due to a change in the age distribution of malaria deaths. Other groups predict that a reduction in transmission intensity would always be associated with either no change in malaria deaths (because the exposure is so high in high transmission settings) or a reduction in malaria deaths. The data to support either prediction are limited

In all models vaccination is predicted to lead to an age shift in malaria incidence. In high prevalence

settings this is predicted to occur sooner than moderate or low transmission settings. The age-shift is predicted to occur sooner for more severe disease endpoints compared to uncomplicated cases. Given the rapid waning of protection of RTS,S in the absence of a fourth dose, the age shift is predicted to occur soon after vaccine introduction. This predicted effect is general to any preventive malaria intervention, and indeed a more pronounced age shift is predicted for seasonal malaria chemoprevention.

The two models that were designed to include indirect effects of vaccination predict little herd protection from RTS,S/AS01 vaccination when introduction is limited to this age group and transmission remains moderate, given the role of infected individuals of all ages in contributing to transmission. One of the two models predicts a substantial indirect effect at low transmission ($PfPR_{2-10} < 5\%$).

The JTEG/IVIR-AC subgroup noted that in the pivotal Phase 3 trial a similar cumulative incidence of severe malaria was reported in the arm that received RTS,S/AS01 without the fourth dose compared to the control arm. This could be interpreted as in apparent conflict with the predictions of the models that RTS,S will have a small but consistently overall positive impact against severe malaria and malaria-related mortality both with and without a fourth dose (even with an age shift). Reasons for such apparent discrepancies include that the efficacy against severe malaria when calculated from clinical trial data is strongly biased towards high intensity transmission settings and that confidence bounds around this estimate span the impact that is predicted by the models. Further it was noted that efficacy estimates against malaria hospitalization and all-cause hospitalization are positive in the ITT analyses for the Phase 3 trial, even without a fourth dose.

In the analysis of six anonymised African countries, transmission intensity was found to be a reasonable predictor of public health impact and cost-effectiveness (Figure 7.2). Results aligned closely with those under harmonised assumptions at the respective transmission, although where differences were evident it was due to model country assumptions concerning transmission heterogeneity and health system factors such as high access to effective antimalarial treatment.

All models predict a substantial additional public health impact of RTS,S in settings with $PfPR_{2-10}$ between 10% and 65% (Table 7.3). Below 10% $PfPR_{2-10}$ the models predict smaller positive impacts down to 5% $PfPR_{2-10}$. Furthermore the predictions diverge between the models below 10%. In the moderate to high transmission settings, median predictions range from 200 to 700 deaths averted per 100,000 vaccinees in a schedule with a fourth dose, and 10% to 28% of all malaria deaths averted in vaccinated children less than five years old. The median of the four model predictions for the costs of routine RTS,S vaccination in a schedule including a fourth dose is 82 USD per DALY averted (assuming 5 USD vaccine costs per dose) in settings with $PfPR_{2-10}$ between 10% and 65% and costs do not exceed 260 USD per DALY averted for $PfPR_{2-10}$ at transmission levels down to 5% PfPR2-10. A 3-dose series without a fourth dose is predicted to be associated with similar costs per DALY averted.

Recently updated MAP (Malaria Atlas Project, the most extensive effort to map malaria parasite prevalence in Africa) estimates show that in many African regions the transmission of *Plasmodium falciparum* malaria has been reduced to $PfPR_{2-10}$ levels below 10% in recent years (see Figure 2.1). In these low transmission settings RTS,S/AS01 is predicted to be less cost effective than in settings with

more intense malaria transmission. Differences between model estimates are also larger at $PfPR_{2-10}$ levels below 10%.

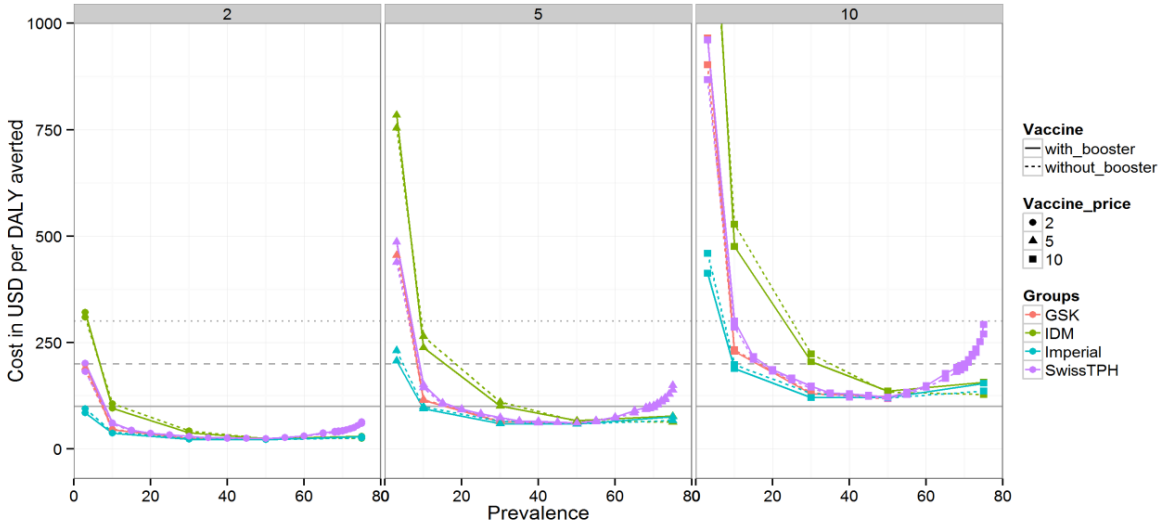


Figure 7.2: Cost (USD) per DALY (median) over 15 years of use of RTS,S via 6-9 month immunisation schedule with and without fourth dose. Columns indicate an assumed vaccine price of either $2, $5, or $10 and colour indicates models (green EMOD DTK (IDM), red GSK, blue Imperial, purple OpenMalaria (SwissTPH)). An immunisation schedule of three doses between 6 and 9 months of age is indicated by dashed lines, and a schedule including the fourth dose by solid lines. Similar ICER estimates were obtained for the schedules with and without a fourth dose because the additional public health benefit of the 4-dose schedule is offset by the incremental cost of implementing the additional dose. The grey reference lines correspond to $100, $200 and $300 per DALY averted by solid, dashed and dotted lines respectively. The cost per DALY averted for the 6-9 month immunisation schedule with 4 doses is the average cost-effectiveness ratio, and not incremental to three-dose schedule. Uncertainty estimates that surround the model predictions are omitted for readability, but overlap one another.

In addition to the harmonised analysis, some individual group predictions compared the cost-effectiveness of RTS,S/AS01 and other malaria interventions. Considered as a package of interventions, RTS,S/AS01 at $5 a dose is likely to be less cost effective than the use of either bed nets or SMC (where applicable) at reducing incidence in children under 5 years up to usage levels around 60-80% for LLIN. Above 60-80% LLIN usage, the costs of achieving greater coverage may become increasingly non-linear with diminishing returns of increased usage for increasing disbursements. This work was not harmonised amongst the groups and further updates on this work would be desirable.

In summary, despite using different model structures and different data sources to supplement the RTS,S/AS01 phase III trial data, estimates of the public health impact and cost-effectiveness of the RTS,S vaccine delivered at 6-9 months of age were consistent for a wide range of transmission settings and indicate a significant public health impact and high level of cost-effectiveness in those settings if implemented after achieving high LLIN usage. Thus, from the health economic perspective, access to LLINs, RDTs and ACT drug courses should be prioritized. In settings where these have been achieved, and where transmission remains above 5-10% $PfPR_{2-10}$ RTS,S/AS01 may be a reasonable

use of resources from both malaria control and immunization perspectives. Given that malaria transmission varies greatly within a country, this also implies, that from a health economic perspective malaria vaccine introduction decisions may need to be made at a subnational level.

From the health economic perspective, in areas of west Africa that are currently recommended by WHO for SMC implementation, it would be more cost-effective to implement SMC first (in addition to LLIN, access to RDT and ACT), and then reassess whether the remaining disease burden justifies consideration of RTS,S/AS01 introduction.

For a comparative review of the cost-effectiveness of malaria vaccine interventions, see *Comparison of the cost effectiveness of LLINs, SMC, the RTS,S vaccine and RTS,S plus IPTi in African settings* (Winskill *et al*, unpublished).

Table 7.3: Estimated deaths per 100,000 fully vaccinated children (FVC) and Incremental Cost Effectiveness Ratios (ICERs) at $5 (USD) per dose. Estimates are presented as median and ranges across the models in parentheses.

Outcome	$Pf Pr_{2-10}$ 10% to 65%	$Pf Pr_{2-10}$ 30% to 50%	$Pf Pr_{2-10}$ 10%	$Pf Pr_{2-10}$ 7.5%	$Pf Pr_{2-10}$ 5%
3-dose schedule					
Deaths averted per 100,000 FVC	394 (127-708)	451 (287-708)	205 (127-251)	146 (106-225)	100 (74-178)
ICER at $5 dose	$80 ($44-279)	$65 ($49-82)	$139 ($117-279)	$189 ($130-334)	$283 ($159-500)
4-dose schedule					
Deaths averted per 100,000 FVC	484 (189-859)	534 (406-859)	229.5 (189-344)	162.5 (147-297)	106.5 (102-249)
ICER at $5 dose	$87 ($48-244)	$73.5 ($49-96)	$158 ($105-244)	$214 ($120-312)	$316 ($143-462)
Incremental impact					
Proportion of additional deaths averted per 100,000 FVC[a]	22% (3%-49%)	22% (6%-41%)	20% (3%-49%)	28% (-2%-42%)	33% (-8%-40%)

[a]by 4-dose schedule compared to 3-dose schedule

7.2.1 Cost-effectiveness of other "recent" vaccines

Summary figures for the cost-effectiveness of other vaccines in Gavi-eligible countries are provided for comparison. Cost-effectiveness has been estimated to be about $42 ($31-$64) per DALY averted for rotavirus vaccine, priced at $1.50-7.50 per dose[61], $100 per DALY averted for 7-valent pneumococcal conjugate vaccine, priced on $5 per dose[62], and $400 ($200-$500) per DALY averted for HPV vaccine, based on $25 per vaccinated girl[63]. However, care should be taken when making inter-vaccine comparisons as the cost-effectiveness of each vaccine is evaluated using different models and hence is based on different modelling assumptions.

8. Additional Scientific Considerations

8.1 Herd protection/effect on transmission

In principle, pre-erythrocytic vaccines such as RTS,S/AS01 could have a beneficial effect on malaria parasite transmission through blocking the malaria life-cycle at the point of human infection from mosquitoes. However in order for substantial transmission effects to occur, coverage with the vaccine would need to be high in the group that transmits malaria to mosquitoes, including older children and adults. Unlike for some vaccine-preventable diseases, it is known that adolescents and adults contribute significantly to onward transmission of malaria parasites. While older children and adults suffer little severe morbidity in a population under stable and moderate to high transmission, this age group still contributes significantly to malaria parasite transmission. The degree of vaccine efficacy would also be very important for transmission effects. Given the relatively modest efficacy of RTS,S/AS01 and the fact that only a small proportion of the infectious reservoir (i.e. young children) are considered for vaccination it is not expected that there will be any substantial transmission reduction effect from paediatric vaccination with RTS,S/AS01. Malaria parasite transmission models do predict that RTS,S/AS01 could have substantial transmission effects when used in a mass immunization approach in areas with fairly low malaria transmission (entomological inoculation rate less than 10). However a first step before any policy recommendation for such a use would be safety and proof-of-concept of efficacy against infection with RTS,S/AS01 in a wide age range from childhood to adolescents and young adults. As there are no clinical trial data to support this use, the potential indication is not discussed further here.

8.2 Safety and efficacy in special populations

A trial in Kenya evaluated safety and immunogenicity of three doses of RTS,S/AS01 (administered on a 0/1/2 month schedule) in 200 HIV-infected children from 6 weeks to 17 months of age (80% in 5-17 month age range; HIV stage I and II) (Data provided by GSK on request). Children were randomized 1:1 to receive RTS,S/AS01 or a control vaccine (rabies). EPI vaccines were given at least 7 days apart from RTS,S/AS01. At the time of the first vaccine dose, 92% of participants were taking co-trimoxazole; and by one month following dose 3, 97% were on anti-retroviral therapy (up from 73% at the initiation of the trial).

