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Prioritisation of vaccine introduction in the UNEPI

Report of Uganda National Immunisation Technical Advisory Group (UNITAG) to Ministry of Health

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Executive Summary

Uganda National Immunisation Technical Advisory Group (UNITAG) is an independent group of experts having various disciplines related to vaccines and immunisation that provides evidence based advice to the Ministry of Health on all issues related to vaccines and Immunisation. UNITAG was formed by a Ministerial Statement issued in December 2014, and is hosted by the Uganda National Academy of Sciences (UNAS) which serves as its executive secretariat. The list of UNITAG members is attached as Annex 1.

The Ministry of Health requested UNITAG to make recommendations on the prioritization of various new vaccines to introduce to the routine immunisation schedule. Challenges to the immunisation program's vaccine introduction efforts such as low coverage and limited financing prompted this request. The five new vaccines proposed for introduction were: Hepatitis B birth dose, Yellow Fever, Meningococcal A, 2nd dose of measles containing vaccine, and a switch from Tetanus Toxoid to Tetanus diphtheria. The letter from the Ministry of Health is attached as Annex 2.

UNITAG assessed each proposed vaccine based on the following criteria in order to justify its introduction into Uganda's routine schedule:

- Disease burden (morbidity and mortality, geographical spread, epidemic potential, risk population)
- Vaccine and immunisation characteristics (supply, safety, efficacy, effectiveness)
- Economic and operational issues (cost-effectiveness, vaccine affordability,)
- Health Policy and Programmatic issues (Feasibility, equity, acceptability, impact on program)

Following a review of evidence obtained through a systematic literature search process, and background information obtained from grey literature including Ministry and immunisation partner documents, and taking into account the country context, UNITAG made the following recommendations for new vaccine introduction:

- **Measles 2nd dose**
  i. Introduce Measles Rubella vaccine at 9 months as Measles Containing Vaccine (MCV1) in routine schedule to control measles and rubella. However, it is important that Government and Immunisation Partners work to increase and sustain MCV 1 coverage in routine to > 95% as recommended by WHO. In addition, prior to introduction into routine, a large scale campaign with MR covering children aged 9 months to 15 years is recommended for 2019.
  ii. Introduce a 2nd dose of Measles Rubella vaccine at 15-18 months into the routine program as a cost effective measure to improve overall measles coverage to higher than 95%, reduce burden of measles and rubella epidemics in the country, and reduce the need and frequency of Supplementary Immunisation Activities.
- **Td Vaccine**
  i. Uganda should switch from TT to Td. This will not only strengthen the protection against tetanus, but also provide additional protection against diphtheria. This also goes with current worldwide trends and Uganda might be left behind if it does not make the switch.
  ii. Uganda should add 3 booster doses of Td to the routine immunization schedule at 12-23 months, 4–7 years of age; and 9–15 years of age. This will provide lifelong protection against tetanus as well address the low coverage problem with pregnant women and help maintain MNT elimination.

- **Meningitis A Vaccine**

  Uganda should introduce a Meningitis A containing vaccine initially in target high risk districts in Northern and Western Uganda at 9 months of age, and fiscal space permitting in future, roll out to entire country.

- **Yellow Fever**

  UNITAG recommends introduction of a Yellow Fever Vaccine in Uganda's routine immunisation schedule at 12 months of age

- **Hepatitis B birth dose**

  UNITAG does not recommend addition of a Hepatitis B birth dose into Uganda's routine immunisation schedule. There is no high quality evidence found to show additional efficacy and effectiveness of a birth dose in a setting where Hep B vaccine is routinely administered at 6, 10 and 14 weeks. More information is required in order to assess the added efficacy of the birth dose.

UNITAG proceeded to select a prioritization framework, building on various existing prioritization tools including the generic tool for vaccine introduction prioritisation developed by the SIVAC Initiative of Health Policy and Development Center (HPID). The tool is adapted from the Institute of Medicine Vaccine Prioritisation Framework presented in Madhavan G et al (2012) and the National Model for Transparent Prioritisation by Broqvist M et al (2011). The process of prioritisation followed the following steps:

1. Formulation of the prioritization objects, that is pairing each policy question/ condition with the recommended intervention.
2. Selection of the assessment criteria
3. Scoring and weighting each specific data for each assessment criteria
4. Ranking

UNITAG concurrently piloted the use of an online tool, the Strategic Multi Attribute Ranking Tool (SMART) to validate the outcomes from the Prioritisation Framework.

The following are the recommendations of UNITAG regarding prioritisation for new vaccine introduction into the country's routine immunisation schedule:

1. The switch from TT to Td, including the introduction of three booster doses at 12-23 months, 4–7 years of age; and 9–15 years of age, and the switch from Mono-valent measles to MR as Measles Containing Vaccine first dose (MCV1) preceded with an MR campaign, and introduction of MR as Measles Containing Vaccine second dose (MCV2) at 15-18 months be considered as top priority for new vaccine introduction into Uganda's routine immunisation schedule.
2. The introduction of Men A containing vaccine in target districts and Yellow Fever Vaccine into the routine immunisation schedule should be considered secondary, fiscal space and programmatic capacity withstanding.
3. The introduction of a birth dose of Hepatitis A is not recommended, until high quality evidence proving its additional benefit in a setting with Hepatitis B vaccine routinely administered at 6, 10 and 14 weeks can be found.

   UNITAG acknowledges limitations that were encountered through this prioritisation process, the main one being lack of standardised evidence across the disease-vaccination intervention pairs assessed. UNITAG therefore makes a strong overall recommendation for government and immunisation partners to strengthen investment in multi-disciplinary research in the field of vaccines and immunisation.

1. Background

- UNITAG

Uganda National Immunisation Technical Advisory Group (UNITAG) is an independent group of experts having various disciplines related to vaccines and immunisation that provides evidence based advice to the Ministry of Health on all issues related to vaccines and Immunisation. UNITAG was formed by a Ministerial Statement issued in December 2014, and is hosted by the Uganda National Academy of Sciences (UNAS) which serves as its Executive Secretariat.

UNITAG's remit is to provide recommendations on all issues related to immunization and vaccines including:

- Immunization policies and strategies within and outside of the Expanded Program for Immunization
- Introduction of new vaccines and immunization technologies
- Vaccine quality and safety
- Vaccine schedules
- Procurement and financing of immunization programs
- Research priorities and strategies
- New and emerging vaccine-preventable diseases and response to public health needs

- Context of the question:

  The Ministry of Health requested UNITAG to make recommendations on the prioritization of various new vaccines[1] to introduce to the routine immunisation schedule. Challenges to the immunisation program's vaccine introduction efforts such as low coverage and limited financing prompted this request. The five new vaccines proposed for introduction are: Hepatitis B birth dose, Yellow Fever, Meningococcal A, 2nd dose of measles containing vaccine, and a switch from Tetanus Toxoid to Tetanus diphtheria.

Vaccines recommended for introduction in the country

- UNITAG recommendations for each vaccine
  - UNITAG assessed each proposed vaccine based on the following criteria in order to justify its introduction into Uganda's routine

i. Disease burden (morbidity and mortality, geographical spread, epidemic potential, risk population)
ii. Vaccine and immunisation characteristics (supply, safety, efficacy, effectiveness)
iii. Economic and operational issues (cost-effectiveness, vaccine affordability,)
iv. Health Policy and Programmatic issues (Feasibility, equity, acceptability, impact on program)

  - UNITAG made the following recommendations regarding introduction of the proposed five vaccines:

    - **Measles 2nd dose**

i. Introduce Measles Rubella vaccine at 9 months as Measles Containing Vaccine (MCV1) in routine schedule to control measles and rubella. However, it is important that Government and Immunisation Partners work to increase and sustain MCV 1 coverage in routine to > 95% as

[1] *New vaccines in this case refers to vaccines not previously introduced into Uganda's routine immunisation schedule.*

recommended by WHO. IN addition, prior to introduction into routine, a large scale campaign with MR covering children aged 9 months to 15 years is recommended for 2019.

ii. Introduce a 2nd dose of Measles Rubella vaccine at 15-18 months into the routine program as a cost effective measure to improve overall measles coverage to higher than 95%, reduce burden of measles and rubella epidemics in the country, and reduce the need and frequency of Supplementary Immunisation Activities.

- **Td Vaccine**
  i. Uganda should switch from TT to Td. This will not only strengthen the protection against tetanus, but also provide protection against diphtheria. This also goes with current worldwide trends and Uganda might be left behind if it does not make the switch.
  ii. Uganda should add 3 booster doses of Td to the routine immunization schedule at 12-23 months, 4–7 years of age; and 9–15 years of age. This will provide lifelong protection against tetanus as well address the low coverage problem with pregnant women and help maintain MNT elimination.
- **Men A Vaccine**
  Uganda should introduce a Men A containing vaccine initially in target high risk districts in Northern and Western Uganda at 9 months of age, and fiscal space permitting in future, roll out to entire country.
- **Hepatitis B birth dose**
  UNITAG did not recommend addition of a Hepatitis B birth dose into Uganda's routine immunisation schedule. There is no high quality evidence to show additional value of birth dose in a setting where Hep B vaccine is routinely administered at 6, 10 and 14 weeks. More information is required in order to assess the efficacy of the birth dose.
- **Yellow Fever**
  UNITAG recommends Introduction of a Yellow Fever Vaccine in Uganda's routine immunisation schedule at 12 months of age.

