EXPERT REVIEWS

Consultation on interactions between National Regulatory Authorities and National Immunization Technical Advisory Groups

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Liliana Chocarro[1], Philippe Duclos[1], Kamel Senouci[†2] and James Southern[3]

[1]*World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland*
[2]*Agence de Médecine Préventive, AMP c/o Institut Pasteur, 25–28 rue du Docteur Roux, 75724 Paris Cedex 15, France*
[3]*Developing Country Vaccine Regulators' Network c/o WHO, 20 Avenue Appia, CG-1211 Geneva 27, Switzerland*
[†]*Author for correspondence: Tel.: +33 153 868 920 ksenouci@aamp.org*

A consultation during the Developing Country Vaccine Regulators' Network meeting of May 2010 considered the interactions between the National Immunization Technical Advisory Group (NITAG) and the National Regulatory Authority (NRA) in various countries. This meeting was co-hosted by the WHO and the Supporting Independent Immunization and Vaccine Advisory Committees Initiative implemented by the Agence de Médecine Préventive in partnership with the International Vaccine Institute. Representatives from Developing Country Vaccine Regulators' Network and representatives from several additional countries' regulatory authorities met representatives from NITAGs and/or the National Immunization Program from these countries (Brazil, Canada, China, Cuba, France, Indonesia, Iran, South Africa, Thailand, Vietnam and the USA). The objectives of the workshop included a discussion on the issues of NRA–NITAG interaction, the assessment of the advantages of different models of interaction and proposals for an optimal coordination process for market authorization and recommendations for use of vaccines. It was concluded that there is need for increased and more formal interactions between NRAs and NITAGs, a clear framework establishing a formal interaction and early interactions before market authorization. NRA experts being at the same time NITAG *ex officio* members and vice versa are solutions which can be adopted by countries. The NRA issues the license based on the evidence submitted by the manufacturer. The NITAG makes recommendations based on scientific evidence, public health needs and policy, and consideration of the license conditions. If there is a need to make recommendations that are not covered by the license evidence then there should be interactions between NITAG, NRA and the license holder to encourage the license-holder to submit appropriate evidence, or to ensure that the justification for the off-label recommendation is communicated to the users of the medicine.

Keywords: decision-making • evidence-based • health policy • immunization • national immunization technical advisory groups • national regulatory authorities • vaccines license

The need for evidence-based decision-making in immunization programs has become crucial in light of multiple health priorities, limited human resources and logistical capacities, as well as the high cost of vaccines relative to limited public funds that are available. Evidence-based decision-making can provide support for immunization programs compared with other health interventions, and within immunization programs, can inform decisions related to new vaccine introduction, vaccine priorities, vaccine schedules, target groups and other issues.

The Global Immunization Vision and Strategy [1] guiding principles state that countries should have ownership for decision-making in immunization policies and systems, and that these decisions should be based on evidence and best practices. An important step that countries can take to encourage well-informed decision-making regarding immunization is to establish a group of national experts to advise the Ministry of Health. So far, most industrialized countries and some developing countries have already constituted National Immunization

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Technical Advisory Groups (NITAGs) to guide immunization policies, while other countries are currently working towards the establishment of NITAGs. The main role of NITAGs is to help health authorities formulate immunization policies according to the specific needs of their country, while taking into account the regional and international context [2].

In addition to the technical support WHO is providing to countries, the Agence de Médecine Préventive, in partnership with the International Vaccine Institute have established, with the financial support of the Bill & Melinda Gates Foundation, the Supporting Independent Immunization and Vaccine Advisory Committees (SIVAC) Initiative [3] in close collaboration with the WHO. The aim of the SIVAC Initiative is to help countries establish or strengthen NITAGs. This support is provided to middle-income countries (according to the World Bank data [4]) and countries that are eligible for support from the Global Alliance for Vaccines and Immunization [5]. Eligibility is determined by national income with all countries with a Gross National Income per capita below or equal to US$1500 qualifying for support. As of 2009, there were 56 Global Alliance for Vaccines and Immunization-eligible countries. The SIVAC Initiative acts through direct technical assistance to 13 countries and, in addition, also contributes to activities and products that can benefit a wider range of countries (e.g., training, development of tools and information sharing between NITAGs through the collaborative NITAG Resource Center [6]).