RTS,S/AS01 was immunogenic among the 99 participants who received the experimental vaccine (anti-CS antibody GMC of 329 EU/mL at 1 month post dose 3). Vaccine efficacy against clinical malaria was estimated over 12 months post dose 3 and was 37.2% (95% CI: -26.5%, 68.8%, ATP cohort). During this observation period, one episode of severe malaria occurred in the RTS,S/AS01 group compared to eight episodes in the rabies vaccine group.

In the first 30 days post vaccination, at least 1 SAE was reported in 20.2% (95% CI: 12.8 to 29.5) of subjects in the RTS,S/AS01 group and 11.9% (95% CI: 6.3 to 19.8) of subjects in the rabies vaccine group. During this time period, there were 13 cases of pneumonia in the RTS,S group and 5 cases in the control group (Table 8.1). By 14 months following the first dose, there were 23 total pneumonia cases in each group. During these 14 months, the proportion of participants reporting at least one SAE was similar in the RTS,S and control groups at 41.4% (95% CI: 31.6, 51.8) in the RTS,S/AS01

group and 36.6% (95% CI: 27.3, 46.8) in the rabies vaccine group. The most common SAEs reported were pneumonia, gastroenteritis, and febrile convulsions. Of nine fatal SAEs, five occurred in the RTS,S group and 4 in the rabies vaccine group, none of which were judged to be related to vaccination. Unsolicited AEs occurred in a similar proportion of subjects in both groups in the 30 days post-vaccination (99%). There was no significant difference between growth parameters.

Table 8.1: Most frequent SAEs within 30 days and 14 months following the first dose by treatment group. Provided by GSK on request.

	Within 30 days		Within 14 months	
SAE	RTS,S/AS01 (N=99)	Control (rabies) (N=101)	RTS,S/AS01 (N=99)	Control (rabies) (N=101)
At least one SAE	20	12	41	37
Pneumonia	13	5	23	23
Gastroenteritis	8	7	21	19
Febrile convulsions	6	3	10	13

There was also no significant difference between the RTS,S and rabies vaccine groups on $CD4^+$ T-cell percentage, $CD4^+$ T-cell absolute counts and WHO AIDS clinical classification. There was no difference in HIV viral load reduction between the two groups by 12 months post dose 3, though there was a trend for a more marked reduction in HIV viral load at 1 and 6 months post dose 3 in the rabies group (not statistically significant).

Reactogenicity among HIV-infected participants was compared to that observed in the Phase 3 trial. There was a trend for higher reactogenicity among HIV-infected participants (Table 8.2).

Table 8.2: Reactogenicity of RTS,S/AS01 in HIV-infected participants in two trials. Provided by GSK.

	Special study Malaria-058 (HIV-infected)		Phase 3 Malaria-055 (5-17 months)	
	RTS,S/AS01	Control	RTS,S/AS01	Control
Pain	18.1%	6.0%	12.4%	5.8%
Redness	6.9%	3.0%	3.1%	2.7%
Swelling	10.8%	4.4%	9.6%	7.6%
Drowsiness	11.1%	5.0%	6.6%	4.4%
Fever	47.1%	18.8%	31.1%	13.4%
Irritability	25.3%	10.7%	11.5%	5.3%
Loss of appetite	17.7%	8.7%	11.4%	7.4%

Within the pivotal Phase 3 trial there was no systematic screening for HIV in all participants. Some children were tested on clinical grounds and through this process, there were 51, 54, and 48 HIV-infected participants identified in the R3R, R3C, and C3C groups, respectively. By 32 months post dose 3, 14 had died from each group. Similar proportions experienced at least one SAE by visit 32 (excluding malaria): 92.2% (95%CI 81.1, 97.8) in the R3R group, 83.3% (95%CI 70.7, 92.1) in the R3C group, and 87.5% in the C3C group (95%CI 74.8, 95.3). Febrile convulsions occurred in 11.8% (95%CI 4.4, 23.9), 9.3% (95%CI 3.1, 20.3), and 6.3% (95%CI 1.3, 17.2) in the R3R, R3C, and C3C groups, respectively.

9. Programmatic Considerations

WHO conducted an assessment of programmatic considerations for introduction of RTS,S/AS01 with a first dose at 5 months. This assessment may be found in the document *"Programmatic Options for Implementation of RTS,S Malaria Vaccination Schedule"*.

9.1 Co-administration with routine infant vaccines

RTS,S/AS01 has been evaluated together with EPI vaccines in a randomized, open-label, Phase 2 trial in Ghana, Tanzania, and Gabon. Five-hundred eleven children were randomized to receive RTS,S/AS01 on a 0/1/2 month schedule or a 0/1/7 month schedule. DTwP,/HepB/Hib+OPV was co-administered at visits 0/1/2, and measles and yellow fever was administered at month 7.

The safety results were consistent with other Phase 2 trials. Serious adverse events occurred in 33.5% of participants in the 0/1/2 RTS,S administration schedule (95%CI 26.5, 41.2), 27.6% in the 0/1/7 RTS,S administration schedule (95%CI 21.1, 35.0), and 28.7% in the control group (95%CI 22.0, 36.1). No serious adverse event was judged to be related to vaccination[64]. Non-inferiority criteria were met for all EPI antigens (diphtheria, tetanus, and polio) with the exception of polio 3, for which antibody titres were lower[55]. Of note, the rate of response to polio 3 was comparable between the RTS,S co-administration group and the non-RTS,S group when the titres at screening were taken into account. OPV responses were retested in the Phase 3 trial and non-inferiority criteria were met. Anti-CS GMTs were lower one month following the third dose of RTS,S co-administered with measles at month 7 (107.8 EU/mL) than one month following the third dose of RTS,S co-administered with DTwP,/HepB/Hib+OPV at month 2 (190.3 EU/mL).

Vaccine efficacy was assessed at 19 months[64]. In the 0/1/2 month RTS,S administration group, vaccine efficacy against all clinical episodes from 16.5 months follow up was 60.6% (95%CI 33.3, 76.7). There was no difference in vaccine efficacy in the 0/1/2 or 0/1/7 RTS,S administration schedules in the 1 year after dose 3; vaccine efficacy was estimated as 58.7% (95%CI 30.7, 75.3) and 58.7% (95%CI 32.0, 74.9), respectively.

In another co-administration trial in Ghana, RTS,S/AS01 was co-administered with EPI antigens, including pneumococcal conjugate vaccine (PCV10) and rotavirus vaccine (Data provided by GSK on request). Non- inferiority criteria were met for pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 19F and 23F, but not for 18C, which is a minor serotype in Africa.

Non-inferiority was also demonstrated for co-administration with rotavirus vaccine. Regarding anti-CS antibodies, anti-CS GMT was 205.5 EU/ml when RTS,S/AS01 was co-administered with the basic EPI vaccines (DTPa/Hib + OPV) alone, 188.5 EU/ml when RTS,S/AS01 was co-administered with basic EPI and rotavirus vaccine, and 142.2 EU/ml when RTS,S/AS01 was co-administered with basic EPI and pneumococcal conjugate vaccine. Of note, during a 7-day follow up period after each vaccine dose, fever occurred in 26.4% of participants in the PCV10/RTS,S/EPI group, in 13.7% of participants in the rotavirus/RTS,S/EPI group, and in 14.2% in the RTS,S/EPI group. Without RTS,S, rates of fever were 13.9% in the PCV/HepB/EPI group and 7.8% in the rotavirus/HepB/EPI group. No febrile convulsions were reported.

RTS,S/AS01 was also co-administered with DTPwHepB/Hib+OPV in the 6-12 week group in the Phase 3 trial, contributing to the safety database for co-administration.

10. Overall JTEG assessment and summary of key recommendations for SAGE/MPAC consideration

The first malaria vaccine has been successfully evaluated in a Phase 3 trial. The trial was executed to a very high quality and met its primary endpoint. In the trial, the overall benefit-risk was positive. This vaccine represents a potentially important tool to decrease malaria morbidity and mortality when used together with existing malaria interventions.

Because the trial was executed with high adherence to the protocol, replicating the results with respect to timely vaccination and coverage with a fourth dose may be difficult when the vaccine is administered in the context of a routine immunization program. The trial was also done in the context of very good access to health care. It is necessary to ensure a positive benefit-risk in the context of large scale deployment and routine use.

10.1 JTEG assessment of vaccine efficacy and vaccine schedule, including rebound

Rationale for age category

In the 5-17 months age category without a fourth dose, through the duration of follow-up, the vaccine conferred significant protection against clinical disease. While at the end of the observation period the incidence of clinical malaria was similar to that in the control group, overall, there was a beneficial effect. An analysis of vaccine efficacy by month of age at vaccination in the 5-17 month group showed no variation in efficacy within this age category. Vaccination at earlier ages in this age window (e.g., starting at 5 months) would prevent more early cases of malaria than initiating vaccination at a later age in this 5-17 month window.

In the 6-12 week age category, the vaccine when administered in the EPI schedule had lower vaccine efficacy, both after the first three doses and fourth dose, compared to giving it in the 5-17 month age category. Similarly to the 5-17 month group, the time-stratified efficacy results in infants suggest a higher level of efficacy immediately following vaccination that declines steadily, with essentially no remaining efficacy against clinical malaria by 2.5 years following the initial three doses.

In summary, vaccine efficacy was notably lower in the 6-12 week age category compared to the 5-17 month age category. Observed efficacy when given to 6-12 week infants does not meet any of the efficacy thresholds discussed in the malaria vaccine roadmap. With the introduction of other malaria control measures, the burden of disease is shifting to older age groups, so fewer cases will occur prior to vaccination if the vaccine is administered outside the EPI schedule than would historically have been the case.

Rationale for schedule

Vaccine efficacy results by interval since vaccination suggest a high level of efficacy immediately following vaccination with three doses that declines steadily, with essentially no remaining efficacy against clinical malaria after a few years.

Among those in the 5-17 months age category who received a fourth dose of RTS,S, additional protection against clinical malaria was conferred that appeared to decline in the period following the fourth dose in a way similar to that seen following the first three doses. Thus, the impact on clinical malaria with a fourth dose would be greater than without a fourth dose. Given the evidence of waning immunity following the fourth dose, it is possible that there is little or no protective effect remaining against clinical malaria 18 months after the fourth dose.

Among 5-17 months participants who only received three doses of RTS,S, there was an initial reduction in severe malaria, but this was balanced by an increase in severe malaria around 18 months after the initial vaccine course. Such an effect is sometimes referred to as rebound. Rebound refers to higher susceptibility to severe malaria among recipients of a malaria-control intervention (in this case the RTS,S vaccine) when the intervention is withdrawn (when vaccine-induced immunity wanes) compared to contemporaneously-followed individuals in the same population who did not receive the intervention.

This rebound effect for severe malaria was most marked in higher transmission settings, possibly because participants in the control group developed immunity through natural infection more rapidly – the malaria vaccine reduced the number of clinical episodes, which in turn reduced acquisition of naturally acquired immunity. Importantly, a rebound effect for severe malaria was not observed among children vaccinated at 5-17 months of age who received four doses of vaccine up to the end of follow-up, or in the group vaccinated at 6-12 weeks in whom vaccine efficacy was lower and prevented fewer episodes of malaria. It is not known if there will be any rebound effect following waning of immunity after the fourth dose in the 5-17 months group. Reassuringly, the trial showed that the incidence of severe malaria is markedly reduced in those in the 5-17 month age category when measured towards the end of the trial in both vaccine and control groups, when children had reached the age of 4 years or so.

Given the evidence of a rebound effect for severe malaria in children vaccinated at 5-17 months of age who did not receive a fourth dose, a fourth dose would seem to be essential. Its feasibility must be considered in the planning phase of vaccine introduction, with realistic consideration of coverage attainable.

The four dose schedule had a notable impact on clinical malaria, severe malaria, and all-cause hospitalizations. In the 5-17 month group, it was estimated that, on average across the trial sites, 1239 (95%CI 908-1552) cases of clinical malaria were averted per 1000 fully vaccinated over 48 months. Thirteen cases of severe malaria (95%CI -3, 29) and 44 hospitalizations (95%CI 0, 86) were estimated to have been averted under the same parameters. The number of cases averted was substantially lower for the 3-dose schedule and in infants.