2. Prioritisation approach

Deciding on the introduction of a vaccine is usually complex, as it depends on several factors, including –but not exclusively- costs and other economic factors. As indicated above UNITAG uses a systematic process to collect and appraise the evidence on a wide range of intertwined elements that inform its recommendation.

Similarly, to advise Ministry of Health with minimum bias on which new vaccines are of priority for the country, UNITAG has followed a systematic approach that allows to be transparent on how priorities are determined.

UNITAG prioritization working group first determined a prioritization framework, building on various existing prioritization tools including the generic tool for vaccine introduction prioritisation developed by the SIVAC Initiative of Health Policy and Development Center (HPID). The tool is adapted from the Institute of Medicine Vaccine Prioritisation Framework presented in Madhavan G et al (2012) and the National Model for Transparent Prioritisation by Broqvist M et al (2011).

The prioritisation framework is presented in Annex 3 of this report.

In addition, the Working group piloted the SMART Tool during this exercise, with support from the USA Forgaty International Center, National Institutes of Health.

The approach used is described below:

1. Formulation of the prioritization objects, that is pairing each policy question/ condition with the recommended intervention. The prioritization objects are:
    a. Measles elimination and Measles containing vaccines in routine EPI
    b. Tetanus control and Tetanus containing vaccine in children above 5 years, adolescents and adults
    c. Meningitis A and MenAfricVac vaccination in routine
    d. Hepatitis B Hepatocellular carcinoma and Hepatitis B vaccination at birth
    e. Yellow fever and Yellow fever vaccination in routine EPI

2. Selection of the assessment criteria:

    a. The WG determined that each condition-intervention pair will be assessed against the following criteria:
        i. Severity of the disease
        ii. Benefits of the intervention to the population
        iii. Economic consideration (Cost-effectiveness, cost benefit and availability of fiscal space)
        iv. Programmatic-Policy factors specified for each condition-intervention (e-g equity, feasibility)

    b. The WG described each assessment criteria based on the specific data considered in the recommendation frameworks for the individual policy questions:
        i. Specific data to determine the severity of the condition
        ii. Specific data to determine benefits to population
        iii. Specific data to determine economic considerations (cost-effectiveness)
        iv. Specific data to determine programmatic and policy assessment criteria

3. Scoring and weighting each specific data for each assessment criteria

    a. Reviewing the evidence presented in the technical dossier that informed UNITAG recommendation on each condition and

        i. Expressing the level of severity, benefits to population, cost effectiveness and programmatic/policy criteria in a scale of very high, high, medium or low for each of the specific data

        ii. Translating the qualitative scale in a numeric scale: 4 (Very high); 3 (high); 2 (medium) and 1 (low)

        iii. Determining the importance/weight to give to each specific data within the overall assessment criteria. Each specific data is assigned a percentage value from 0-100. Zero means that the data is not counted at all, 100 means that the data is taken into account at its full value.

    b. Attributing a summary weight for each assessment criteria

4. Ranking

   The WG ranked the vaccines in order of priority based on the numeric value arrived at after the final scoring and weighting for each disease and associated interventions.

5. Validation with the SMART tool

   Data used in the Prioritisation Framework was input into the SMART tool to compare outcomes. The four main criteria used in the Framework were assigned a percentage weight obtained by averaging the assigned weights given by the core group members through the Delphi process.

The next section presents the justification for the ranking of the recommended interventions

3. Presentation of the evidence

Refer to the Recommendation framework for the specific data that define assessment criteria in Annex 4, and the disease-vaccine specific reports for the detailed evidence used by the UNITAG.

3.1. Measles elimination and Measles Containing vaccine:

3.1.1. Severity of the disease:

Epidemic potential: rubella infections are highest between 9 months and 16year olds peaking at 6 years, hence risk of infection over a long period of time, and exposure possible to pregnant women (UVRI Surveillance Data).

Data show that 819 (78%) of 1,053 of the serologically confirmed measles cases for the 4-year surveillance period occurred during the 2006 outbreaks (Baliraine et al 2011)

Incidence of morbidity and mortality: Uganda experiences measles epidemics every 3 years (Baliraine et al 2011**),** with sporadic outbreaks throughout the year. Incidence of measles is highest at 2years of age (UVRI surveillance data).

3.1.2. Benefits to patients of proposed interventions

Safety profile: Adverse reactions following measles vaccination are generally mild and transient [WHO (2009). Measles vaccines: WHO position paper].

Efficacy: all licensed rubella vaccines induce in 95–100% of susceptible persons aged 12 months and older a sero-conversion rates of approximately 95% or higher after a single dose. The effectiveness of 1 dose of an RCV is ≥95% even at age 9 months, the immune responses to rubella antigens are not affected by the other components of the vaccine in the combinations MR, MMR or MMRV [(WHO (2011). Rubella vaccines: WHO position paper].

3.1.3. Economic considerations

Cost effectiveness ratio of vaccination programme: Cost benefit: There is high benefit to cost ratio for measles 2 dose vaccination, with noted 4.5/1 ratios in Israel. Higher benefit to cost ratios should be expected for countries with higher incidence rates like Uganda (Tulchinsky et al, 1993)

Availability of fiscal space: Government covering current monovalent vaccine. GAVI covers cost of vaccine campaign cost. Government to cover cost of full MR for 1st dose, 2nd dose GAVI covers R component. No fiscal space to cover the government additional cost. (Ministry of Health 2017. Financial Sustainability Plan for Uganda's Immunisation Program 2016/17 – 2020/21) estimated at $900,000 (Ministry of Health, 2017)

3.1.4. Programmatic & Policy issues

Availability of vaccine and long term supply: MR vaccine supply less than MMR (UNICEF website).

For MV vaccine: 2015 year-to-date(June) estimated MV vaccine requirements could reach up to ~180million doses in response to routine country demand, outbreak response, and supplementary immunization activities(SIAs). An additional 114.6 million doses were awarded in January 2015 to increase supply from an initial 65 million doses of MV vaccine to meet these requirements. In anticipation of 2016-forecast country demand, UNICEF made separate additional awards of 100 million doses of MV vaccine in March2015, increasing secured supply to 145million doses from an initial 45million doses for next year.MV vaccine production capacity is sufficient to meet forecasted demand, but is vulnerable with one manufacturer producing~90% of supply. This manufacturer also produces the only WHO prequalified MR vaccine.

3.2. Tetanus control and Tetanus containing vaccine in children > 5 years, adolescents and adults

3.2.1. Severity of the disease

Incidence: Although Uganda had been certified as having achieved MNT elimination in 2011, there are reported cases of MNT from 2012. Regionally, Uganda has highest cases of non-neonatal tetanus, 2,522 cases 2003-2014 The trajectory of cases is going up. High cases among females 5+ years. Case fatality rates are very high ranging from 40 to 70%, even with good intensive care (Zziwa 2009).

3.2.2. Benefits to patients of proposed interventions

Safety: Tetanus containing vaccines are effective and safe, with mild side effects like injection site pain and mild fevers commonly reported and major adverse events are extremely rare. The rates and severity are influenced by the number of prior doses, level of antibodies before booster vaccination, the type and quantity of adjuvant, and the presence of other substances such as preservatives. None of the combination vaccines have produced any adverse events that had not been observed with the individual components.

The safety profile of TT and Td is comparable, both in children and pregnant women. Diphtheria toxoid vaccines boost the immunogenicity of other vaccines, including tetanus.

Tetanus-diphtheria (Td, low-dose diphtheria toxoid) formulations are licensed for use from 5 years of age. TTCV are considered very safe. None of the combination vaccines have produced any adverse events that had not been observed with the individual components (WHO 2017).

Efficacy/effectiveness: Immune response of primary series (3 doses of DPT) decreases with time. Data from serological studies suggest that a primary series of 3 TTCV doses in infancy plus a booster during the second year of life will provide 3–5 years of protection. A further booster dose (e.g. in early childhood) will provide protection into adolescence, and another booster during adolescence will induce immunity that lasts through much of adulthood, thus protecting women through their childbearing years. Ten years after immunization, tetanus antibody levels still exceeded pre-immunization levels and remained protective (≥0.10 IU/ml) in ≥97% of adolescents and adults (WHO 2017).

Sero-conversion rates of TT and Td are similar, above 95% (Aboud and Lyamuya 2002).

3.2.3. Economic considerations

Vaccine affordability: The costs per dose for Tt and Td are similar ranging from $0.07 to $0.09 per dose. (UNICEF website) Packaging volumes are similar too, with 10 dose vials, indicating that the financial implications of the switch may not be significant. The additional financial costs will be due to addition of three booster doses targeting both sexes. If booster doses are effectively administered, the need for immunizing pregnant women would be eliminated eventually, hence saving costs. Vaccines costs to be borne by Government. Women of child bearing age already have 2 doses budgeted for in government, additional costs are 1 additional dose for women and 3 additional doses for boys.

Estimated introduction costs for Td boosters per cohort is $ 2.6 million (Healthnet Consult, 2017).

3.2.4. Programmatic and Policy issues

Feasibility: The second year of life provides a platform for vaccination against several diseases including, measles, and meningococcal A conjugate vaccines. The pre-adolescent and adolescent vaccination platform includes HPV vaccination. Early childhood interventions, child days plus, school health. However these platforms are currently not fully functional, and would need to be strengthened. (UBOS and ICF 2017).