The role & responsibilities of NITAGs

NITAGs provide public health immunization policy makers with evidence-based recommendations. They should be a neutral, credible source of advice.

NITAG functions include:

- Formulation of immunization policies and strategies optimal for the local conditions
- Monitoring the National Immunization Program through collection and analysis of immunization and safety data
- Maintaining scientific and practical expertise in developments in vaccines and vaccine-preventable diseases

A NITAG is solely a technical advisory body, and should not be involved in policy implementation or regulatory functions.

National Immunization Technical Advisory Groups should be formally established with defined operating procedures, suitable budgets and multidisciplinary membership including scientists and clinicians. *Ex officio* members may include officials from the Ministry of Health, the Public Health Immunization Program and National Regulatory Authorities (NRAs). It is normal that a NITAG will interact with both the NRA and the National Immunization Program to ensure that appropriate vaccines are available for use and to provide guidance on the optimal use of these vaccines in the national context. Recommendations on optimal use of vaccines may include a cost–benefit analysis by the NITAG.

A global survey of existing NITAGs has highlighted some key issues that need to be addressed. Among these issues, the most common were: NITAG members not being independent from the National Immunization Program; the difficulty to recruit a sufficiently broad and relevant expertise; the lack of cooperation of private health delivery systems; the lack of declaration of potential conflicts of interest; the need for public transparency in decision-making; and the need for more interactions between NRAs and NITAGs/Expanded Program on Immunization.

The role & responsibility of the NRA in the field of vaccines

The NRA has the task of ensuring the quality, safety and efficacy of medicines used in the country. This is achieved through the six WHO-defined vaccine-related functions of an NRA:

- Marketing authorization and licensing activities
- Post-marketing surveillance including monitoring of adverse events following immunization
- Lot release
- Laboratory access
- Regulatory inspections
- Regulatory oversight of clinical trials

The licence for market authorization of medicines and vaccines requires evidence of safety and efficacy in the intended population. The mode of use is set out in the prescribing information and this is based on the evidence supporting the licence application. It is not the role of the NRA to recommend use of a vaccine in a public health program, although it may take steps to ensure that manufacturers provide evidence of suitability if it is likely that the vaccine may be used in that way.

Interaction between the NRA & the NITAG

The Global Immunization Vision and Strategy calls for an optimized interaction between NITAGs with National Immunization Programs and the NRA. Preliminary analysis has shown that for many countries, the NRA and NITAG operate independently and that there may be little connection between the vaccine licence (market authorization), registered conditions of use, and the NITAG recommendations for use in public health programs. There is a perception that this could lead to problems in public health programs, such as vaccines being used in ways other than the registered indication or schedule.

An initial consultation (coordinated jointly by the WHO and SIVAC Initiative) held at the 2009 3rd Global Meeting on Implementing New and Under-utilized Vaccines, revealed that for many participants (representing countries, international organizations, technical agencies, non-governmental organizations and manufacturers):

- Relations between NRAs and NITAGs are not considered satisfactory (78% of responding participants);

- Exchange of information between the NRA, immunization program and NITAG is reported as insufficient;
- Vaccines may not be used in the National Immunization Program as indicated in the registered indication, as has happened in some countries with oral polio vaccines, pneumococcal conjugate vaccines and Bacille Calmette–Guérin vaccine, amongst others;
- Some NRAs consider that once they make a decision, they do not have to be involved in the decisions to implement the use of the vaccine in the National Immunization Program, or the NRA may not be consulted during this decision-making;
- Respective roles of NRAs and NITAGs are not clear for all stakeholders.

The consultation provided evidence that there are several examples of discrepancy between the way in which vaccines are used and the evidence of safety and efficacy used to support the marketing authorization, and that improved interaction could result in better consistency between authorization for use (NRA decision) and recommendation for use (NITAG recommendation).