Additional considerations

One or more further doses (e.g., fifth) may be desirable. It is critical to obtain data on the effects of further doses, both for safety and efficacy.

Of the 2,806 participants in the group who received the first three doses of RTS,S, 2,444 received the fourth dose of RTS,S (87%). Given this was a trial setting, it may be optimistic to achieve this level of coverage in a routine program. In the trial, the main reason for not receiving the fourth dose was migration (Figure 3.4).[2]

For a variety of reasons, including the access to care and the size of the trial, it was not possible to detect any impact on the overall or malaria-related mortality. In fact a non-statistically-significant excess of deaths among the vaccinated group for both all-cause mortality and malaria-related mortality was observed. JTEG considers the closest surrogate for malaria-related mortality in the trial is severe malaria, but it is critical to evaluate the impact of the vaccine on mortality in routine program settings.

10.2 JTEG assessment of vaccine safety

Assessment of meningitis, febrile convulsions, and cerebral malaria

The meningitis signal was first observed among individuals who received three doses of RTS,S at ages 5-17 months. The signal persisted in the period more than 18 months after the initial vaccine course with or without a fourth dose. Although the excess of meningitis was nominally statistically significant, it is unclear whether or not the excess was causally related to the vaccine. Several aspects of the meningitis signal are currently unexplained. The cases of meningitis had a variety of aetiologies. The incidence of meningitis appeared to be very low in the control group, and more information on background rates of meningitis would aid interpretation. Most of the excess cases of meningitis came from two sites not in the meningitis belt. The possibility cannot be excluded that the signal may be due, at least in part, to a chance deficit of meningitis cases in the control arm. Continued monitoring of meningitis following vaccination is critical to understand whether excess in meningitis is causally related to the vaccine and if so, the mechanism behind it.

The trial demonstrated an increased risk of febrile seizures within seven days of vaccination among those vaccinated at age 5-17 months. In children in the younger age category an excess risk was apparent only after the fourth dose (when the children were older). These febrile seizures resolved without long-term consequence and are not unique to this vaccine.

JTEG noted an increase in cerebral malaria in the malaria vaccine older age category, although these cases comprised only a small proportion of all cases of severe malaria. This finding was in an unplanned subgroup analysis and its significance in relation to vaccination is unclear. The hypothetical concern is of changing the disease manifestation due to vaccination or because of delayed age of exposure. In the trial, participants were diagnosed with malaria and treated earlier than in routine health care settings, so the finding, if real, may not reflect what would be seen with

[2] Examples of vaccine coverage achieved for other vaccines (DTP3, MCV1, and MCV2) in countries in the WHO African Region may be found in Appendix 7.

wider deployment. The sub-group analysis showed that children with cerebral malaria had higher case fatality rates than other forms of severe malaria. An imbalance of cerebral malaria was not seen in children vaccinated in the younger age category.

Pharmacovigilance systems should be strengthened, not only for febrile seizures, cerebral malaria and meningitis, but for other potential adverse effects occurring at a frequency too low to have been detected in the Phase 3 trial. Such surveillance is also important because there is a relatively small database for the new adjuvant (AS01) in the vaccine. Because RTS,S/AS01 is a new vaccine with a relatively new adjuvant system, there should be surveillance for potential adverse effects, such as autoimmune disease.

GACVS has agreed to propose detailed protocols for safety studies of RTS,S if the vaccine is recommended for any large-scale use.

10.3 RTS,S/AS01 in the context of other malaria control measures

There are other proven strategies for malaria prevention and control. LLINs are one of the most cost-effective public health interventions. Sufficient coverage with existing interventions should be a priority and funds should not be diverted to vaccination from existing malaria control activities. RTS,S could represent a complementary tool to be used in conjunction with other control measures.

10.4 JTEG key conclusions and recommendations for SAGE/MPAC consideration

There is a need to evaluate initial introductions before wider scale-up is considered to address a number of issues that remain following the conclusion of the trial. The primary issues are:

- The extent to which the protection demonstrated in the Phase 3 trial could be replicated in the post-licensure phase because of the challenge of implementing four doses at the population level, including the need for new immunization contacts
- The safety signals of most concern (i.e. imbalances in meningitis and cerebral malaria) in the trial may be chance findings, but further evaluation is necessary when the vaccine is given to larger numbers of children
- The impact on mortality could not be assessed in the Phase 3 trial and as this is the main driver of the public health impact and cost-effectiveness of the vaccine, it is important to assess the mortality reduction following large-scale vaccination.

Based on the data from the Phase 3 trial, JTEG does not recommend the use of the malaria vaccine in the younger (6-12 weeks) age category. With respect to the older age category (5-17 months), JTEG recommends the initial introduction of 4 doses of the malaria vaccine in 3-5 distinct epidemiological settings in sub-Saharan Africa, likely at subnational level, to generate critical information on the issues described above (large demonstration projects). These settings should be selected such that

- they cover a range of moderate-to-high transmission settings, with at least one setting with strongly seasonal malaria transmission.
- it is possible to ascertain and diagnose cases of meningitis and severe malaria and record deaths.
- the population vaccinated should be of sufficient size to allow evaluation of the impact on mortality, probably through a phased introduction of the vaccine within the selected settings. It is likely that several hundred thousand vaccinated children will be included in each setting and that phased introduction would need to be randomized to ensure comparability of vaccinated and unvaccinated groups. Each initial introduction will be a large demonstration project.
- there should be high existing coverage of other proven malaria control measures including LLIN (or IRS), access to RDTs and ACT, and SMC in highly seasonal areas.

JTEG strongly recommends that WHO oversees the design and evaluation of these phased introductions and monitors the emerging findings. If appropriate, SAGE and MPAC may broaden recommendations on the basis of these emerging findings.

JTEG notes that it would be appropriate for WHO to recommend countrywide introduction if concerns about safety have been resolved, and if favourable implementation data become available, including high coverage of the fourth dose.

As JTEG recommends introduction in 3-5 moderate-to-high transmission settings, where there is a significant burden of malaria in the first year of life, it is important to vaccinate at a young age within the 5-17 month age range. There is no evidence that vaccine efficacy varied according to the month of age at which vaccination was started within this age category. In the phased introduction of the vaccine, JTEG recommends a three dose initial series of the malaria vaccine with a minimum interval between doses of four weeks, followed by a fourth dose at 15-18 months following the third dose. It is encouraged that the first dose be initiated as close as possible to age five months and the third dose be completed by nine months of age, if possible. Co-administration has been evaluated with measles and DTP-containing vaccines and is considered acceptable.

Prior to any phased introduction appropriate communication materials should be developed and disseminated with particular emphasis on the partial efficacy of the vaccine and the importance of the fourth dose. Messages should include the importance of maintaining usage of non-vaccine malaria preventive measures and the likelihood that febrile episodes in vaccinated children may still be due to malaria.

Research recommendations

There are currently no data to support a fifth dose. Therefore, evaluation of safety and effectiveness of a fifth dose could be included in the proposed phased introductions.

JTEG recommends monitoring of the emergence of vaccine-resistant strains following widespread use of the vaccine.

JTEG recommends that there is further exploration of alternative schedules, including schedules adapted to highly seasonal settings, and other strategies to improve the efficacy of the vaccine.

JTEG recommends an exploration of how to capitalize upon the new immunization contacts for general improvements in child health, including increasing coverage with other vaccines.

JTEG recommends that there is an evaluation of the malaria vaccine in the context of elimination, including studies evaluating administration and effectiveness against infection over a wide age range. A high priority geographic area for such an evaluation is South-East Asia in areas of artemisinin resistance.

Table 10.1: Risk/benefit assessment over median 48 months follow-up per child in those aged 5-17 months, based on Phase III trial results

	BENEFITS	RISKS	UNCERTAINTIES
3 dose schedule	VE2.5-SE clinical malaria: 26.2% (95%CI 20.8, 31.2)	<u>Identified risk</u> Excess of febrile convulsion after any of the first three doses (0.5/1000 doses within 7 days of vaccination) <u>Potential risk</u> Meningitis (numerical excess, no clear association with time since vaccination, biological model not well established, excess predominantly in only 2 of 11 sites)	Relevance of imbalance of cerebral cases, possibly due to chance
4 dose schedule	VE2.5-SE clinical malaria: 39.0% (95%CI 34.3, 43.3) VE2.5-SE severe malaria: 31.5% (95%CI 9.3, 48.3) VE2.5-SE all-cause hospitalization: 14.9% (95%CI 3.6, 24.8)	<u>Identified Risk</u> Excess of febrile convulsion after any of the first three doses (0.5/1000 doses within 7 days of vaccination) after fourth dose (2.0/1000 doses within 7 days of vaccination) <u>Potential Risk</u> Meningitis (numerical excess, no clear association with time since vaccination, biological model not well established, excess predominantly in only 2 of 11 sites)	Uncertain overall protection against severe malaria beyond trial period Beneficial overall effect on severe malaria is dependent on delivery of fourth dose Relevance of imbalance of cerebral cases, possibly due to chance

With the three-dose schedule, there was no significant protection against VE2.5-SE against severe malaria, or for VE 2.5-SE against all-cause hospitalizations in the 5-17 month age category.

Table 10.2: Risk/benefit assessment over median 38 months follow-up in those aged 6-12 weeks, based on Phase III trial results

	BENEFITS	IDENTIFIED RISKS	UNCERTAINTIES
3 dose schedule	VE 2.5 – SE clinical malaria: 18.2% (95%CI 11.4, 24.5)	None	NA
4 dose schedule	VE 2.5-SE clinical malaria: 26.7% (95%CI 20.5, 32.4)	Excess of febrile convulsion after fourth dose (1.6/1000 doses within 7 days of vaccination)	NA

With the three-dose or four-dose schedule, there was no significant protection against VE2.5-SE against severe malaria, or for VE 2.5-SE against all-cause hospitalizations in the 6-12 week age category.

Table 10.3: Evidence to Decision Table, GRADE_DECIDE Framework.

Question: Should 4 doses of RTS,S/AS01 given on a 0/1/2/20 month schedule to children aged 5 months be introduced into national immunization programs of countries with medium-high malaria transmission?	
Population: Children aged 5 months	
Intervention & Comparison: 4 doses of RTS,S/AS01 given on a 0/1/2/20 month schedule vs. no malaria vaccine	
Setting (if relevant): Countries with medium-high malaria transmission	
Decision domain	Summary of reason for decision
Quality of evidence (QoE) *Is there high or moderate quality of evidence* Yes ☐ No ☐ Mixed ✓	Quality of Evidence for benefits: High ✓ Moderate ✓ Low☐ Very Low ☐ Quality of Evidence for harms: High ☐ Moderate ☐ Low ✓ Very Low ☐
Balance of benefits and harms *Is there certainty that the benefits outweigh the harms?* Yes ☐ No ✓	Summary of benefits and harms of the Intervention. • There is partial efficacy against clinical and severe malaria, as well as all-cause hospitalization. • The benefits against malaria-related mortality and all-cause mortality are unknown. • There is an identified risk of febrile convulsions following vaccination. • There is a potential risk of meningitis following vaccination. • It is uncertain whether the imbalance of cerebral malaria cases seen in the trial is relevant. The benefits outweighed the risks for a 4-dose schedule in the clinical trial. However, there is concern that attaining high coverage of 4-dose schedule is not feasible, and the risk profile of the vaccine requires further evaluation to understand the benefit/risk in the context of what can be implemented.
Values and preferences *Is there confidence in the estimate of relative importance of outcomes and patient preferences?*	There is a strong public desire to reduce malaria cases, particularly severe and life-threatening malaria. There is increasing resistance to multiple injections at a single visit, suggesting new vaccination visits would be preferable.