Availability: UNICEF anticipates overall TT/Td forecasted demand to reach 165 million doses a year during 2016-2017, and anticipates an increasing share of Td vaccines. However, Td vaccine country demand forecasts remain somewhat uncertain and are dependent on country TT/Td transition decisions and timing.

UNICEF launched its TT/Td vaccine tender in June 2015 to supply 165 million doses a year over 2016 -2017 to meet country demand for RI and campaign activity. UNICEF awarded long-term arrangements (LTA) in October 2015 to five suppliers.

(UNICEF website https://www.unicef.org/supply/files).

Based on previous experience of globally driven new vaccine introductions experience, increased demans may lead t stock outs and hence uncertain supplies, as was the case with IPV (UNICEF 2016. Inactivated Polio Vaccine Supply

update. https://www.unicef.org/supply/files/Inactivated_Polio_Vaccine_(IPV)_-_september_2016.pdf.) Also having no Gavi support in setting the demand by committing the manufacturers, puts sustainable supply at risk.

3.3. Meningitis A and MenAfricVac in routine EPI

3.3.1. Severity of the disease

Burden of disease: Part of northern Uganda is located in Meningococcal Meningitis A belt of Africa. Northern Uganda and parts of Western Uganda have experienced regular, focal outbreaks of meningitis since 2004 and a large epidemic occurred in 2007 with 4098 cases reported. Meningitis A represents a significant disease burden in the country with high fatalities, considering that in a ten-year period (2004-2014-week 22), 10,630 cases were reported through Integrated Disease Surveillance and Reporting IDSR, with a case fatality ratio of 8%. Neisseria meningitides serogroup A is the most predominant cause identified in 64% of the laboratory confirmed epidemic cases tested at the Central Public Health Laboratory in that time period.(Lingani et al, 2014)

Men A Burden going down may be due to regular preventive campaigns every 10 years in target districts. Other sero-types emerging since 2009 (UNEPI pers. comms).

3.3.2. Benefits to patients of proposed interventions

Safety: Evidence shows no serious adverse events related to Men A vaccination were reported in individuals aged 9-24 months of age, following large vaccination campaigns in other African countries including Chad, Niger and Mali. Mild reactions such as redness, swelling and pain at the site of injection may occur. This is similar to the safety profile of measles vaccine administered at 9 months of age (WHO pp). Following campaign introduction of Men A vaccine in early 2017 targeting 1-29 year olds in northern Uganda, no serious Adverse Events Following Immunisation (AEFI) were recorded (UNEPI pers. comms)..
Co-administration of Men A with other vaccines has been shown to have no interference effects. The lack of data on co-administration with PCV and Rota is not a limiting factor as the two doses should be administered much earlier in age than Men A (WHO 2015).

Efficacy and effectiveness: b) A single dose of 5 micrograms administered to children aged 9-24 months has a proven protective effect for 27 months (WHO 2015, Tang et al., 2015). A mathematical model showed that at 60% coverage in routine schedule, the vaccine resulted in significant reduction of Men A cases (Karachaliou et al, 2015).

Uganda experience, no men A cases since 2009, showing effectiveness of Men A campaigns targeting 1-29 years, coverage attained 80%. (UNEPI pers. comms)

3.3.3. Economic considerations

Cost-effectiveness (O) of introducing Men. A conjugate vaccine into routine immunization (I) vs. mass campaigns (C) in the country (P):

Uganda experience has demonstrated effectiveness of campaigns. Direct costs of campaigns (funded by Gavi), compared to routine, targeted preventive campaign in Uganda may be more cost effective.

Studies from Burkina Faso show that preventive campaigns and routine vaccinations are both more cost effective than reactive campaigns (Colombini et al, 2015)

Cost benefit of vaccination: Ultimately, each dollar invested in routine immunization generates savings of an additional 1.3 USD, and each dollar invested in the combination strategy (routine and campaign) saves 1.2 USD (Colombini et al., 2015).

3.3.4. Programmatic and Policy issues

Availability of vaccine and long term supply: Historical UNICEF records show that so far there haven't been challenges with Men A vaccine supply, however, there was no evidence to show sustainable future supplies.

Accessibility to all inhabitants: The vaccine may be administered at 9 months of age, coinciding with measles vaccination, as there are no contra-indications for co-administration. Measles coverage UDHS 2016 is 85% Acholi region and 75% Lango region, the targeted areas for routine and campaign introductions. (UBOS and ICF 2017)

3.4. Hepatitis B hepato carcinoma and HepB vaccination at birth*

**This disease intervention pair was not assessed as it was not recommended by UNITAG.*

3.4.1. Severity of the disease

Hepatitis B disease epidemiology:

3.4.2. Benefits to patients of proposed intervention

Safety

Efficacy/ effectiveness:

3.4.3. Economic considerations

Cost effectiveness if an extra dose of Hep. B vaccine is given at birth vs. current schedule in Uganda

Cost benefit to Uganda if an extra dose of Hep. B vaccine is given at birth vs. the current schedule

3.4.4. Programmatic and Policy issues

Feasibility

3.5. Yellow fever and YF vaccination in routine EPI

3.5.1. Severity of the disease

Epidemiology of the disease: Uganda in global YF belt. 2 recent sporadic outbreaks, 2010, 2014. High CFR 21.3. 2010-2011, 272 suspected YF cases including 58 deaths (CFR 21.3%) were reported from the 14 districts as of 10 March 2011. 26 March to 18 April 2016, 30 cumulative suspected cases, including 7 deaths, were reported from Masaka, Rukungiri, Ntungamo, Bukomansimbi, Kalungu, Lyantonde, and Rakai. Of these, 6 cases and 2 deaths were confirmed. (WHO,2012 and WHO WEBSITE http://www.who.int/csr/don/02-may-2016-yellow-fever-uganda/en/)

Risk groups for disease: Everyone is at risk, outbreaks occurred in different geographical zones (northern, western, and central), YF naïve population, and presence of vectors. (WHO, 2012)

Potential of the disease for global pandemic spread: Epidemic potential only, not pandemic (WHO 2013).

3.5.2. Benefits to patients of proposed intervention

Safety: Evidence shows no serious adverse events related to yellow fever vaccination in individuals over 8 months of age. Mild reactions include fevers with low rates of upper respiratory symptoms or injection site symptoms. (Belmusto-Worn et al., 2005, Nordin et al, 2013)

Yellow fever live virus vaccine can cause severe, often fatal, multi-systemic illness, yellow fever vaccine-associated viscerotropic disease (YEL-AVD). Predominantly a neurological disease termed yellow fever vaccine-associated neurotropic disease (YEL-AND). Incidence is reduced if vaccine if administered to individuals older than 6 months, and increased risk for in Thymectomized individuals (treatment of thymoma), Thymus disease, severe malnutrition and severely immunocompromised (Seligman, 2014)

Efficacy and effectiveness: Sero conversion rates over 90%, one dose, 30yrs protection possibly life (Belmusto-Worn et al., 2005, Gotuzzo et al 2013), Sero-conversion negatively affected by co-administration with MMR vaccine (Collabgroup, 2015).

3.5.3. Economic considerations

Cost-effectiveness of routine YF vaccine to all children in Uganda vs. to only children in high risk areas?

Routine immunisation (targeting 1 year olds) – at $ 1 million introduction cost (Healthnet Consult 2017) , long term effect, routine 7-8 times more cost effective than preventive in the long term (Monath and Nasidi 1993**)**.

3.5.4. Programmatic considerations

Feasibility, ability to evaluate and supply

Feasibility: cannot be given together with measles (Collabgroup, 2015), targeting 12 months old (WHO 2013), beyond existing immunisation platform, risk of drop out.

AEFI – suboptimal system in place (Ministry of Health 2014)

Supply – Global shortage, demand outstripped supply in 2016 (UNICEF Website)

4.Assessment results

Based on the evidence presented, the criteria are assessed as shown in the tables below:

4.1. Measles elimination- Measles containing vaccine in routine EPI

Assessment criteria	component (specific data)	Score (Very high, High, Medium, Low)	Score Value in numeric scale (4-1)	Weight (percentage)	(percentage value x score)	Summary Weight
Severity of the disease both measles and rubella	Epidemic potential:	Very High	4	0.20	4 x 0.2 =0.8	0.8+ 2.1+0.2= 3.1
	Incidence of morbidity	High	3	0.70	3 x 0.7 =2.1	
	mortality:	medium	2	0.10	2 x 0.1 = 0.2	
Benefit to population of proposed interventions of 2 doses of MCV	Safety profile	Very High	4	0.2	4 x 0.2 = 0.8	0.8 +3.2 =4
	Efficacy: Effectiveness	Very High	4	0.8	4 x 0.8 = 3.2	
Economic considerations	Cost effectiveness ratio of vaccination programme:	Medium	2	0.6	2 x 0.6 = 1.2	1.2+0.3+0.6 = 2.1
	Cost benefit of vaccination:	High	3	0.1	3 x 0.1 = 0.3	
	Availability of fiscal space	Medium	2	0.3	2 x 0.3 =0.6	
Programmatic &Policy issues	Availability of vaccine and long term supply	Low	1	1.0	1 x 1 =1	1.0
						SUMMARY 3.1+4.0+2.1+1.0 =10.2