During the 3rd Global Meeting on Implementing New and Under-utilized Vaccines, participants agreed on several recommendations for the WHO and SIVAC initiative:

- To design specific studies to assess the real interactions between NRAs and NITAGs;
- To include existing NRA forum networks and NITAGs in global, regional or specific meetings to discuss ideal interactions;
- To reinforce the support for the establishment and strengthening of NITAGs and NRAs;
- To improve the dissemination of existing guidelines relevant to roles and responsibilities of NRAs and NITAGs.

The Developing Country Vaccine Regulators' Network

Established by the WHO in 2004 [7], the Developing Country Vaccine Regulators' Network (DCVRN) comprised representative members from NRAs of developing countries: Brazil, China, Cuba, Republic of Korea, India, Indonesia, South Africa and Thailand. The DCVRN has a focus on cooperation to strengthen regulatory control of vaccines through improving regulatory capacity in member countries and support for similar WHO activities in other regions. Past activities have concentrated on the regulatory pathways of vaccine clinical trials and establishing procedures and mechanisms to ensure that these meet internationally accepted norms. Scientific sessions have provided up-to-date information on new vaccines, vaccines in development and postmarketing issues following vaccine introduction. The DCVRN provides a forum for debate between member NRAs and formulates considerations for WHO expert committees. This consultation with NITAG representatives is within the terms of reference of the DCVRN and broadens the existing activities.

Following the 3rd Global Meeting on Implementing New and Under-utilized Vaccines, the WHO and SIVAC Initiative agreed that a consultation with NRAs and NITAGs should be coordinated as soon as possible, and that existing regulatory networks should be utilized for this purpose. As the DCVRN brings together senior regulators from eight developing countries, it was proposed, and agreed, that the NITAG/NRA consultation could be part of the DCVRN meeting. Additional high-income countries with well established NITAGs and NRAs were invited to enrich the discussion (Canada, France and the USA).

The objectives of this consultation included:

- Briefing on the 3rd Global Meeting on Implementing New and Under-utilized Vaccines in 2009
- Reports of existing NRA–NITAG interactions
- Assessing opportunities for NRA–NITAG coordination
- Validation of issues raised at the 3rd Global Meeting on Implementing New and Under-utilized Vaccines in 2009

The expected outcomes included:

- A report defining the relative roles and responsibilities of NRAs and NITAGs
- The compilation of perceived benefits/problems in these interactions
- A proposal for a general procedure for improved interaction

Specific country NRA–NITAG experience

During this workshop, representatives from several countries had the opportunity to present the manner in which their respective NITAG and the National Immunization Program interact with the NRA.

Brazil: Maria Fernanda RS Thees (Agencia Nacional de Vigilância Sanitária [ANVISA], Brazil) & Reinaldo de Menezes Martins (Comitê Técnico Assessor de Imunizações [CTAI], Brazil)

The laws empowering the Brazilian NRA, ANVISA, and its activities were outlined. CTAI is the Brazilian NITAG and it was established in terms of national regulation in 1991. It has contributed to policy making with advice, advisory documents and reports on the inclusion and use of vaccines in the National Immunization Program.

The CTAI includes representation from ANVISA and has been successful in its tasks.

Indonesia: Sri Rezeki Hadinegoro (Indonesian Technical Advisory Group on Immunization [ITAGI], Indonesia) & Lucky Slamet (National Agency of Food and Drug Control [NAFDC], Indonesia)

The laws empowering the Indonesian NRA and its activities were outlined. The Indonesian Technical Advisory Group on Immunization was established by ministerial decree in 2006. Activities include advice to national government on vaccines, immunization choices and strategies, new vaccines and new delivery technologies, and assistance in evidence-based

decision-making. NITAG's core members are independent from the Ministry of Health and then can express a neutral point of view. Core members include academic and professionals with a representative from the public immunization program. *Ex officio* representatives from the NRA and other Ministries are included. This arrangement has functioned well.