Yes✓ No ☐	
Resource implications *Are the resources worth the expected net benefit?* Yes☐ No ☐ Unknown ✓	• The relative benefit/risk in the context of programmatic use is dependent upon adherence to four doses and additional information on mortality impact and vaccine safety. • Resources will be required for adding new vaccination visits (at least 1 for first 3 doses and an additional visit for fourth dose). • GSK has committed to at-cost (plus 5%) pricing. • Gavi will consider providing financial support. • Malaria prevention/control funds are allocated to proven interventions (e.g. LLIN, IRS, ACT)– there should be no diversion of funds from existing measures. • Other proven malaria preventive interventions are more cost-effective, hence the need to ensure that resources are not diverted from these to the vaccine. • Predictions of RTS,S/AS01 cost-effectiveness are comparable with other new vaccines, recommended for use by WHO.
Overall strength of recommendation: *Does the strength of recommendation adequately express the certainty?*	JTEG recommends use of RTS,S/AS01 in 3-5 settings in order to confirm implementation of a fourth dose and benefit/risk in the context of a routine immunization setting.
Implementation and considerations *How might implementation affect access to care and outcomes in disadvantaged and privileged groups?*	In many settings it will be challenging to implement and achieve high coverage of the four-dose schedule at the population level, particularly given the need for new immunization contacts. Close monitoring and evaluation of implementation will be needed. Good communication will be needed to ensure continued acceptability of RTS,S in the context of continued susceptibility to malaria after vaccination, as well as continued care seeking.
Research priorities *What are some of the additional research (surveillance, impact of immunization on disadvantage population, etc.) necessary after making a recommendation?*	• Pilot introductions are needed to assess the programmatic feasibility of implementing a 4-dose vaccine schedule, the impact of RTS,S vaccination on all-cause mortality, as well further assessment of the possible risks of meningitis and cerebral malaria. • There are currently no data to support a fifth dose. Therefore, evaluation of safety and effectiveness of a fifth dose could be included in the proposed phased introductions. • Monitoring of the emergence of vaccine-resistant strains following widespread use of the vaccine. • Further exploration of alternative schedules, including schedules adapted to highly seasonal settings, and other strategies to improve the efficacy of the vaccine. • Exploration of how to capitalize upon the new immunization contacts for general improvements in child health, including increasing coverage with other vaccines. • JTEG recommends that there is an evaluation of the malaria

	vaccine in the context of elimination, including studies evaluating administration and effectiveness against infection over a wide age range. A high priority geographic area for such an evaluation is South-East Asia in areas of artemisinin resistance.

11. Acknowledgements

JTEG would like to acknowledge the Partnership between the Malaria Vaccine Initiative at PATH and GSK. JTEG would also like to thank GSK for their data sharing and responsiveness to additional data requests important to the policy-making process. At WHO's request GSK/PATH published several methods papers outlining design aspects in detail. GSK provided WHO with all analyses requested, including statistical reports, and clinical study reports. GSK/PATH promptly published and publicly disclosed four comprehensive reports from the Phase 3 trial.

12. GRADE Tables

GRADE Table 1

Is there demonstrated short term efficacy of three doses of RTS,S/AS01 in preventing clinical malaria in children?

Population : 5-17 month old children living in malaria-endemic areas

Intervention: 3 doses of RTS,S/AS01 administered at least 4 weeks apart

Comparison: Placebo/Control vaccine

Outcome : Clinical malaria occurring within 12 months of completion of the primary series

What is the short-term efficacy of three doses of RTS,S/AS01 in preventing clinical malaria in children?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[2]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a high level of confidence that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**RTS,S demonstrates statistically significant vaccine efficacy against clinical malaria in the first 12 months following vaccination with three doses.**

[1] A multicenter efficacy trial was conducted at 11 sites in seven countries and included 8,922 participants assigned in the 5-17 month age category. It was a randomized, controlled, participant and observer-blinded trial (intervention and control vaccines differ in appearance, so study personnel who administered vaccines were aware of the treatment allocation. The unblinded vaccinators played no other part in the study)(NCT00866619). Vaccine efficacy against clinical malaria was estimated to be 32.9% (95%CI 26.3, 38.9) in the 12 months following a primary series (3 doses) of vaccine. A number of smaller Phase 2 studies also found statistically significant vaccine efficacy against infection and clinical malaria. The point estimates vary by follow up time given the waning efficacy even over the first year. Although only one RCT is the primary source of data, given the number of study subjects involved and the multi-center nature, it was determined not to downgrade.

[2] A large effect is noted in the first 6 months of follow up (VE=67.6%, 95%CI 63.8, 71.0), but it waned in the second 6 months of follow up to 38.9% (95%CI 33.2, 44.0).

GRADE Table 2

What is the short-term efficacy of three doses of RTS,S/AS01 in preventing severe malaria in children?

Population : 5-17 month old children living in malaria-endemic areas

Intervention: 3 doses of RTS,S/AS01 administered at least 4 weeks apart

Comparison: Placebo/Control vaccine

Outcome : Severe malaria occurring within 12 months of completion of the primary series

What is the short-term efficacy of three doses of RTS,S/AS01 in preventing severe malaria in children				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious[2]	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[3]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a high level of confidence that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**RTS,S demonstrates statistically significant vaccine efficacy against severe malaria in the first 12 months following vaccination with a primary series.**

[1]A multicenter efficacy trial was conducted at 11 sites in seven countries and included 8,922 participants assigned in the 5-17 month age category. It was a randomized, controlled, participant and observer-blinded trial (intervention and control vaccines differ in appearance, so study personnel who administered vaccines were aware of the treatment allocation. The unblinded vaccinators played no other part in the study)(NCT00866619). Vaccine efficacy against severe malaria was estimated to be 44.5% (95%CI 23.8, 59.6) in the 12 months following a primary series (3 doses) of vaccine.

[2]The number of severe malaria cases was very low in the trial; however here may be differences in the presentation of severe malaria among vaccinated individuals, as a numerical imbalance was seen for severe malaria in RTS,S-vaccinated subjects. It is uncertain how this will play out in larger scale use outside a trial setting. It was determined not to downgrade for these uncertainties, but they are noted.

[3]A large effect is noted in the first 6 months of follow up (VE=70.1%, 95%CI 49.0, 82.5), but it quickly wanes (see GRADE Table 3).

GRADE Table 3

Is there need for a fourth dose following immunization with the first three doses of RTS,S/AS01 in children to prevent severe malaria?

Population : 5-17 month old children living in malaria-endemic areas

Intervention: 3 doses of RTS,S/AS01

Comparison: Placebo/Control vaccine

Outcome : Severe malaria occurring at >12 months following the primary series.

Is there need for a fourth dose following immunization with the first three doses of RTS,S/AS01 in children to prevent severe malaria?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**Among vaccinees who do not receive a fourth dose, in high transmission settings there is an increased risk of severe malaria following waning vaccine efficacy; therefore, a fourth dose is essential.**

[1]A multicenter efficacy trial was conducted at 11 sites in seven countries and included 8,922 participants assigned in the 5-17 month age category. It was a randomized, controlled, participant and observer-blinded trial (intervention and control vaccines differ in appearance, so study personnel who administered vaccines were aware of the treatment allocation. The unblinded vaccinators played no other part in the study)(NCT00866619). All participants were followed up for 32 months (approximately 30 months following the primary series). At study end, participants in this age category were followed up for a median of 48 months. Vaccine efficacy against severe malaria during the full trial period (2.5 months following 3rd dose to study end) in the absence of a fourth dose (i.e. primary series alone) was estimated to be -2.2% (-31.3, 20.4), suggesting that the primary course alone had no effect on the overall incidence of severe malaria. When efficacy/comparative incidence was analysed by time interval, efficacy against severe malaria was high in the first 6 months of follow up at 70.1% (95%CI 49.0, 82.5), but steadily declined to -47.9% (95%CI -134.6, 6.8) between 19-30 months after the primary series, and to -74.2% (95%CI -220.0, 5.2) between 31 months after the primary series and the end of the observation period. Thus, the apparent protective effect in the first 18 months being balanced by a rebound of cases in the period from 18 months to the end of the trial. Although only one RCT is the primary source of data, given the number of study subjects involved and the multi-center nature, it was determined not to downgrade. Among trial participants who received a fourth dose, the vaccine efficacy against severe malaria from the primary series to the end of the trial was 31.5% (95%CI 9.3, 48.3).

[2]Given the rapid reduction of vaccine efficacy/comparative incidence of a primary series as well as a fourth dose (see Background Paper), it is of interest what the effect of a fourth dose is on severe malaria beyond the trial conclusions, as well as whether subsequent doses (e.g. a 5th dose) are safe and efficacious. There are no data available to inform these questions.

GRADE Table 4

What is the risk of meningitis following vaccination with RTS,S/AS01 in children?

Population : 5-17 month old children living in malaria-endemic areas

Intervention: One or more doses of RTS,S/AS01

Comparison: Placebo/Control vaccine

Outcome : Meningitis due to all causes

What is the risk of meningitis following vaccination with RTS,S/AS01 in children?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	Very serious[2]	-2
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[3]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports limited confidence in the estimate of the effect on the health outcome.**
	Conclusion			**RTS,S/AS01 may or may not be causally-related to an increased risk of meningitis**

[1] A multicenter efficacy trial was conducted at 11 sites in seven countries and included 8,922 participants in the 5-17 month age category. It was a randomized, controlled, participant and observer-blinded trial (intervention and control vaccines differ in appearance, so study personnel who administered vaccines were aware of the treatment allocation. The unblinded vaccinators played no other part in the study)(NCT00866619). In the 20 months following the first dose, meningitis was reported as an SAE in 16 of the 5949 5-17 month old participants in the RTS,S group, and in 1 of the 2974 5-17 month old participants in the control group, a relative risk of 8.0 (95%CI 1.1, 60.3).

[2]There were a variety of etiologies, although in many of the meningitis cases no pathogen was identified. There was no clear temporal clustering, and most cases occurred at two study sites. The number of meningitis cases in the control group appears to be unusually low.

[3]The relative risk is large (8.0); however, given the other uncertainties, it was deemed not appropriate to upgrade the quality of the evidence.

GRADE Table 5

What is the risk of other (non-meningitis) serious adverse events following vaccination with RTS,S/AS01 in children?

Population : 5-17 month old children living in malaria-endemic areas

Intervention: One or more doses of RTS,S/AS01

Comparison: Placebo/Control vaccine

Outcome : Serious adverse events (non-meningitis)

What is the risk of other (non-meningitis) serious adverse events following vaccination with RTS,S/AS01 in children?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports limited confidence in the estimate of the effect on the health outcome.**
	Conclusion			**Febrile seizures are an identified risk of RTS,S/AS01 administered to children. The relevance of the imbalance of cerebral malaria cases in the RTS,S/AS01 group is uncertain. There is no evidence of an association to other SAEs[4].**

[1]A multicenter efficacy trial was conducted at 11 sites in seven countries and included 8,922 participants assigned in the 5-17 month age category. It was a randomized, controlled, participant and observer-blinded trial (intervention and control vaccines differ in appearance, so study personnel who administered vaccines were aware of the treatment allocation. The unblinded vaccinators played no other part in the study)(NCT00866619). In the 5-17 month group, between the first dose to the trial end, Serious Adverse Events (based on MEDRA preferred terms) were slightly less frequent in the RTS,S groups compared to the control group (R3R-24.2%, R3C-25.3%, C3C- 28.4%)(Table 6.1) and this remained so when malaria was excluded as an SAE (R3R-22.6%, R3C-23.7%, C3C- 26.4%). In the 5-17 month age category, the incidence of generalized convulsions (Brighton Collaboration diagnostic certainty level of 1 to 3) within the seven days following vaccination during the primary series was 1.04 per 1000 doses (95%CI 0.62, 1.64) in the RTS,S/AS01 groups (R3R + R3C) and 0.57 per 1000 doses (95%CI 0.19, 1.34) in the control group (C3C) (Table 4.3), a risk ratio of 1.8 (95%CI 0.6, 4.9). Following a fourth dose of RTS,S (R3R group), the incidence of generalized convulsions increased to 2.5 per 1000 doses (95%CI 0.9, 5.3) in the R3R group (Table 4.4). The incidence in the RTS,S group without a fourth dose of RTS,S/AS01 (R3C – received rabies vaccine as control fourth dose) was still 1.2 per 1000 doses (95%CI 0.3, 3.5), while the incidence in the control group (C3C) was 0.4 (95%CI 0.0, 2.3). Based on an unplanned subgroup analysis, there was an imbalance of cerebral malaria episodes in the RTS,S groups compared to the control group. In the 0-20 month time period, there were 24 episodes of cerebral malaria or cerebral malaria + anaemia in the RTS,S group and 6 episodes in the control group (2:1 randomization). In the 21 month to

study end time period, there were 9 episodes in the R3R group, 12 episodes in the R3C group, and 4 episodes in the C3C group (1:1:1 randomization).