4.2. Tetanus control and Tetanus containing vaccine in children > 5 years, adolescents and adults

Assessment criteria	component (specific data)	Score (Very high, High, Medium, Low)	Score Value in numeric scale (4-1)	Weight (percentage)	(percentage value x score)	Summary Weight
Severity of the disease	**Incidence:**	Very High	4	1.0	4 x 1.0=4.0	4.0
Benefit to patients of proposed interventions	**Safety**	Very High	4	0.2	4 x 0.2= 0.8	1.8 + 0.8 + 0.8 =3.4
	Efficacy	Very high	4	0.2	4 x 0.2 =0.8	
	Effectiveness	High	3	0.6	3 x 0.6 =1.8	
Economic considerations	**Vaccine affordability**	Very High	4	1.0	4 x 1.0= 4.0	4.0
Programmatic& policy issues	**Feasibility** **Availability**	Medium Medium	2 2	0.7 0.3	2 x 0.7 =1.4 2 x 0.3 = 0.6	1.4+0.6=2.0
						SUMMARY 4.0+3.4+4.0+2.0= 13.4

4.3. Meningitis A and MenAfricVac in routine EPI

Assessment criteria	component (specific data)	Score (Very high, High, Medium, Low)	Score Value in numeric scale (4-1)	Weight (percentage)	(percentage value x score)	Summary Weight
Severity of the disease	Burden of disease:	Medium	2	1.0	2 x 1=2.0	2.0
Benefit to patients of proposed interventions	Safety:	Very High	4	0.2	4 x 0.2 = 0.8	0.8+0.8 +1.8 =3.4
	Efficacy	Very High	4	0.2	4 x 0.2 = 0.8	
	Effectiveness	High	3	0.6	3 x 0.6 = 1.8	
Economic considerations	Cost-effectiveness (O) of introducing Men. A conjugate vaccine into routine immunization (I) vs. mass campaigns (C) in the country (P)	Medium	2	0.7	2 x 0.7 = 1.4	1.4 + 0.3 =1.7
	Cost benefit of vaccination	Low	1	0.3	1 x 0.3 =0.3	
Programmatic considerations	Availability of vaccine and long term supply:	High	3	0.5	3 x 0.5 = 1.5	1.5 + 1.5 =3
	Accessibility to all inhabitants:	High	3	0.5	3 x 0.5 =1.5	
						SUMMARY 2+3.4+1.7+3= 10.1

4.4. Hep B hepato-cellular carcinoma and hepB vaccination at birth*

Assessment criteria	component (specific data)	Score (Very high, High, Medium, Low)	Score Value in numeric scale (4-1)	Weight (percentage value x score)	Summary Weight
Severity of the disease	Hepatitis B disease epidemiology	-	-	-	-
Benefit to patients of proposed interventions	Safety:	-	-	-	-
	Efficacy and effectiveness		-	-	
Economic considerations	Cost effectiveness if an extra dose of Hep. B vaccine is given at birth vs. current schedule in Uganda	-	-	-	-
	Cost benefit to Uganda if an extra dose of Hep. B vaccine is given at birth vs. the current schedule	-	-	-	-
Programmatic &Policy		-	-	-	-
					SUMMARY =-

*See section 3.4

4.5. Yellow fever and YF vaccination in routine EPI

Assessment criteria	component (specific data)	Score (Very high, High, Medium, Low)	Score Value in numeric scale (4-1)	Weight (percentage)	(percentage value x score)	Summary Weight
Severity of the disease	Burden of disease	Low	1	0.1	1 x 0.1 = 0.1	0.1+0.9+0.3+1.5= 2.8
	Severity of disease	High	3	0.3	3 x 0.3 = 0.9	
	Risk groups for disease:	High	3	0.1	3 x 0.1 = 0.3	
	Potential of the disease for epidemic spread	High	3	0.5	3 x 0.5 =1.5	
Benefit to population of proposed interventions	Safety:	High	3	0.2	3 x 0.2 = 0.6	0.6+3.2 =3.8
	Efficacy and effectiveness	Very High	4	0.8	4 x 0.8 = 3.2	
Economic considerations	Cost effectiveness	Medium	2	1.0	2 x 1 =2.0	2.0
Programmatic &Policy issues	Feasibility	Medium	2	0.4	2 X 0.4 = 0.8	0.8+0.2+0.5= 1.5
	Ability to evaluate AEFI	Medium	2	0.1	2 X 0.1 = 0.2	
	Global vaccine supply	Low	1	0.5	1 X 0.5 =0.5	
						SUMMARY 2.8+3.8+1.5+2= 10.1

4.5. Ranking

- Presentation of the final scoring and weighting for each disease/condition and associated intervention

Disease-intervention pair	summary weighted criteria severity	summary weighted criteria benefit to population	summary weighted criteria cost-effectiveness	summary weighted criteria Programmatic& policy	Total	rank
Tetanus control-TCV	4.0	3.4	4.0	2.0	13.4	1
Measles elimination-MR	3.1	4.0	2.1	1.0	10.2	2
Meningitis A-MenAfricVac	2.0	3.4	1.7	3.0	10.1	3
Yellow fever-YF routine EPI	2.8	3.8	2.0	1.5	10.1	3
Hep B- birth dose*	-	-	-	-	-	-

*See section 3.4

5. Validation with SMART

The Prioritisation Framework model assigned equal importance to all the four criteria, which was not reflective of Uganda's situation. Percentage weights to the criteria were assigned using the Delphi process: UNITAG members individually assigned percentage weights to the four criteria which were then averaged. The SMART tool was set to reflect the outcomes of the Prioritisation Framework, and the average percentage weights applied to the four criteria. The average scores and SMART Tool outcomes are attached as Annex 5.

6. Conclusions and recommendations

- Based on UNITAG judgement of the assessment results
- Taking into account the local context and other factors

6.1. Conclusions

The outcomes of the prioritisation framework tally with the overall judgement of the UNITAG based on the evidence reviewed.

The switch from TT to Td is viewed as an inevitable global move. A combination of the overall population susceptibility, increasingly high incidence of tetanus in the population- particularly females 5+years, high cost of treatment, lack of adequate ICU facilities in the country, high case fatality rates, the high efficacy rates of the vaccine, relatively cheap cost per dose of Td vaccine; comparable to TT, the existing government fiscal space for TT, all make a compelling case for switching from TT to Td, and introduction of booster doses.

The increasingly high incidence of rubella cases among the infant population, the sporadic outbreaks of measles in different parts of the country despite relatively high coverage of MCV1, plateauing of measles vaccine coverage at 80% over the past few years, the availability of Gavi funding for the mass campaign introduction of Measles Rubella vaccine and the rubella component of MCV2, and the high efficacy rates of rubella vaccine, the regional efforts to eliminate CRS, place this vaccine at a competitive advantage in terms of priority for introduction.

The fact that the preventive campaigns using Men A vaccine have achieved high coverage and been effective at suppressing Men A cases, with the last confirmed cases having been seen in 2009, the limited geographical spread of Men A outbreaks, the uncertainty of the duration of protection proffered by the vaccine make the introduction of MenAfriVac of relatively lower priority in Uganda. However, because of the severity of the disease- the high case fatality rates, the high number of survivors left with serious and permanent sequelae, the risk of spread from the endemic neighbouring countries, efforts to prevent its occurrence, including introduction of the vaccine in the routine immunisation schedule, especially targeting the high risk districts are encouraged, fiscal space permitting.

Yellow Fever- Yellow Fever Vaccine pair scored relatively lower points largely due to the low disease incidence in terms of number of cases recorded over time, the low risk of outbreaks according the latest WHO risk assessment report, the unsustainable vaccine supply, and the efficacy challenges which make it unsuitable for co-administration with measles vaccine. However, the limitations notwithstanding, it is acknowledged that Yellow Fever infection is a severe disease with high case fatality rates associated with its hepato-failure, has a high potential for epidemic spread due to its association with vector carriers, evidence of circulation virus in the country, and recent sporadic outbreaks in different parts of the country make it an issue of concern. Current efforts to control yellow fever including mandatory vaccination of travellers and reactive vaccinations should be maintained. Fiscal space permitting, the vaccine should be introduced into the routine program for children aged 12 months.

UNITAG found no high quality evidence to show that a birth dose of Hepatits B confers significant additional protection in a system with hepatitis B vaccine routinely administered at 6, 10 and 14 weeks, as is the case for Uganda. UNITAG therefor has no basis to recommend the introduction of a birth dose into Uganda's routine Immunisation schedule. The lack of evidence to support introduction of a Hep B birth dose underscores the need to support local high quality research particularly in the field of vaccine and immunisation.

6.2. Recommendations

6.2.1. Prioritisation for new vaccine introduction

1. UNITAG recommends that the switch from TT to Td, including the introduction of three booster doses, and the switch from Mono-valent measles to MR as Measles Containing Vaccine first dose (MCV1) preceded with an

MR campaign, and introduction of MR as Measles Containing Vaccine second dose (MCV2) be considered as top priority for new vaccine introduction into Uganda's routine immunisation schedule.

2. The introduction of Meningitis A containing vaccine in routine schedule in target districts and Yellow Fever Vaccine into the country routine immunisation schedule should be considered secondary, fiscal space and programmatic capacity permitting.

3. The introduction of a birth dose of Hepatitis A is not recommended, until high quality evidence proving its additional benefit in a setting with Hepatitis B vaccine routinely administered at 6, 10 and 14 weeks can be found.