Canada: Elwyn Griffiths (Biologics and Genetic Therapies Directorate [BGTD], Canada) & Joanne Langley (National Advisory Committee on Immunization [NACI], Canada)

The laws empowering the Canadian NRA and its activities were outlined. Responsibility for regulatory oversight of vaccines rests with Health Canada (the NRA) while the Public Health Agency is responsible for control and prevention of infections diseases. The Provincial & Territorial Governments implement provincial immunization programs.

The National Advisory Committee on Immunization (NACI) provides advice on the use of registered vaccines but is not consulted during the clinical development market authorization. Members are multidisciplinary volunteers from academic and professional organizations, and provide advice to the Public Health Agency of Canada. NACI recommendations may differ from the registered prescribing conditions. Meetings and advice statements are public and open to legal challenge.

USA: Melinda Wharton (CDC), Norman Baylor (US FDA) & Jean Clare Smith (CDC), although unable to join, contributed to the preparation of the presentation

In the USA, the FDA provides the regulatory control and licence for vaccines and includes a Vaccines and Related Biological Products Advisory Committee (VRBPAC).

The NITAG in the USA is the Advisory Committee on Immunization Practices (ACIP), which advises the CDC and Department of Health and Human Services (HHS) on vaccine use recommendations. The ACIP drafts policy recommendations for vaccines and related agents that are licensed by the FDA for prevention of diseases; recommendations are reviewed and, if accepted by the CDC/HHS, become national policy. Membership is multidisciplinary, academic and professional, but includes added non-voting *ex officio* members from federal agencies (including the FDA) and representatives of liaison and stakeholder organizations. Meetings are public, but most work is done in closed work groups. The ACIP works with public information and with unpublished information. The ACIP may make off-label recommendations.

France: Daniel Floret (Comité Technique des Vaccinations [CTV], France) & Isabelle Morer (Agence Française de Sécurité Sanitaire des Produits de Santé [AFSSAPS], France), although unable to join, contributed to the preparation of the presentation

Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), the French Health Products Safety Agency, was legally established in 1998 with specialized working groups for evaluation of biological medicines including vaccines. Vaccination policy is developed by the Haut Conseil de la Santé Publique that includes the expert advisory Technical Vaccine Committee (CTV), the NITAG. CTV membership is multidisciplinary and includes *ex officio* members from AFSSAPS, and health and other ministries. Working groups are set up to address specific issues where AFSSAPS will advise on evidence for vaccine efficacy and safety. Experience has shown that strong cooperation between CTV and AFSSAPS is needed at various steps of the process and that personal interactions may frequently speed up the process.

Discussion

Group discussions were conducted to allow NRAs and NITAGs to independently assess their separate roles and current interactions. Subsequently, combined groups formulated proposals for the appropriate level and mode of interaction that could result in an optimal decision-making process. These ideas were then presented for consideration by the entire meeting.

Participants in the workshop generally agreed on the importance of NRA and NITAG interactions. Off-label recommendations by a NITAG have occurred in many countries, particularly with regard to dosing, schedule and/or indications. This NITAG advice has been the result of careful consideration of the risks and benefits in the local situation, and after consultation with the NRA. The NRA may require appropriate testing by the manufacturer to confirm these recommendations, and the vaccinators requested to ensure adequate monitoring.

The following points were made:

- It was recognized that the legal situation will vary from country to country and that NRA–NITAG interactions will be governed by these laws;
- The majority of representatives had the general impression that the reported NRA–NITAG interactions have improved, but that there is still some room to increase the collaboration especially by formalizing the interactions;
- Inclusion of NRA *ex officio* members in the NITAG is one way of ensuring these interactions;
- It is also important that the NRA consult with the National Immunization Program and the NITAG when evaluating vaccines that may be used in National Immunization Programs;
- The NRA issues the license based on the evidence submitted by the manufacturer. The NITAG makes recommendations based on scientific evidence, public health needs and policy, and consideration of the license conditions. If there is a need to make recommendations that are not covered by the license evidence then there should be interactions between the NITAG, NRA and license holder to encourage the license holder to submit appropriate evidence, or to ensure that the justification for the off-label recommendation is communicated to the users of the medicine;
- It was also agreed that where manufacturers are developing vaccines for use in a particular country, consultation with the NRA and NITAG during the clinical development

could ensure that important concerns for including the vaccine in a national public health program are addressed at an early stage;