[2]The trial did not have the power to detect more rare SAEs.

[3]For cerebral malaria, this was an unplanned subgroup analysis. Some cases of other coma-inducing diseases may have been misclassified as cerebral malaria.

[4]SAEs excluding meningitis, cerebral malaria and febrile seizures.

13. JTEG Membership and Terms of Reference

WHO Initiative for vaccine research/global malaria programme joint technical expert group (JTEG) on malaria vaccines entering pivotal phase 3 trials & beyond (established April 2009)

Terms of reference

JTEG provides advice to WHO on activities related to the development of malaria vaccines at or nearing the pivotal phase 3 trial stage. The specific responsibilities of the group are to provide recommendations on:

1. The clinical trial data necessary and desirable for evaluation of the public health impact of a malaria vaccine in malaria endemic countries
2. The design, conduct, analyses and interpretation of Phase 2, Phase 3 and Phase 4 trials of malaria vaccines.
3. The duration and nature of follow-up of participants in planned Phase 3 trials of malaria vaccines.
4. The minimum safety and efficacy data to be collected in clinical trials, and data on any impact of malaria vaccines on the immunogenicity of other vaccines, to enable evaluation by WHO for policy recommendations.
5. The evaluation of immunogenicity of malaria vaccines in Phase 3 trials and beyond, in particular with regard to possible development of surrogate markers for efficacy.

Composition

Peter Smith, Chair (London School of Hygiene and Tropical Medicine, UK)
Fred Binka (University of Health and Allied Sciences, Ho, Ghana)
Kalifa Bojang (MRC Laboratories, The Gambia)
Blaise Genton (University of Lausanne, Switzerland)
Robert Johnson (National Institutes of Allergy and Infectious Disease, USA)
Kamini Mendis (Independent Consultant, Colombo, Sri Lanka)
Paul Milligan (London School of Hygiene and Tropical Medicine, UK)
Malcolm Molyneux (University of Malawi, Malawi)
Mahamadou Thera (University of Bamako, Mali)
Janet Wittes (Statistics Collaborative Inc., USA)
Claire-Anne Siegrist (University of Geneva, Switzerland)
Fred Were (University of Nairobi, Kenya)

WHO Secretariat

Vasee Moorthy (IVR)
Andrea Bosman (GMP)
Georges Ki-Zerbo (MAL, AFRO), then Issa Sanou (MAL, AFRO)
Bartholomew D. Akanmori (IVD, AFRO)
Kirsten Vannice (IVR)

Declarations of interest

All members completed a declaration of interest. 3 members reported the following interests:

Professor Fred Binka reported working with the Indepth-Network Malaria Clinical Trials Alliance (MCTA), a group which trains personnel and improves infrastructure at African clinical trials sites for conduct of clinical trials of malaria drugs and vaccines. Indepth/MCTA was funded by a $17 million grant from the Bill and Melinda Gates' Foundation (BMGF). The work of Indepth/MCTA included partnering with PATH Malaria Vaccine Initiative (MVI) for site strengthening of RTS,S/AS01 phase 3 clinical trial sites. BMGF are also the main funders of the phase 3 trial of RTS,S/AS01 through support to PATH MVI. In addition Professor Binka reported a research grant for the Indepth Network for Effectiveness and Safety Studies (INESS) for $28 million. This platform is intended to support Phase IV studies of antimalarial drugs. These interests were assessed as non-personal, non-specific and financially significant*.

Professor Malcolm Molyneux reported that he currently serves as Chair of the Independent Data Monitoring Committee for RTS,S/AS01 paediatric clinical trials, for which his institution receives a limited fee. This interest was assessed as non-personal, specific and not financially significant*.

Dr Janet Wittes reported that her institution has performed statistical consulting services for GSK for a study on asthma and another on cardiovascular diseases, totaling less than $50,000. The most recent consulting contract with GSK terminated in 2010. Her institution has also received funding for malaria vaccine-related statistical services from PATH Malaria Vaccine Initiative and from Seattle Biomed. None of this funding relates to the RTS,S malaria vaccine. These interests were assessed as non-personal, non-specific and financially significant*.

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* According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by expert's organization, from any single vaccine manufacturer or other vaccine-related company exceeds 10,000 USD in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company in excess of 1,000 USD would also constitute a “significant shareholding”.

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15. List of Appendices

Available on web

Appendix 1. Clinical studies conducted with RTS,S/AS01 in subjects older than 17 months at first dose or with RTS,S/AS02

Appendix 2. Representative ITT Vaccine Efficacy Analyses

Appendix 3. Case counts and vaccine efficacy against clinical and severe malaria for Phase III trial (Mal-055)

Appendix 4. Results from long-term follow-up of Phase 2b trials of RTS,S/AS02 and RTS,S/AS01

Appendix 5. Hepatitis B immunogenicity and indication

Appendix 6. Incidence of malaria in the control group by site

Appendix 7. 2014 Estimated Vaccine Coverage for Select Vaccines, by Country in AFR

Related materials

Available on web

Additional Background Paper: "Programmatic Options for Implementation of Malaria RTS,S Vaccination Schedule for Young Children". Developed by WHO.

"Report on public health impact and cost-effectiveness of malaria vaccine RTS,S/AS01". This summary highlights key outcomes from a systematic comparison of estimates of the potential public health impact and cost-effectiveness from four modelling groups.

"Comparison of the cost effectiveness of LLINs, SMC, the RTS,S vaccine and RTS,S plus IPTi in African settings." MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London

2015 ASSESSMENT REPORT OF THE GLOBAL VACCINE ACTION PLAN

STRATEGIC ADVISORY GROUP OF EXPERTS ON IMMUNIZATION

DRAFT - For SAGE discussion October 2015

EXECUTIVE SUMMARY

The Global Vaccine Action Plan set ambitious but achievable goals, to save thousands of lives through vaccination in this Decade of Vaccines to 2020.

The Decade of Vaccines is not on course to achieve its true potential. Good progress has been made in some countries, including those where large numbers of unimmunized children live. **These isolated improvements will have to become the norm if the plan is to get back on track.**

In recommending what needs to change, this report focuses on **two major problems** that are holding back progress in the Decade of Vaccines:

- The elimination strategies for maternal and neonatal tetanus, and for measles and rubella, and their implementation, are in urgent need of change and adequate resourcing.
- The monitoring and accountability framework for the Global Vaccine Action Plan has gaps in its mechanisms for accountability, undermining the translation of the plan's goals into reality.

At this critical midpoint of the Decade of Vaccines, SAGE makes seven recommendations, focusing squarely on the major issues.

Recommendations to improve the leadership and accountability framework:

- **Country** vaccine action plans must be in place, informed by the Global Vaccine Action Plan and the relevant regional vaccine action plans and setting out each country's commitments
- **Regional** vaccine action plans must be in place, providing a framework for review of country progress towards global and regional goals
- **Global partners** must support countries to improve leadership and accountability towards the Global Vaccine Action Plan goals.

Recommendations to address the shortfalls apparent in disease-specific areas of the Global Vaccine Action Plan's implementation involving global partners, regions and countries:

- For maternal and neonatal tetanus, achieving and sustaining the elimination goal
- For measles and rubella, revisiting the approach and addressing the funding gap to achieve the elimination goal.

Recommendations to help countries where large numbers of children remain unimmunized or under-immunized:

- Countries to focus on improvements that strengthen immunization and health systems
- Global partners to detail their contributions to helping countries achieve this
- WHO to provide guidance for countries and partners on immunization during conflict and chronic disruption.

The recommendations are stated in full at the end of the report.

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1. A DECADE OF VACCINES – THE HALFWAY POINT

All countries committed themselves to the goals and strategies of the Global Vaccine Action Plan, to eliminate maternal and neonatal tetanus, measles, congenital rubella syndrome and polio, to free all children from vaccine-preventable diseases no matter where they live, and to explore the potential for vaccines to save more lives.

One year ago, SAGE published a report critical of the progress being made towards the Global Vaccine Action Plan goals. It would not be feasible to expect the major indicators to have changed substantially. Not only because there is a lag in the data collection process, but because change takes time. Understanding what needs to be achieved at every level, by when, and by whom, is an important step.

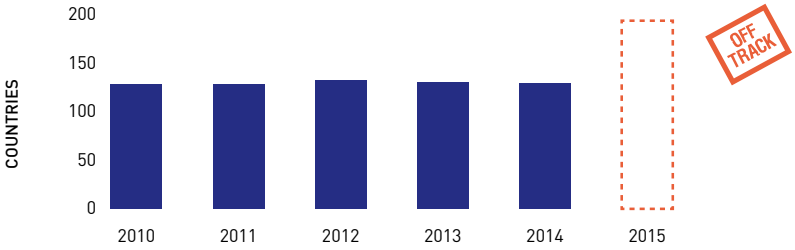
Between now and 2020, each time the Global Vaccine Action Plan targets are missed, so too are opportunities to increase the number of children living their lives free of killer diseases. In the second half of this Decade of Vaccines, countries, regions and global partners can and must achieve results.

This third report of the SAGE focuses on **leadership and the accountability systems for countries, regions and at global level** that can take the Global Vaccine Action Plan forward towards success.

2. WHERE ARE THE UNVACCINATED PEOPLE?

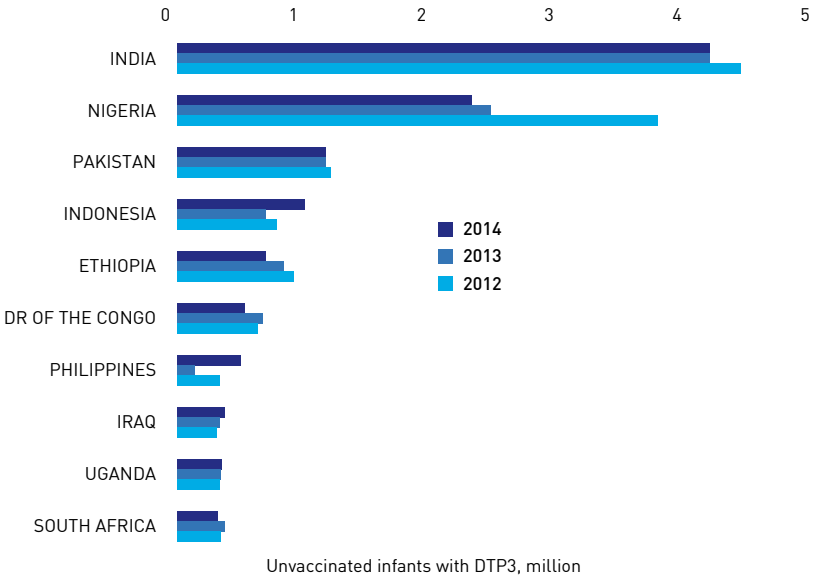
The 2014 SAGE Report focused on five key disease targets of the Global Vaccine Action Plan that are off-track. The first of these, national DTP3 coverage, shows how many of a country's children are protected from diseases. It is also an indicator of the functionality of the immunization programme and more broadly of the health system.

The target was to achieve coverage of 90% in all 194 countries by 2015. In 2014, only 129 countries achieved coverage of 90%, one less than in 2013 and only one more than in 2010.



THE TEN COUNTRIES WHERE MOST UNVACCINATED CHILDREN LIVE

Worldwide, 86% of children receive DTP3 and this has not shifted markedly in the last five years. The ten countries with the largest numbers of unvaccinated or under-vaccinated children are all low-income or lower-middle income countries. In most of these countries, large populations and weak performance combine to create the overall large numbers of unvaccinated children. In some countries, there may also be data quality issues.



Many countries other than these will have geographic areas with low immunization rates. Only 54 member states were able to report reaching national DTP3 coverage of 90% as well as coverage in all districts of 80% or more which is the second part of the target for national vaccination coverage. Data are still not available at district level in 73 countries.

Transitory migrant populations in cities and peri-urban areas, and indigenous populations are under-served. Rapid urbanization has opened new gaps in immunization coverage where health services are unable to meet demand. In countries where children are missed, there are now adolescent and adult unvaccinated populations. Some countries experience natural disasters and conflict which bring particular challenges.