6.2.2. Over-arching recommendations

1. UNITAG cannot over-emphasize the importance of improving program effectiveness, as the back bone to successful introduction and integration of the approved new vaccines in the routine schedule, and the immunisation program as a whole.

2. Government and immunisation partners need to make greater investment in multi-disciplinary research in the field of vaccines and immunisation in order to generate the evidence required to guide policy decisions.

3. A significant amount of investment is required to generate evidence based recommendations in terms of Human Resource, logistics for systematic evidence searches and expert time. Consumers of this advice need to invest in the process.

4. The recommendations provided in this report are based on the prevailing conditions at the time of its submission. Should there be significant changes in the factors considered, the recommendations should be appropriately revised to reflect those changes.

7. Study limitations

UNITAG acknowledges that this was a novel exercise and lessons learnt need to be documented to further improve the process for future use.

The issue of standardization from the onset, in terms of data collected is particularly important. In this study, data comparisons across disease-vaccine pairs were not strictly uniform, due to lack of standardised data, and this may have introduced systemic errors in the process.

The Prioritisation Framework used does not offer a calibrated system of measurement in terms of scoring and weighting of different criteria, and may thus be subject to subjective biases. UNITAG employed the use of consensus scores and weights as a means of minimising bias, but may not have eliminated it altogether.

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Annexes

Annex 1: List of UNITAG Members

Name	Membership	Specialty
Prof. Nelson Sewankambo	Chair	Medicine
Prof. George B Kirya	Co-Chair	Micro Biology
Prof. Sarah Kiguli	Core Member	Pediatrics
Dr. Sabrina Bakeera-Kitaka	Core Member	Pediatrics and Adolescent Health
Assoc. Prof. Peter Waiswa	Core Member	Public Health
Assoc. Prof. Jesca Lukanga Nakavuma	Core Member	Vaccinology
Ms. Charlotte M Zikusoka	Core Member	Health Economics
Dr. Lawrence Kaggwa	Core Member	Health Systems
Hon. Benson Obua-Ogwal	Core Member	Sociology
Dr. Jesca Nsungwa-Sabiiti	Ex-Officio Member	Child Health (MoH)
Dr. Immaculate Ampaire	Ex-Officio Member	UNEPI (MoH)
Dr. Eva Kabwongera	Liaison Member	UNICEF
Dr. Patrick Kadama	Liaison Member	Health Policy Expert, ACHEST
Dr. Annet Kisakye	Liaison Member	WHO
Dr. Emmanuel Mugisha	Liaison Member	PATH

Annex 2: Advise Request Letter from Ministry of Health

Telephone: General Lines: 340874/ 231563/9
Permanent Secretary's Office: 256 - 41 - 340872
Fax: 256 - 41 - 231584

THE REPUBLIC OF UGANDA

Ministry of Health
P.O. Box 7272
Kampala
Uganda

IN ANY CORRESPONDENCE ON
THIS SUBJECT PLEASE QUOTE NO: **ADM:215/306/01**

22nd June 2016

Dr. Nelson Sewankambo,
Chairperson for NITAG Uganda,

RE: REQUEST TO NITAG TO ADVICE THE IMMUNIZATION PROGRAM TO PRIORITIZE WHICH NEW VACCINES SHOULD BE INTRODUCED

The goal of immunization program is to ensure that every child and high-risk group is fully vaccinated with high quality and effective vaccines against the target diseases according to recommended strategies through five operational components: vaccine supply and quality, logistics, service delivery, surveillance, advocacy and communication.

SAGE has made several recommendations to countries to introduce new vaccines into their routine immunization program following evidence presented to them to show that they are effective and efficacious. Over the last three years, Uganda has introduced three new vaccines into the routine immunization program and plans to introduce yellow fever vaccine, Measles and Rubella Vaccine including second dose, Men A and Tetanus Diptheria(Td) Vaccine.
However along the way the program has observed some challenges and anticipates more to come as more new vaccines are introduced into the routine immunization program. Among these challenges, includes fulfilling co financing requirements for the recently introduced vaccine affecting the performance of new vaccine introduction

In line with the WHO recommendation, Uganda established the NITAG to provide evidence based advice to the Ministry of Health on immunization.

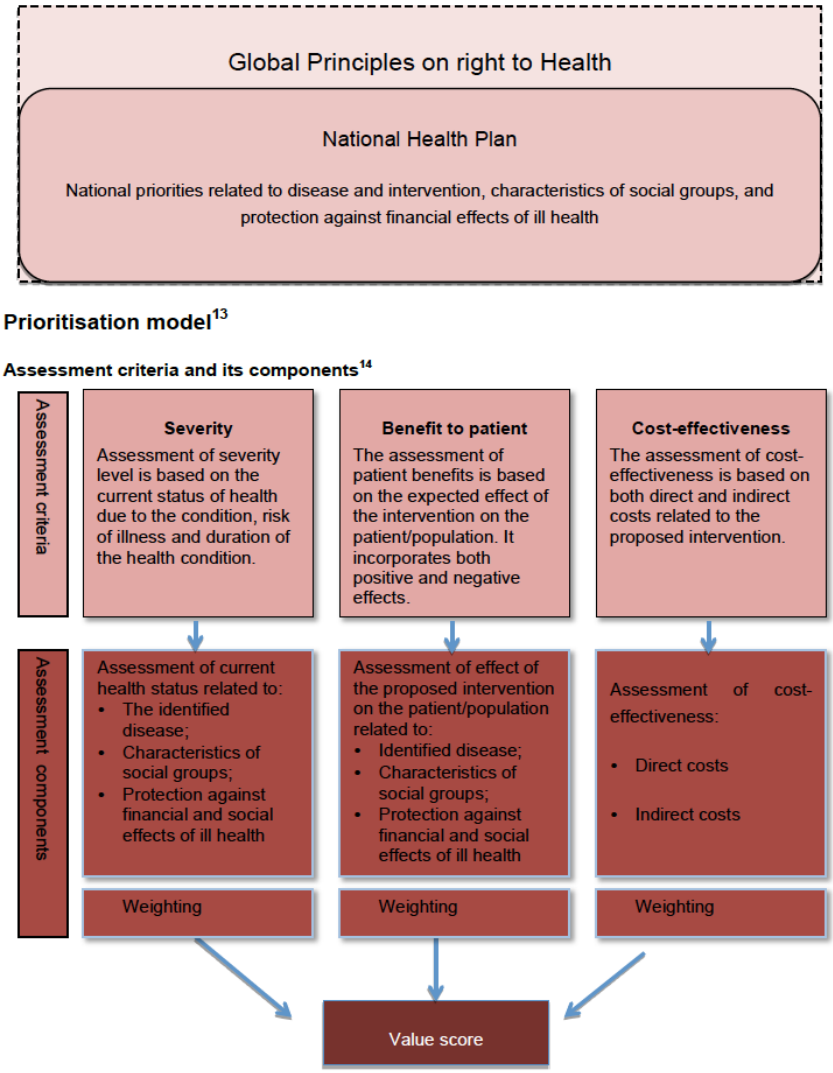
The purpose of this letter is therefore to request the NITAG to provide guidance on which new vaccine Uganda's immunization program should prioritize in order of importance in the next five years. Your response will highly be appreciated preferably by end of 2016.

Prof. Anthony K. Mbonye
FOR DIRECTOR GENERAL HEALTH SERVICES

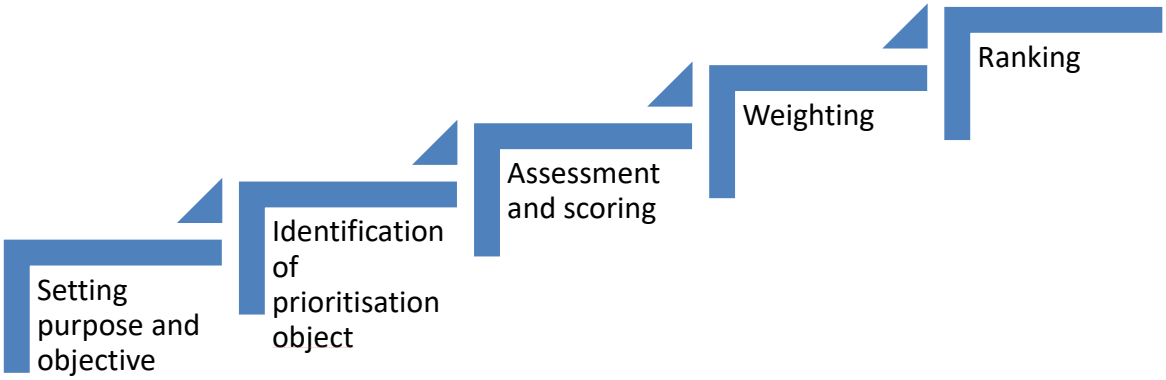
Cc: The Permanent Secretary, Ministry of Uganda
Cc: The Director Health Services, Clinical and Community
Cc: Commissioner Health Services, National Disease Control
Cc: The Program Manager, UNEPI

*Hepatitis B birth dose was added to the list later through verbal communication at the 6th Meeting g UNITAG.