- NRA evaluation of applications for licence of a vaccine could be assisted by input from the local NITAG, although it is usually the case that the NRA would confine its evaluation to the quality, safety and efficacy of the vaccine, and the need for inclusion in the public health program should only be a consideration when the evidence conflicts with immunization practice in that country. The NITAG input would be most useful in developing appropriate postmarketing safety surveillance or effectiveness assessment activities for vaccines included in National Immunization Programs;
- There is a constraint to information sharing between NRAs and NITAGs owing to the proprietary and confidential nature of the information in licence applications. This may be addressed through discussion and agreement with the applicant and confidentiality agreements by NITAG members;
- It is possible that a NITAG could advise the Public Health Program of the need to prepare to implement or include a certain vaccine in the vaccination program once it is licensed even while the NRA license evaluation is in progress;
- This can enable suitable preparations for implementation if the licence is seen to be imminent. In these situations, input and advice from the NRA regarding evidence of safety and efficacy of the vaccine can aid the NITAG recommendation;
- NITAG recommendations should not be confined to the Public Health Immunization program, but there should be a mechanism for conveying these recommendations to the whole population and private healthcare providers in particular;
- In the postmarket situation, the NITAG may have access to important safety surveillance information that should be shared with the NRA, or the NITAG may request information from the NRA on quality/safety issues relating to a vaccine already in use (e.g., the detection of porcine circovirus DNA fragments in rotavirus vaccines in 2010).

The H1N1 influenza pandemic in 2009 showed that active and focused interactions between the different agencies (and different companies and countries) were possible and enabled expedited actions during vaccine development, evaluations and trials, and for implementation of vaccination programs.

Alternatively, regular publication of a paper setting out the NITAG position on topical issues would provide the public with reliable information.

There may be value for each country to organize a meeting every 2 or 3 years between the NITAG, the Public Health Immunization Program, private immunization professionals, vaccine suppliers and the NRA, to discuss the success of interactions between these groups.

Expert commentary

The roles and responsibilities of the NRA and NITAG have been discussed and examples from a range of countries considered. Discussions between representatives from these groups and from SIVAC have consolidated opinions and considerations. These considerations could form the basis for an internationally agreed set of guidelines for the constitution and remit of NITAGs in those countries where they have not been established, or where they require strengthening. SIVAC will continue with the activities already defined to strengthen specific NITAGs.

Five-year view

It is expected that in 5 years time:

- Many low-income and lower-middle income countries will have established their NITAGs and formal NRAs;
- Almost all of these countries will have introduced important vaccines (e.g., pneumococcal conjugate vaccine, rotavirus vaccine, human papillomavirus vaccines) and some delays or misuse may occur if NRAs and NITAGs do not collaborate closely;
- Regional network of NITAGs and NRAs will have been established/strengthened to ensure sharing of knowledge and experience;
- The WHO and its technical partners (SIVAC) will have developed material adapted to each region on the best way for NITAGs and NRAs to collaborate efficiently.

Acknowledgements

Key issues

- The roles and responsibilities of the National Regulatory Authority (NRA) and National Immunization Technical Advisory Group (NITAG) have been discussed and examples from a range of countries considered in a WHO–Supporting Independent Immunization and Vaccine Advisory Committees–Developing Country Vaccine Regulators' Network workshop held in Bali on May 2010.
- The NRA issues the license based on the evidence submitted by the manufacturer.
- The NITAG makes recommendations based on scientific evidence, public health needs and policy, and consideration of the license conditions.
- The general impression was that the reported NITAG–NRA interactions have improved, but that there is still some room to increase the collaboration, especially by formalizing the interactions.
- Several recommendations were made to improve collaboration between NRAs and NITAGs.
- If there is a need to make recommendations that are not covered by the license evidence, then there should be interactions between the NITAG and NRA to ensure that the justification for the off-label recommendation is communicated to the users of the medicine.

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