In seven countries fewer than half of all children are immunized.

DTP3 NATIONAL COVERAGE FOR 2014 IN THE SEVEN COUNTRIES WHERE MORE THAN 50% OF CHILDREN ARE UNVACCINATED OR UNDER-VACCINATED.

Equatorial Guinea	**24**
South Sudan	**39**
Somalia	**42**
Syrian Arab Republic	**43**
Chad	**46**
Central African Republic	**47**
Haiti	**48**

In countries in which wars and natural disasters have decimated health systems, an unvaccinated diaspora have fled to neighbouring countries or further abroad. There are internally displaced children who cannot access immunization services and areas where ongoing fighting makes vaccination very challenging. WHO has finalized a framework for decision-making about selecting vaccines in acute humanitarian emergencies[1] but more guidance is needed in relation to implementation of sustainable immunization in ongoing conflict or crisis among both internally displaced people and those who have become refugees in other countries.

[1] Vaccination in acute humanitarian emergencies: a framework for decision making, WHO, 2013, http://apps.who.int/iris/bitstream/10665/92462/1/WHO_IVB_13.07_eng.pdf

CASE STUDY: HARD-WON IMPROVEMENTS IN SOMALIA

Somalia on the Horn of Africa experiences child mortality that is achingly high, with 20% of children not seeing a fifth birthday. The leading cause of death is an infectious disease controlled in many parts of the world by vaccination. Two decades of civil war and faction fighting have left the Somali healthcare system decimated, which, combined with malnourishment, has created the perfect storm needed for an opportunistic virus like measles to thrive.

Somalia has only the faintest echoes of the healthcare system components within which an effective immunization programme would operate. The central government has collapsed and there is no legal or governance framework for immunization. Many healthcare professionals have left, and facilities have been destroyed. Violence and conflict continue in some regions. There are vast numbers of internally displaced people, poor security conditions and a scattered nomadic population struggling to survive in the face of repeated droughts and food insecurity.[2]

In a rebuilding process over the last decade, an immunization programme has been established, filling a coordination vacuum that has existed among the 40 partners involved in immunization in Somalia. The national unit was set up in 2012, following establishment of units in Somaliland and Puntland in 2008. Improvements are starting to be seen in those parts of the country that are now accessible. The fledgling immunization system faces enormous challenges of access, governance, staffing and resources.

Despite these difficult circumstances, Somalia has succeeded in stopping two major polio outbreaks, thanks to the commitment of community health workers and local immunization champions. But improvements in routine immunization are hard-won. Coverage is hampered and only 30 to 40% of children are immunized against major childhood diseases. Inaccessible areas are home to more than half a million children still requiring catchup vaccination. Child health days supported by WHO and UNICEF have increased coverage by 20% but the strategy is costly, requiring $4.5 million per round, which needs to be externally funded. The funds are not available.

UNVACCINATED CHILDREN AT INCREASED RISK

The hard face of inequity -children at greater risk of diseases also least likely to be immunized.

The reality is that the child who doesn't have access to immunization is likely to be marginalized, living in poorly-served rural or remote areas, deprived urban settings, fragile states or strife-torn regions.[3] He or she is more susceptible in the first place to the diseases vaccines help prevent, with less access to treatment. It is unacceptable that children die of diseases for which vaccines are readily available.

More children in these countries need to be immunized and immunization needs to be sustainable. Improvements over time and against a country's own previous performance are of key importance. Notably, Nigeria and India have fewer unvaccinated infants in 2014 than in 2012. It is also these two countries that have seen major leaps forward in disease elimination. Both have achieved their outcomes through accountability systems binding all partners to their agreed actions, leading to real results.

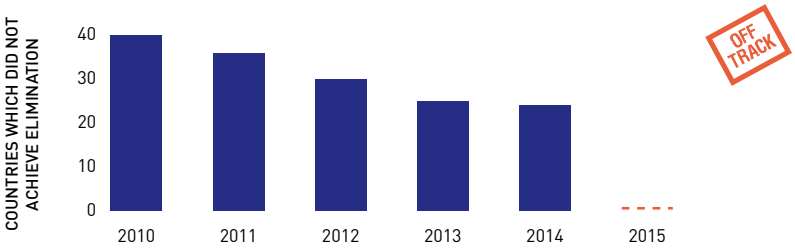
[2] Country Cooperation Strategy for WHO and Somalia 2010–2014, WHO, 2010; http://applications.emro.who.int/docs/CCS_Somalia_2010_EN_14487.pdf

[3] State of the world's vaccines and immunization, 3rd edition, 2009, WHO, Unicef and the World Bank http://apps.who.int/iris/bitstream/10665/70114/1/WHO_IVB_09.10_eng.pdf

3. DISEASE TARGETS: CHALLENGES AND OPPORTUNITIES

MATERNAL AND NEONATAL TETANUS

24 COUNTRIES DID NOT ACHIEVE ELIMINATION IN 2014

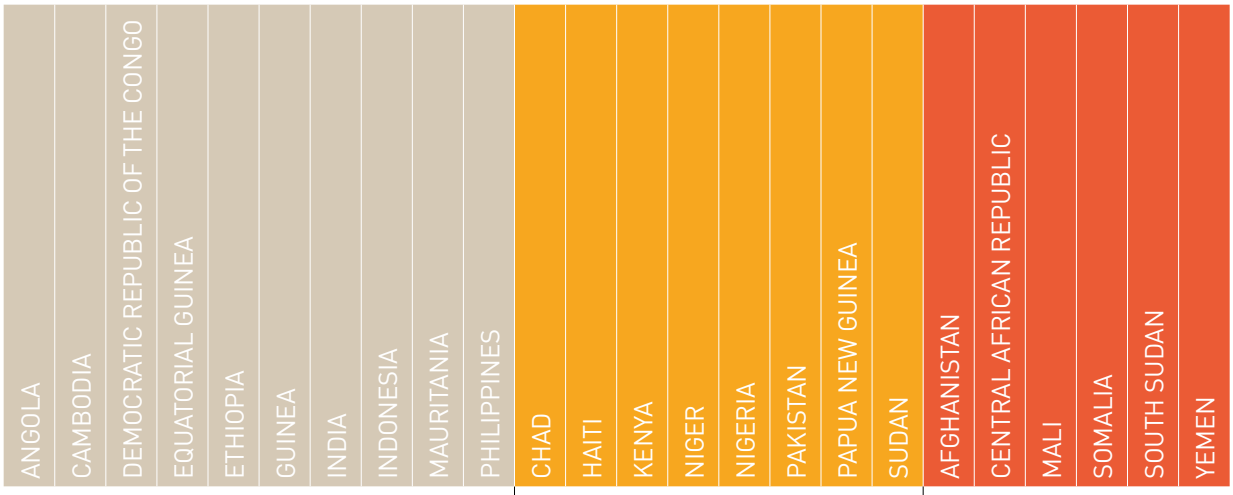


The Global Vaccine Action Plan's key disease targets included the achievable target to eliminate the terrible disease of maternal and neonatal tetanus by the end of 2015. That target will now almost certainly be missed. It is frustrating for countries, regions and the world to see a door left open to a disease that exploits those with few resources and visits needless suffering on innocents.

Sustainable maternal and neonatal tetanus elimination is achievable

Maternal and neonatal tetanus is a stark reminder of the shocking inequity in healthcare provision. The bacterium that causes tetanus will never be eradicated, but clean birth and umbilical cord care, and vaccinating mothers during pregnancy, stops maternal and neonatal tetanus from developing, saving mothers and babies.

The funding gap to rid the world of maternal and neonatal tetanus is estimated at $130 million, which is miniscule compared with the $1.1 billion spent in 2014 by Gavi, the Vaccine Alliance on new and underused vaccines programmes. In the second half of the Decade of Vaccines, there is an opportunity for countries and global partners to reorient efforts and meet and sustain the elimination goal.



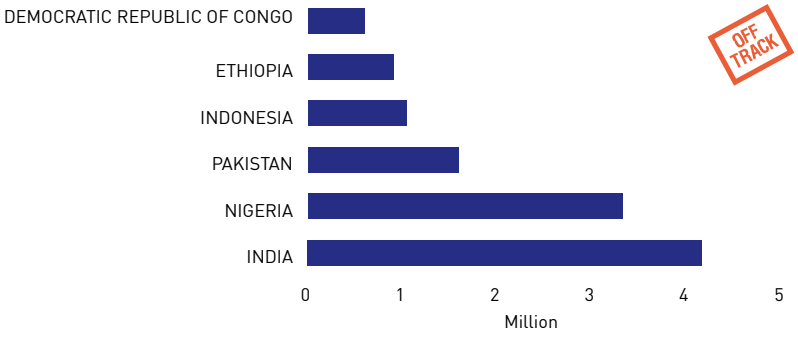
MEASLES AND RUBELLA

Three WHO regions – the Eastern Mediterranean, European and Western Pacific – vowed to wipe out measles by the end of 2015. All regions have vowed to do so within the decade. The first target will be missed and 2020 is not far away. Worse, disease is flaring in places that have forgotten what measles is like, imported from countries where vaccination rates are not high enough to stop disease spreading among the inadequately vaccinated or haphazardly or intentionally unvaccinated.

Measles is infectious and opportunistic. Children need two doses of the vaccine and countries need 95% coverage or better – nationally and across every district – to achieve elimination. But world coverage at around 85% has flatlined for the last five years.

Half of the 20.6 million children in the world who were not vaccinated at all for measles in 2014 live in six countries, which accounted for two-thirds of the conservatively estimated 145,000 measles deaths in 2014.

UNVACCINATED INFANTS FOR MEASLES FIRST DOSE, IN MILLIONS, 2014



Measles and rubella elimination – an opportunity being missed

The Global Vaccine Action Plan included a key disease target to eliminate rubella from two WHO regions by the end of 2015. Although the Americas Region has achieved elimination in 2015, the target will almost certainly be missed for the other regions. The South East Asian, African and Eastern Mediterranean WHO regions have not established elimination goals for rubella and the Western Pacific region has no target date for elimination. Europe has a goal for elimination in 2015 but is off-track.

Rubella is usually a mild illness but in early pregnancy it can cause birth defects and fetal death or lifelong disabilities due to congenital rubella syndrome. By December 2014, 140 countries had introduced rubella-containing vaccines. Global coverage is increasing but remains low, 46% in 2014 (compared with 41% in 2010). Coverage has not increased in many countries and 54 countries still do not include rubella-containing vaccines in their national schedule.

The combined vaccine for measles and rubella offers an economic solution, and the failure to link the elimination of rubella to the elimination of measles is so far a missed opportunity.

The world needs to get serious about the goal to eliminate measles along the lines of what countries, regions and global partners have mobilized to rid the world of polio. Rubella needs to be included in a new strategy so that both goals can see real progress.

4. SUCCESSES THAT CAN BE THE NORM

Performance against key immunization targets remains off-track globally in 2015, but some countries have made major breakthroughs and some targets are on-track.

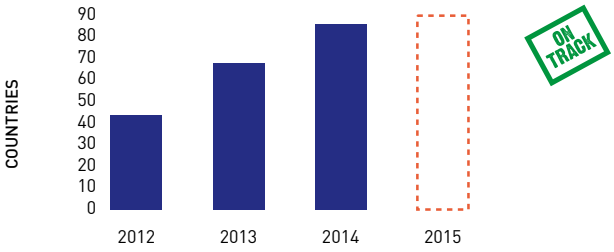
→ BREAKTHROUGHS IN NEW VACCINES

The Global Vaccine Action Plan target for introduction of new or under-utilized vaccines is on track worldwide, with 86 low and middle-income countries introducing (and sustaining for at least one year) a total of 128 vaccines since 2010.
The Ebola candidate vaccines were developed and tested swiftly with potential to protect against a terrible disease.

Although this target is on track, coverage remains low at global level and sustainability in countries eligible for Gavi, the Vaccine Alliance support continues to be of concern, along with the ability of middle-income countries ineligible for Gavi support to provide vaccines. The coverage with rotavirus and pneumococcal vaccines worldwide remains low (19% and 31% respectively in 2014).