Annex 3: Prioritisation Framework



Steps in the Prioritisation Framework



Annex 4: Recommendation frameworks

MEASLES ELIMINATION - MCV VACCINE:

Assessment criteria	Component (specific data)
Severity of the disease **Which of the epidemic, mortality or morbidity count more?** Rubella is morbidity because of CRS (disability) circulation of the infection; measles is both	**Epidemic potential:** . How frequently do Measles infection outbreaks occur in Uganda (with 1st dose part of routine)? How frequently do Rubella infection outbreaks occur in Uganda?
	Incidence of morbidity and mortality: What is the current age specific incidence of Rubella infection in Uganda? Who is the population at risk and can they spread the disease? (focused on rubella) Number of cases/ Incidence of morbidity and mortality? What is the frequency of measles outbreak?
Benefit to patients of proposed interventions	**Safety profile**: How does the safety profile (O) of MR vaccine (I) compare to other vaccines (C) given to children at 9 months and 2nd year of life (P)?; How does the safety profile (O) of monovalent Measles vaccine (I) compare to other vaccines (C) given to children in the 2nd year of life (P)? s it safe to administer multiple doses of MR vaccine as compared to monovalent Measles vaccine?
	Efficacy: How efficacious is MR vaccine in Rubella elimination (O) when administered in children (P) as a single dose in the 2nd year of life (I) compared to two doses i.e. at 9 months and in the 2nd year of life (C)?
Economic considerations	**Cost effectiveness ratio of vaccination programme:** Cost effectiveness (O) of Measles only elimination (C) versus Measles Rubella elimination (I) in Uganda (P); Cost effectiveness (O) of CRS elimination (C) versus Rubella elimination (I) in Uganda (P)
	Availability of fiscal space
	Cost benefit of vaccination: Cost benefit (O) of Measles only elimination (C) versus Measles Rubella elimination (I) to the EPI (P); Cost benefit (O) of CRS elimination (I) versus Rubella elimination (C) to the EPI (P)
Programmatic- Policy issues	Availability of vaccine and long term supply

YELLOW FEVER - YF VACCINE IN ROUTINE EPI

Assessment criteria	Component (specific data)
Severity of the disease	**Epidemiology of the disease,:** What is the current prevalence of YF in Uganda? What is the case fatality rate from yellow fever infection? What is the potential of a YF epidemic occurring within the country?
	Risk groups for disease: What is the population at risk of acquiring YF infection in Uganda?
	Potential of the disease for global pandemic spread: What is the likelihood of a YF pandemic crossing into Uganda from neighbouring countries?
Benefit to patients of proposed interventions	**Safety:** What is the safety profile of YF vaccine in children aged 6 to 24 months of age? Is it safe to co-administer YF vaccine with other vaccines administered between 6-24 months of age
	Efficacy and effectiveness: What is the efficacy of YF vaccine in preventing YF infection when administered to children aged 6-24 months?
Economic evaluation	**What is the cost-effectiveness** of routine YF vaccine to all children in Uganda vs. to only children in high risk areas?

HEPATO CELLULAR CARCINOMA-HEPB BIRTH DOSE:

Assessment criteria	Component (specific data)
Severity of the disease	**Hepatitis B disease epidemiology**: What is the prevalence of HBsAg and HBeAg positivity in pregnant women in Uganda?
Benefit to patients of proposed interventions	**Safety:** How does the safety profile of Hep. B vaccine compare to other vaccines administered in newborn babies at less than one week of age (e.g. BCG, OPV)?
	Efficacy/ effectiveness: What is the efficacy of Hep. B vaccine in reducing the risk of Hep. B transmission and HCC when the first dose is given at birth vs. current schedule (i.e. 6 weeks)?
Economic considerations	**Cost effectiveness** if an extra dose of Hep. B vaccine is given at birth vs. current schedule in Uganda
	Cost benefit to Uganda if an extra dose of Hep. B vaccine is given at birth vs. the current schedule
Programmatic & policy issues	

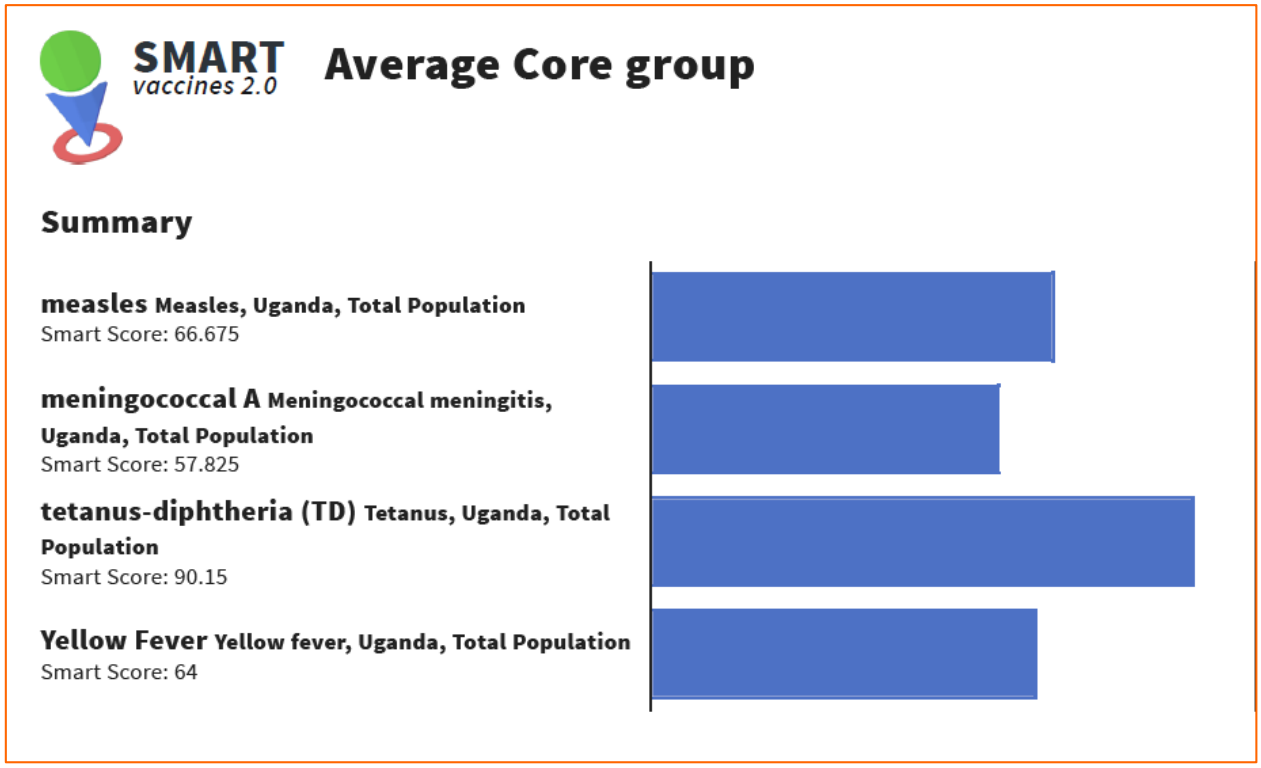
MENA OUTBREAKS- MENAFRICVAC IN ROUTINE EPI

Assessment criteria	Component (specific data)
Severity of the disease	**Burden of disease:** epidemic potential, incidence of morbidity and mortality of Meningococcal disease; Risk groups for meningococcal disease; Disease occurrence and epidemiology over time
Benefit to patients of proposed interventions	**Safety**: How does the safety profile (O) of Men. A conjugate vaccine (I) in children under two years (P) compare to MCV (C)?
	Efficacy and effectiveness: i. How does the immunogenicity (O) of Men. A conjugate vaccine if given as 1-dose (I) compare to a 2-dose schedule (c) in children under 2 yrs (P)?; i. How efficacious is Men A Conjugate vaccine 5 mcg in preventing Meningococcal disease in children under 2 years ?
Cost-effectiveness	**Cost-effectiveness** (O) of introducing Men. A conjugate vaccine into routine immunization (I) vs. mass campaigns (C) in the country (P)
	Cost benefit of vaccination; Cost benefit (O) to the country (P) of introducing Men. A conjugate vaccine intro routine immunization (I) vs. mass campaigns (C)
Others	
	Availability of vaccine and long term supply: Is there sufficient international stock of Men A vaccine, with reliable potential supply for Uganda?
	Accessibility to all inhabitants: Are immunization services accessible to the unique population groups in Uganda who are most at susceptible to Meningococcal disease?

TETANUS CONTROL- TCV IN CHILDREN > 5 YRS, ADOLESCENTS, AND ADULTS

Assessment criteria	Component (specific data)
Severity of the disease	**Incidence:** What is the incidence of tetanus in children above 5 years, adolescents and adults in Uganda?
Benefit to patients of proposed interventions	**Safety:** What are the adverse events of Td in children above 5 years, adolescents and adults
	Efficacy/effectiveness: What are the determinants of the immune response with Td vaccine in children above 5 years, adolescents and adults?
Economic considerations	**Vaccine affordability:** What would be the annual fiscal implications to the Ugandan government if Td vaccine is introduced in routine immunization of children above 5 years, adolescents and adults? -Cost-effectiveness in introducing TT vaccine into routine immunization program of children above 5 years?
Programmatic and Policy issues	**Vaccine availability:** there sufficient international stock of Td vaccine, with reliable potential supply for Uganda?

Annex 5: Outcomes from the SMART Tool.