New vaccines on track but much more potential to save lives

LOW- AND MIDDLE-INCOME MEMBER STATES THAT HAVE ADDED AT LEAST ONE NEW AND UNDER-UTILIZED VACCINE TO THEIR NATIONAL IMMUNIZATION PROGRAMME AND SUSTAINED VACCINE USE FOR AT LEAST 12 MONTHS



→ BETTER DATA ON VACCINE PRICING

Following the resolution by the World Health Assembly on vaccine pricing[4], the WHO secretariat has worked with countries to share pricing data. To date, 40 countries have shared information with WHO.

Countries recently graduated from aid have access to Gavi pricing and UNICEF procurement but they remain vulnerable in the transition period where they need to increase domestic resources. Middle-income countries that have never received significant Gavi aid and rely on self-procurement are vulnerable to vaccine pricing and stockout issues. Vaccine supply, discussed later, continues to be an issue.

→ SUCCESS ELIMINATING DISEASES

While worldwide progress against disease targets remains sluggish, some countries have achieved breakthrough success.

- India has been declared free of maternal and neonatal tetanus, demonstrating that it is possible to eliminate this terrible disease even

[4] WHA68 Resolution WH68.6 on Global Vaccine Action Plan : procurement and vaccines pricing, http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R6-en.pdf

in challenging circumstances. India is among the countries with the largest numbers of unimmunized and under-immunized children. India joins Cambodia and Mauritania, which were also declared free of maternal neonatal tetanus in the first half of 2015, and Madagascar, declared free in 2014.

- Africa has not had a case of wild poliovirus since August 2014 – an enormous achievement. Nigeria is no longer a polio-endemic country, leaving just two – Afghanistan and Pakistan. Only these two countries have had wild polio cases in 2015. India was able to make use of polio infrastructure in its recent immunization successes. Similarly, polio resources were brought to bear in containing the outbreak of Ebola virus in Africa.
- The Americas region is the first to eliminate rubella and congenital rubella syndrome, a major achievement.

Isolated examples of success that need to become the norm

5. FACTORS COMMON TO SUCCESSFUL ENDEAVOURS

The SAGE has focused its earlier report on, among other things:

- data quality
- community involvement
- vaccine supply.

These three ingredients were part of the mix in the countries where significant gains against disease targets were made in 2015.

QUALITY DATA

Without knowing who has been vaccinated for which diseases at local, country, regional and global level, it is impossible to allocate limited resources where they will provide the most return or to understand how to improve programme effectiveness or efficiency. Data need to be useful and inform strategy at every level.

In India, the strategy to eliminate maternal and neonatal tetanus was data-driven. Elimination was supported by Mission Indradhanush (Rainbow), a 2015 vaccination campaign that made good use of resources by targeting low vaccination coverage areas to maximize success. Data drove every step of Mission Indradhanush, from understanding why children were being missed and implementing strategies to overcome, to targeting districts where vaccination rates were low. Data were also available at delivery level, with meticulous planning of vaccination sessions to locate missed children and constant monitoring of outcomes. Data informed India's maternal and neonatal tetanus elimination strategy more broadly too, to determine education and training needs so that health workers and nurses would be in place – 500,000 frontline health workers were trained – to upgrading primary health care clinics to accommodate birth care in response to community demand, and to integrate immunization and antenatal care to maximize success.

Data quality is of key importance and perhaps no country understands this better than Mexico, which had to see a 'drop' in vaccination rates in order to improve them.

CASE STUDY: 'POOR' PERFORMANCE LEADING TO REAL IMPROVEMENTS

During 2013, Mexico started a process to improve data for its immunization programme. This included revising population figures as well as replacing an antiquated information system.

The improvement process resulted in 2013 immunization coverage figures lower than previously recorded.

As the data quality improvements were implemented in each state and more accurate counts were able to be done, 2014 coverage rates improved and will likely continue to do so.

Mexico has persisted courageously with its data quality improvement plan and is now, with better data, moving forward towards filling gaps in immunization coverage in a more targeted manner.

COMMUNITY OWNERSHIP

A WHO review of the countries that have successfully eliminated maternal and neonatal tetanus put a high value on early and active community engagement. The effectiveness of community health worker interventions is well documented especially in rural and marginalized populations.[5]

In Africa, polio eradication has been transformed by involvement of community leaders at local and district levels and by armies of community workers, even in countries with chronic disruption like Somalia.

India's success with maternal and neonatal tetanus similarly relied heavily on community health workers and civil society organizations. The key factor is that volunteers are from the communities in which they work.

VACCINES AVAILABLE

In 2014, the SAGE drew attention to a lack of good data on vaccine affordability and supply of vaccines. In order to increase vaccination rates, vaccines must be available.

A total of 33 countries reported interruptions in service because of vaccine shortages during 2014. More than half the stockouts were caused by problems within countries. Stockouts at national level caused stockouts at district level that interrupted immunization services.

Clearly, this problem needs to be addressed in legislative frameworks for procurement and in national immunization plans. Running out of vaccines because of poor procurement mechanisms or a lack of planning will imperil vaccination programmes. A child arrives ready for vaccination and there's no vaccine. This needs to be avoided at all cost, as a demotivated caregiver will not return which means that large numbers of under-immunized children are at risk. It must be addressed in country planning and governance processes for immunization.

CASE STUDY: MORIBUND PROCUREMENT SYSTEM LEAVES CHILDREN AT RISK

The Philippines has been funding its immunization programme since the 1990s but in recent years the complicated procurement process applying to all government-bought goods and services has led to long delays and restarts in procurement.

Vaccine stockouts continue to plague delivery of immunization and coverage has now been affected and in 2014 the immunization rate dropped below 80%.

[5] How effective are community health workers? an overview of current evidence with recommendationsfor strengthening community health worker programs to accelerate progress in achieving the health-related millennium development goals, Perry H and Zulliger R, Johns Hopkins Bloomberg School of Public Health , September 2012; http://www.coregroup.org/storage/Program_Learning/Community_Health_Workers/review%20of%20chw%20effectiveness%20for%20mdgs-sept2012.pdf

6. LEADERSHIP AND ACCOUNTABILITY - THE WAY FORWARD

For more than one year, there has not been a single case of wild poliovirus in Nigeria. On 25 September 2015, the Director-General of WHO announced that Nigeria is no longer a polio-endemic country. Ask anybody involved what was responsible for this momentous success. They soon mention one word: accountability. The country and its technical partners established and enforced clear accountability systems, to measure results, reward those who achieve them, and to discipline or part company with those who did not. This was not the only factor, but it was a crucial one.

Leadership - the difference between failure and success

While SAGE would not expect there to be major shifts against key disease targets globally year on year, the SAGE has examined what has changed in vaccination programmes themselves over the last year. Accountability has improved a little, but nowhere near the extent it needs to. Accountability is key to success.

In the successful programmes reviewed by the SAGE in 2015, in-country leadership has been of key importance. In Somalia, a lack of national leadership has affected service delivery, staffing, information and especially financing. Even if vaccines are provided and delivered by external aid agencies and campaigns, the underlying healthcare system issues mean change will be unlikely to be sustained.

In India, the successful strategy to eliminate maternal and neonatal tetanus had many strengths but there is no doubt that one of them was leadership to build accountability at every level.

CASE STUDY: LEADERSHIP CHARACTERIZES SUCCESS IN MISSION INDRADHANUSH

India's Mission Indradhanush (Rainbow) was underpinned by leadership at every level. This campaign throughout India over four months of 2015 combined with routine immunization to vaccinate an additional 6.65 million children and 1.73 million pregnant women.

The Indian Government resourced Mission Indradhanush and was committed to its success at the highest level. The Prime Minister made a national statement. The Minister for Health wrote to all frontline health workers involved in the programme. This was followed up by district and local leaders.

Another aspect of leadership was community-based. Research had suggested awareness and apprehension were key factors in children being missed for vaccination. The strategy to recruit an army of local community health workers who played a key social mobilization role combined with others such as translation to local language to aid success, along with an integrated media strategy.

Leadership ensured that Mission Indradhanush was supported. Leadership gave Mission Indradhanush its authority and resources. Leadership also ensured resources would be delivered where needed. And finally, leadership mobilized civil society organizations who could in turn play a community leadership role.

The SAGE heard from a number of support organizations that are working innovatively with countries towards better leadership, partnering low-income countries with recently Gavi-graduated countries that have a good understanding of the challenges to be faced. Gavi, the Vaccine

Alliance, through its planning process, is able to make major steps toward not only improving healthcare systems for sustainability but also improving leadership in-country so that sustainability can be guaranteed and accountability can be clear.

Accountability to ensure achievement of the Global Vaccine Action Plan's goals needs to occur at three levels:

- In countries – where the difference is made
- In WHO regions – where the Global Vaccine Action Plan is translated into a regional framework, support ensured and best practices shared
- At global level – where the Global Vaccine Action Plan partners can do much to support countries towards accountability and SAGE can help them.

COUNTRY ACCOUNTABILITY

Accountability for achieving the GVAP goals rests with countries

Countries dedicated themselves to achieving the goals of the Global Vaccine Action Plan. As part of the accountability system, every country should have in place a national vaccine action plan. Currently 72 countries supported by Gavi, the Vaccine Alliance, along with 9 other countries, have comprehensive multi-year plans as part of the planning system. The new planning guidelines reflect the Global Vaccine Action Plan goals and strategies and 61 plans recently revised or in process of revision have been or will be prepared with the new guidelines. Other countries will have national immunization plans which now need to be aligned to the Global Vaccine Action Plan and its regional counterpart.

Progress towards outcomes set out in plans should be reviewed annually by an independent body with technical expertise such as the country's national immunization technical advisory group (NITAG) and a body with management expertise such as an inter-agency coordinating committee (ICC). In 2014, 123 countries reported having a NITAG, and only 25 of these were Gavi-eligible countries. Only 81 countries had a NITAG that met WHO criteria for functionality, and only 15 of these were Gavi-eligible countries. All countries should have an independent technical advisory group with a range of responsibilities, not least of which must be a key role in accountability.

Human and physical resources must be in place to deliver plans; and integration with other healthcare services can create efficiencies and reduce missed opportunities. Where these building blocks of sustainable healthcare systems are not in place, global partners can be of great support.

With most unvaccinated and under-vaccinated children living in either particular geographical areas where there is inequity within countries or within countries where health systems are weak, national plans must have strategies to promote equity in immunization, across the lifespan and different population groups.

It is far better that plans be useful than tick boxes and for this reason those who implement plans should have a key role in developing them. Underpinning country-level plans: there should be more detailed district implementation plans to ensure that the limited resources are being allocated where they will do most good.

WHO REGIONAL ACCOUNTABILITY

Last year, WHO regions were asked to finalize their own vaccine action plans. In 2015, mid-decade, three of the six regions have a regional vaccine action plan in place. Regions play a leadership role in ensuring that the Global Vaccine Action Plan's goals are made relevant to the particular region and a key role in the accountability system for the plan.

Africa, Europe and the Western Pacific regions have developed regional plans. At the time of writing, the Americas and Eastern Mediterranean regions are in the process of adopting plans. The South East Asian region needs to complete its plan as a high priority and certainly all plans must be finalized by the end of 2015 and adopted in 2016, to give countries guidance in their own planning processes.

Regional plans provide the accountability framework for countries

When the Global Vaccine Action Plan was adopted by the World Health Assembly in 2012, countries were urged to report yearly to their regional committees during the Decade of Vaccines on lessons learned, progress made, remaining challenges and updated actions. Each region should now have in place formal monitoring and accountability processes. Country performance against plans should be reviewed at regional level by the regional immunization technical advisory group and regional committee.

Last year the WHO convened a meeting of countries in which vaccination rates were below 80%. This year, the SAGE has focused on the ten countries where most unvaccinated and under-vaccinated children live and the seven countries where vaccination rates are below 50%. Regions should ensure that they are working with countries where vaccination rates are low to support them to strengthen healthcare systems and improve immunization rates.

GLOBAL ACCOUNTABILITY

At global level, SAGE remains unclear about accountability mechanisms. Each partner organization has its own planning and evaluation frameworks. It is not clear how leadership and accountability operate to ensure contribution to achievement of the Global Vaccine Action Plan's goals. In areas where the plan is furthest behind – maternal and neonatal tetanus and measles and rubella – coordination is of key importance but there also needs to be wider accountability if the Global Vaccine Action Plan is to reach its goals.

Countries are primarily accountable for achievement of the Global Vaccine Action Plan, and support from technical partners must always be aligned to country-owned strategies and frameworks. But many countries could benefit from more help from technical partners in developing their accountability frameworks. Partners therefore have an important part to play in strengthening the accountability mechanisms that exist in countries, focusing on building leadership and health system improvements.

Global partners need to strengthen country accountability

As part of the WHA resolution adopting the Global Vaccine Action Plan, WHO was asked to foster alignment and coordination of global immunization efforts by all stakeholders to support the plan. At this midpoint, the global partners - including the GVAP core group of WHO, UNICEF, Gavi, The Bill & Melinda Gates Foundation and the National Institute of Allergy and Infectious Diseases – should align their efforts and contributions to achieving the GVAP's goals going forward, both in relation to specific disease targets and to the broader immunization agenda. They can best do this by supporting countries towards better healthcare systems and improved accountability. Gavi, the Vaccine Alliance already achieves this through its processes for comprehensive multi-year plans, providing accountability and ensuring resources are used effectively towards changes in healthcare systems. Global partners

have leverage – they provide resources and technical support – to achieve much.

This is critical to ensure that support to countries for the implementation of the Global Vaccine Action Plan during the remaining half of the Decade of Vaccines is transformative and goes away from the incremental and 'business as usual' approaches observed thus far.

SAGE, which through its Decade of Vaccines Working Group has the key role in assessing progress towards the Global Vaccine Action Plan goals, will use reports from global partners – on their efforts to support countries to strengthen leadership and accountability and on their contributions to strengthening healthcare systems – as well as reports from WHO regions on progress in countries, as the framework for future annual reports to 2020.

7. CONCLUSION AND RECOMMENDATIONS

The Decade of Vaccines is at its critical mid-point. The Global Vaccine Action Plan remains off-track, though this report details reasons to be optimistic. If the successes won by some countries, through leadership and accountability at all levels, can be replicated, the Global Vaccine Action Plan will see global progress in the second half of the Decade of Vaccines.

SAGE RECOMMENDS:

To improve accountability to achieve the Global Vaccine Action Plan goals:

1. **Countries** finalize by mid-2016 national vaccine action plans to 2020, consistent with the Global Vaccine Action Plan and relevant regional vaccine action plans, and establish an annual process for monitoring and accountability through an independent body, for example the National Immunization Technical Advisory Group (NITAG).
2. Once regional vaccine action plans are finalised (by December 2015),**WHO regional offices** establish a process of annual progress review through their regional technical advisory committees and report annually to the respective Regional Committees. This process should involve receiving reports from each country against achievement of outcomes, and working with countries to address shortcomings. The first such annual review should take place in the first half of 2016. WHO Regional Committees reports should be made available annually to SAGE as part of the global review process.
3. **Global, regional and national development partners** align their efforts to support countries in strengthening their leadership and accountability frameworks and in implementing their national plans. Decade of Vaccines secretariat agencies to report in 2016 to SAGE on their supporting activities conducted in the 10 countries where most of the unvaccinated and under-vaccinated children live. This reporting mechanism should include regional technical advisory groups.

To address the shortfalls in disease-specific areas of the Global Vaccine Action Plan's implementation:

4. Given poor progress and the relatively small funding gap, WHO and UNICEF convene a meeting of **global partners and the remaining 24 countries** to agree an action plan, resources and respective responsibilities so that the goal to eliminate maternal and neonatal tetanus is achieved by not later than 2017 and strategies are in place to sustain elimination in all countries.
5. **Global, regional and national development partners support countries** in securing the required resources and in implementing their measles and rubella elimination or control goals taking into account the results and recommendations of the midterm strategy review to be conducted in 2016.

To improve immunization coverage especially where many unvaccinated and under-vaccinated children live:

6. **Global, regional and country development partners to** align their efforts to support countries to immunize more children by strengthening their healthcare delivery systems, combined with targeted approaches to reach children consistently missed by the routine delivery system, particularly in the countries where vaccination rates are below 80 per cent.
7. **WHO** to provide guidance for countries and partners on implementation of immunization programmes and immunization strategies during situations of conflict and chronic disruption.

ANNEX: STRATEGIC ADVISORY GROUP OF EXPERTS ON IMMUNIZATION (SAGE) DECADE OF VACCINES WORKING GROUP MEMBERS

SAGE MEMBERS

- Narendra Arora (Chair of the Working Group), Executive director, International Clinical Epidemiology Network, India
- Yagob Al-Mazrou, Secretary General - Health Services Council of the Kingdom of Saudi Arabia, Saudi Arabia
- Alejandro Cravioto, Senior Epidemiologist, Global Evaluative Sciences, Seattle, USA (as of February 2015 and previously Chief Scientific Officer, International Vaccine Institute, Seoul, Republic of Korea) (SAGE member as of October 2015)

EXPERTS

- Fuqiang Cui, Epidemiology Professor, Deputy Director National Immunization Program, China CDC, China
- Elizabeth Ferdinand, Associate Lecturer, University of the West Indies – Cave Hill, Barbados (affiliation as of September 2014 and previously Senior Medical Officer of Health and EPI Manager, Barbados)
- Alan Hinman, Senior Public Health Scientist - Task Force for Global Health, USA
- Stephen Inglis, Director, National Institute of Biological Standards & Control, Health Protection Agency, UK
- Marie-Yvette Madrid, Independent Consultant, Geneva, Switzerland (as of June 2014 to replace Shawn Gilchrist)
- Amani Mahmoud Mustafa, Project Manager, Sudan Public Health Training Initiative, The Carter Center, Sudan (affiliation as of May 2014 and previously EPI Manager, Ministry of Health, Sudan)
- Rebecca Martin, Director, Global Immunization Division, US CDC, USA
- Rozina Mistry, Lecturer and Course Director, Aga Kahn University, Pakistan
- Helen Rees, Executive Director - Reproductive Health Research Unit, University of Witwatersrand, South Africa (former SAGE Chair 2010 - 2013)
- David Salisbury, Associate Fellow, Centre on Global Health Security, Chatham House, London, UK (affiliation as of January 2014 and previously Director of Immunization, Department of Health, UK and former SAGE Chair 2005 - 2010)
- Independent consultant: Mary-Rose McColl

WORKING GROUP SECRETARIAT

- Bill & Melinda Gates Foundation
- Gavi, the Vaccine Alliance
- United States National Institute of Allergy and Infectious Diseases
- United Nations Children's Fund
- World Health Organization

Global vaccine action plan

The Sixty-eighth World Health Assembly,

Having considered the report on the global vaccine action plan;[1]

Emphasizing the importance of immunization as one of the most effective interventions in public health and access to immunization as a key step towards access to health and universal health coverage;

Acknowledging the progress made in global immunization and the commitment under the 2011–2020 Decade of Vaccines to achieve immunization goals and milestones;

Recalling resolutions WHA58.15 and WHA61.15 on the global immunization strategy, resolution WHA65.17 on the global vaccine action plan, resolution WHA61.21 on the global strategy and plan of action on public health, innovation and intellectual property, resolution WHA54.11 on the WHO medicines strategy and resolution WHA67.20 on regulatory system strengthening for medical products;

Noting with concern that globally immunization coverage has increased only marginally since the late 2000s; and that in 2013 more than 21 million children under one year of age did not complete the three-dose series of diphtheria-tetanus-pertussis (DTP) vaccine;

Recognizing that the availability of new vaccines against important causes of vaccine-preventable diseases such as pneumonia, diarrhoea and cervical cancer can prevent leading causes of childhood and women's death;

Acknowledging that successful national immunization programmes require sustainable political and financial support of Member States;

Appreciating the contributions of WHO, UNICEF, the Gavi Alliance, and all partners in their efforts to support the introduction of new vaccines in developing countries and strengthen immunization services;

Concerned that inequities between Member States are growing, inter alia, due to the increased financial burden of new vaccines and based upon those that are eligible or ineligible for financial and technical support from global partners;

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[1] Document A68/30.

Concerned that many low- and middle-income countries may not have the opportunity to access newer and improved vaccines, particularly because of the costs related to the procurement and introduction of these vaccines; and concerned at the increase of costs of overall immunization programmes because of increase in price of the WHO-recommended vaccines;

Recognizing that publicly available data on vaccine prices are scarce, and that the availability of price information is important for facilitating Member States' efforts towards introduction of new vaccines;

Recalling many Member States' interventions on the Health Assembly's immunization agenda item each year, expressing concern over the unaffordable cost of new vaccines and appealing to the global community to support strategies that will reduce prices;

Recalling the WHO global framework for expanding access to essential drugs, and its four components: the rational selection and use of medicines, reliable health and supply systems, sustainable financing, and affordable prices;

Taking into account the importance of competition to reduce prices and the need to expand the number of manufacturers, particularly in developing countries, that can produce WHO-prequalified vaccines and create a competitive market;

Stressing the critical life-saving role of vaccines and immunization programmes and striving to make immunization available to all;

Noting with concern the global shortage of certain traditional routine vaccines, for example BCG vaccine and combined measles-rubella vaccine;

Acknowledging that shortages of vaccines are quite often an important cause of disruption of vaccination schedules and that therefore the establishment of effective and sustainable vaccine production, supply, procurement and delivery systems is essential to ensure access to all the necessary vaccines of assured quality at the right time;

Concerned that scepticism against vaccination is continuing to grow in society despite the proven efficacy and safety of modern vaccines, and that many children do not receive life-saving vaccines as a result of insufficient information to parents or health care workers or even of active anti-vaccination propaganda,

1. URGES Member States:[1]

(1) to allocate adequate financial and human resources for the introduction of vaccines into national immunization schedules and for sustaining strong immunization programmes in accordance with national priorities;

(2) to strengthen efforts, as and where appropriate, for pooling vaccine procurement volumes in regional and interregional or other groupings, as appropriate, that will increase affordability by leveraging economies of scale;

[1] And, where applicable, regional economic integration organizations.

(3) to provide, where possible and available, timely vaccine price data to WHO for publication, with the goal of increasing affordability through improved price transparency, particularly for new vaccines;

(4) to seek opportunities for establishing national and regional vaccine manufacturing capacity, in accordance with national priorities, that can produce to national regulatory standards, including WHO-prequalification;

(5) to create mechanisms to increase the availability of comparable information on government funding for vaccine development and work towards strategies that enhance public health benefit from government investments in vaccine development;

(6) to support the ongoing efforts of various partners coordinated by WHO to design and implement the strategies to address the vaccine and immunization gaps faced by the low- and middle-income countries that request assistance;

(7) to improve and sustain vaccine purchasing and delivery systems in order to promote the uninterrupted and affordable safe supply of all the necessary vaccines and their availability to all immunization service providers;

(8) to strengthen immunization advocacy and provide training to health professionals and information to the public regarding immunization issues in order to achieve a clear understanding of the benefits and risks of immunization;

2. REQUESTS the Director-General:

(1) to explore ways to mobilize funding to fully support collaborative efforts with international partners, donors, and vaccine manufacturers in order to support low- and middle-income countries in accessing affordable vaccines of assured quality in adequate supply;

(2) to continue developing and adequately managing publicly available vaccine price databases, like the WHO Vaccine Product, Price and Procurement project, working with Member States to increase availability of price information;

(3) to monitor vaccine prices through annual reporting of the global vaccine action plan;

(4) to provide technical support and facilitate financial resources for establishing pooled procurement mechanisms, where appropriate, for use by Member States;

(5) to strengthen the WHO prequalification programme and provide technical assistance to support developing countries in capacity building for research and development, technology transfer, and other upstream to downstream vaccine development and manufacturing strategies that foster proper competition for a healthy vaccine market;

(6) to report upon technical, procedural and legal barriers that may undermine the robust competition that can enable price reductions for new vaccines, and address other factors that can adversely affect the availability of vaccines;

(7) to assist in mobilizing resources for countries that request assistance in the introduction of new vaccines in line with the global vaccine action plan and in accordance with national priorities;

(8) to continue to assist Member States to improve and sustain their vaccine delivery systems and to continue to provide technical support to Member States to strengthen the knowledge and skills of their health care professionals in vaccination programmes;

(9) to report on progress in implementing this resolution to the Health Assembly through the Executive Board in the annual report on the global vaccine action plan.

Ninth plenary meeting, 26 May 2015
A68/VR/9

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