Scoring Breakdown

Measles, Uganda, Total Population

Name	Weight	Adverse	Favourable	Value	Score
Severity of Disease	36%	0	40	31	77.5
Benefit to Population	19%	0	40	40	100
Economic Considerations	31%	0	40	21	52.5
Prog & Policy	14%	0	40	10	25

Meningococcal A Meningococcal meningitis, Uganda, Total Population

Name	Weight	Adverse	Favourable	Value	Score
Severity of Disease	36%	0	40	20	50
Benefit to Population	19%	0	40	34	85
Economic Considerations	31%	0	40	17	42.5
Prog & Policy	14%	0	40	30	75

Tetanus-diphtheria (TD) Tetanus, Uganda, Total Population

Name	Weight	Adverse	Favourable	Value	Score
Severity of Disease	36%	0	40	40	100
Benefit to Population	19%	0	40	34	85
Economic Considerations	31%	0	40	40	100
Prog & Policy	14%	0	40	20	50

Yellow Fever Yellow fever, Uganda, Total Population

Name	Weight	Adverse	Favourable	Value	Score
Severity of Disease	36%	0	40	28	70
Benefit to Population	19%	0	40	38	95
Economic Considerations	31%	0	40	20	50
Prog & Policy	14%	0	40	15	37.5

APPENDICES

1. Technical Dossier on Meningitis A containing vaccine in routine immunisation program
2. Technical Dossier on Measles and Rubella Vaccine in routine immunisation program
3. Technical Dossier on Yellow Fever Vaccine in routine immunisation program
4. Technical Dossier on Hepatitis B vaccine in routine immunisation program
5. Technical Dossier on Tetanus Diphtheria vaccine in routine immunisation Program
6. Cost Estimates for Introduction of New Vaccines

Uganda Immunization Technical Advisory Group

Recommendation on Men.A vaccine in routine immunization schedule:

Uganda Immunization Technical Advisory Group

Recommendation on Men. A vaccine in routine immunization schedule:

SHOULD MEN. A CONJUGATE VACCINE BE INTRODUCED INTO UGANDA'S ROUTINE IMMUNZATION SCHEDULE FOR CHILDREN?

SEPTEMBER 2017

Contents

Executive summary

The Ministry of Health asked the Uganda National Technical Advisory Group (UNITAG) to make recommendations on the prioritization of various new vaccines to be introduced intoto the routine immunisation schedule. Current challenges to the immunisation program's vaccine introduction efforts such as low coverage and limited financing prompted this request. The five new vaccines proposed for introductions are : Hepatitis B birth dose, Yellow Fever, Meningococcal A, 2nd dose of measles containing vaccine and a switch from Tetanus Toxoid to Tetanus diphtheria.

The vaccine considered in this dossier is the Meningitis A conjugate vaccine. Meningococcal meningitis is a serious infection that affects the brain membrane. The disease is caused by different bacteria, the commonest being *Neisseria meningitidis* which as different serogroups including: A, B, C, Y and X. Sero group A is the most dominant cause of Meningitis epidemics in the African Meningitis belt. Part of northern Uganda is located in Meningococcal Meningitis A belt of Africa. Northern Uganda and parts of Western Uganda have experienced regular, focal outbreaks of meningitis since 2004 and a large epidemic occurred in 2007 with 4098 cases reported. Most untreated cases of meningococcal meningitis are fatal and even with treatment, a 10% fatality rate is reported. Men. A represents a significant disease burden in the country. In a 10-year period, there were 10,630 cases reported through Integrated Disease Surveillance and Reporting IDSR. The disease spreads rapidly through contact with nasal drops and is fatal if untreated. About 10-20% of survivors are left with permanent sequelae like deafness, blindness and epilepsy. Diagnosis for Men A is by performance of a lumbar puncture to obtain cerebral spinal fluid for laboratory analysis.

WHO recommends that countries with high (>10 cases/100 000 population/year) or intermediate endemic rates (2–10 cases/100 000 population/year) of invasive meningococcal disease and countries with frequent epidemics introduce appropriate largescale meningococcal vaccination programs. Men A conjugate vaccine was prequalified by WHO in June 2010, as MenAfriVac, containing 10 µg of purified Men A polysaccharide antigen conjugated with tetanus toxoid (PsA-TT) per dose for use in those aged 1–29 years, and MenAfri- Vac 5 µg, containing 5 µg of PsA-TT per dose for use in infants and children aged 3–24 months. Uganda carried out a preventive mass vaccination campaign with Men. A conjugate vaccine in identified high risk districts in northern and western Uganda in January 2017. WHO recommends the introduction of Men.A vaccines into the routine immunisation program within 5 years of campaign introduction targeting children under 2 years, with catch-up round targeting unvaccinated children aged 1–4 years.

Evidence shows no serious adverse events related to the Men. A conjugate vaccination in individuals aged 9-24 months other than mild reactions like redness, swelling and pain at the site of injections. After the campaign introduction of Men. A vaccine in early 2017 targeting 1-29 yr olds in Northern Uganda, no serious adverse events were recorded. A single dose of vaccine given to children 9-24 months has proven protective for 27 months and a 60% coverage in routine schedule resulted in a significant reduction of Men A cases in other Men A belt countries in Africa. However, Men A conjugate vaccne has no impact on other meningitis sero groups. The co-administration of Men. A with other vaccine has shown no effects of interference. Men. A conjugate vaccine has been shown to result in a reduced carriage of Men A and a result, a reduced number of cases in countries along the African Men. A belt (confers herd immunity).

Economic modeling studies showed that routine immunization is more cost-effective in the long run than campaign vaccination. It is roughly estimated to cost 1 million dollars to introduce Men. A to Uganda's routine immunization schedule. Men. A vaccination is supported by Gavi for both preventative campaigns and introduction into the routine immunization schedule, however, co-funding must be secured from the government.

Based on this evidence, the working groups made these following recommendations:

a. Introduction of a Men A Vaccine in Uganda's routine immunisation schedule in targeted high risk districts at 9 months of age, at the same time as measles but at a separate injection site. As fiscal space becomes available, the vaccine can be rolled out in the entire country.
b. Vaccine effectiveness studies should be continued to determine the long term protective effect of Men A Vaccine beyond 27 months, and guide decisions for the need of a booster dose.

I. Introduction

a. Context of the question

The Ministry of Health (MoH) in Uganda through its Comprehensive Multiyear Plan 2016-2020, proposed to introduce five new vaccines into the routine immunisation program, one of which is Meningococcal vaccine in 2018. MoH requested Uganda National Immunisation Technical Advisory Group (UNITAG) for advice on which new vaccines Uganda should prioritise in the next five years, in view of challenges facing the immunisation program new vaccine introduction including under-performance and limited financing. (Annex 1)

b. General information on the issue

Meningococcal meningitis is a bacterial form of meningitis, which is a serious infection of the meninges that affects the brain membrane. *Neisseria meningitides* (Nm), a gram-negative diplococcal bacterium, is recognized as a leading cause of meningitis and fulminant septicemia. N. meningitides is classified into 12 serogroups (A, B, C, 29E, H, I, K, L, W135, X, Y and Z) based on the structure of the polysaccharide capsule. Although meningococcal strains usually reside harmlessly in the nasopharynx, with reported carriage rates of 4%–35% of healthy adults, transition from asymptomatic carriage to invasive disease may occur owing to a number of factors, including differences in the genetic composition and capsule structure of pathogenic and non-pathogenic strains. Most untreated cases of meningococcal meningitis and/or septicemia are fatal. Even with treatment a 10% fatality rate is reported.

Treatment for Invasive Meningicoccal Disease (IMD) involves empiric therapy with cefotaxime or ceftriaxone while awaiting confirmation of diagnosis. Once the diagnosis is confirmed, treatment can be changed to intravenous penicillin G. In certain developing countries where penicillin resistance is high, intramuscularly administered chloramphenicol is the standard treatment, but emerging resistance to this drug is a cause for concern. Septicemic shock and raised intracranial pressure in meningitis are particular problems in the management of meningococcal disease. In addition to antibiotics, intensive care measures are required.

A risk assessment for meningococcal meningitis was performed by WHO with the District Prioritization Tool (DPT) conducted in Uganda in 2014, which observed that Northern Uganda and parts of Western Uganda have experienced regular, focal outbreaks of meningitis since 2004. The reported outbreaks occurred primarily during the dry season (January-June) and the majority were due to serogroup A (NmA), which is a typical pattern observed in Meningitis Belt countries. A large epidemic occurred in 2007 with 4098 cases reported.

WHO recommends that countries with high (>10 cases/100 000 population/year) or intermediate endemic rates (2–10 cases/100 000 population/year) of invasive meningococcal disease and countries with frequent epidemics should introduce appropriate largescale meningococcal vaccination programs. In these countries, the vaccine may be administered through routine immunization programs, supplementary immunization activities (SIAs), for example during outbreaks, or through private vaccination services. Depending on the national epidemiology and socioeconomic resources, countries should select and implement the most appropriate control policy.

A MenA conjugate vaccine, intended for use mainly in the African meningitis belt, was licensed in 2010. The vaccine is licensed for vaccination of individuals 1–29 years of age as a single intramuscular dose. WHO's updated recommendations call for introduction of MenA vaccines into the routine immunisation program within 5 years of campaign introduction targeting children under 2 years, with catch-up round targeting unvaccinated children aged 1–4 years. Uganda carried out a targeted preventive mass vaccination campaign with MenA in identified high risk districts in northern and western Uganda in January 2017.

Sources: WHO position paper, Updates to position paper 2015 and Meningitis DPT Uganda report June 2014

Methodology

c. Establishment of a working group

In line with its internal procedures Manual, the UNITAG Chair in consultation with the Secretariat commissioned a working group to develop a Recommendation Framework on Men A vaccine introduction in Uganda's routine immunisation program, and conduct a systematic review of relevant evidence based on which, recommendations would be proposed. The Working Group was chaired by the Medical Bacteriologist Core-member representative and comprised of the following UNITAG members: Health system specialist, Public health expert, vaccinologist, and a co-opted epidemiology specialist.

d. Recommendation framework

The working group reviewed evidence on Burden of Meningococcal Disease in Uganda, efficacy and safety of Men A vaccine, Programmatic and Economic Considerations, and Acceptability. A detailed Recommendation Framework is attached as Annex 2.

e. Evidence search and assessment

The Working group followed the steps outlined below in its evidence search and assessment:

- Step 1: Framing questions for the review

The queries in the Recommendation Framework were reviewed to ensure that they were specified in the form of clear, unambiguous and structured questions before beginning the review work. Queries were categorised as those that required a systematic review, and those that could be answered using background information. Once the review questions had been set, modifications to the protocol were allowed only if alternative ways of defining the populations, interventions, outcomes or study designs became apparent. Queries requiring systematic reviews proceeded to step 2, while grey literature (Ministry of Health Reports, Immunisation partner surveys, websites and unpublished local reports) were searched for information to answer background data queries.

- Step 2: Identifying relevant peer reviewed articles

Search strategies were developed to ensure that search terms covered all known terms relevant to the question. Multiple journal resources (Pubmed, Scopus, Embase and Cochrane for safety and efficacy queries) were searched with English language restriction to generate relevant title-abstracts.

Selection criteria were set for each query to flow directly from the review question and was specified a priori. Reasons for inclusion and exclusion were recorded.

- Step 3: Assessing the quality of articles

Selected title abstracts were extracted in full text and subjected to a more refined quality assessment by use of design-based quality checklists, CASP[1]. These detailed quality assessments were used for exploring for bias by evaluating methodological quality, certainty of results, and relevance to the question, hence informing decisions regarding suitability of meta-analysis (Step 4).

- Step 4: Summarizing the evidence

Selected full text articles were read and relevant findings under each query were summarised in a standard UNITAG working group outline report. These were then presented to the Working Group members for review, and discussion.

- Step 5: Interpreting the findings

The working group provided technical backstopping by checking that the issues highlighted in each of the four steps above were met. The risk of publication bias and related biases was explored to help determine whether the summary reports can be trusted, and, if the summaries were generated from high-quality studies that could be used for generating recommendations.

The working group members deliberated the evidence presented and developed recommendations which were graded by reference to the strengths and weaknesses of the evidence.

II. Presentation of the evidence

NOTE: In this section, each query indicated in the recommendation framework is listed and the source of evidence on the same is indicated alongside. It is in bullet points to facilitate the reporting but afterwards the working group will write it in a narrative form. Note this section only presents the findings, and the discussion (judgment/sense -making in the country context) takes place in the next section. Based on that, recommendations/options are then proposed in the subsequent section

• Vaccine and immunization characteristics

i. Safety

- The safety profile (adverse events) of Men. A vaccine compared to other vaccines (i.e. Measles vaccine) administered in children under two years

  WHO 2015 Position Paper

  All meningococcal conjugate vaccines have an excellent safety record. None have been associated with any serious adverse effects, either during clinical trials or in post-marketing surveillance. Redness, swelling and pain at the site of injection may occur. Such reactions usually start within the first day after immunization and last 1 to 3 days. Less commonly, children may develop a fever or be irritable for a short period.

[1] http://www.casp-uk.net/casp-tools-checklists

- Risk factors that predispose to adverse events following Men. A vaccination in children under 2 yrs
- Are there any contraindications to administering Men A vaccine in children under 2 years?

  WHO 2015
  Type of study: WHO Position Paper
  Result:
  The MenA conjugate vaccine has been used in large vaccine campaigns in Burkina Faso, Mali, and Niger and it is being progressively introduced in other countries of the African meningitis belt. For grading of scientific evidence for the efficacy and safety of MenA conjugate vaccine, the reader is directed to the footnote: Grading of scientific evidence – Table V a & b (safety of MenA conjugate vaccine). Available at
  http://www.who.int/entity/immunization/meningococcalA_grad_safety.pdf

- Safety of co-administration of Men. A vaccine with other vaccines in children under 2 years (i.e. Measles, Rubella, YF, PCV, Rota)

  WHO 2015

  After administration of a total of 3315 doses of monovalent MenA conjugate in the Ghana and Mali double blind randomized trials reported by WHO position paper, there were no significant increases in systemic reactions due to concomitant vaccination with monovalent MenA conjugate vaccine compared to the other routine vaccines administered alone. No statistically significant differences in the frequency or severity of adverse events within 28 days of vaccination were observed among infants receiving monovalent MenA conjugate vaccine along with the other routinely administered vaccines compared to other routinely administered vaccines alone, indicating a comparable safety profile. The safety database shows a comparable safety profile for MenAfriVac 5 µg and MenAfriVac 10 µg when co-administered with the other recommended routinely administered vaccines in young children and did not reveal any signals for a specific adverse event to occur in excess. Both clinical studies provide evidence that both MenAfriVac formulations (5 µg and 10 µg) were well tolerated and safe

ii. Efficacy and effectiveness

- Immunogenicity and duration of protection (O) of Men. A conjugate vaccine if given as 1-dose (I) compared to a 2-dose schedule (c) in children under 2 yrs (P)

WHO 2011, 2015

Two double-blind randomized controlled studies of monovalent MenA conjugate vaccine have been conducted which were designed to assess safety and immunogenicity of different doses of antigen and different vaccination schedules before 2 years of age: a dose-ranging study in 1200 healthy infants and young children in Ghana and a dose-confirmation study in 1500 healthy infants and young children in Mali. The studies demonstrated MenA conjugate vaccine is immunogenic in a 1-dose schedule for those aged 9–24 months or in a 2-dose schedule for those aged 3–9 months. Duration of protection beyond 27 months after the final dose is unknown but continues to be monitored.

- Efficacy of Men A Conjugate vaccine in preventing Meningococcal disease in children under 2 years?

Karachaliou et. al. 2015

Type of study: Mathematical age structured model

Objective:
Investigate the potential impact of a range of immunization strategies through a model of MenA transmission and disease and how best to sustain population protection in the long term with MenA vaccination

Method
- The model is age structured and includes classes of susceptible, carrier, ill, and immune people (who may be vaccinated or unvaccinated);
- Comparison of different vaccination strategies: mass vaccination campaigns targeting 1–29-year-olds alone (1), followed by periodic campaigns targeting 1–4 year-olds (2) or by routine vaccination at 9 months of age with (3) or without (4) an initial catch-up campaign among 1–4 year-olds
- Model incorporates seasonal transmission
- Model parameters were primarily derived from African sources and can describe the typical annual incidence of meningitis in the pre-vaccine era.

Results:

- There was considerable overlap in the distribution of results but routine EPI immunization at 9 months of age resulted in lower average annual incidence than regular mass campaigns of 1- 4-year olds
- Following initial mass vaccination of 1- to 29-year-olds, the model predicted a resurgence in disease after approximately 15years, assuming an average of 10 years of vaccine protection
- Model limitation: (1) the model was parameterized using appropriate published and unpublished data specific to African populations as far as possible. Some model parameters were unknown, including the transmission rate and duration of natural immunity. (2) Quantifying the duration of natural immunity following infection is particularly difficult; estimation is hampered by codependence with other parameters, and empirical measurement is problematic

WHO 2015

Two double-blind randomized controlled studies of monovalent MenA conjugate vaccine have been conducted which were designed to assess safety and immunogenicity of different doses of antigen and different vaccination schedules before 2 years of age: a dose-ranging study in 1200 healthy infants and young children in Ghana and a dose-confirmation study in 1500 healthy infants and young children in Mali. The studies demonstrated MenA conjugate vaccine is immunogenic in a 1-dose schedule for those aged 9–24 months or in a 2-dose schedule for those aged 3–9 months. Duration of protection beyond 27 months after the final dose is unknown but continues to be monitored.

Tang et al, 2015

Type of study: RCT

Objectives:
Analyse the impact of age at which subjects were vaccinated on immune response and persistence Post immunization with PsA-TT

Method:

- The immunogenicity results of a single 10-µg dose of PsA-TT from 3 African trials are investigated
- In study A, healthy toddlers aged 12–23 months were recruited from Mali and The Gambia. In study B, healthy subjects aged 2–29 years were recruited from Mali, The Gambia, and Senegal; In study C, healthy infants of 14–18 weeks of age were recruited from Ghana. All were randomly assigned to receive PsA-TT

Results

- Prior to immunization, the study demonstrated that younger subjects showed lower SBA. Subjects who were to receive PsA-TT at the youngest ages (14–18 weeks, 9–12 months, and 12–18 months) had the lowest SBA GMTs, whereas subjects in the oldest age groups (2–10, 11–17, and18–29 years) had the highest SBA GMTs.
- After vaccination with MenAfriVac, it was shown that toddlers tended to have greater immune response than infants. In addition, an early sharp antibody decline was observed, with more rapid waning in infants than in toddlers, reaching lower levels 1 year postvaccination. No further decline was observed at 2 years postvaccination, and SBA titers remained sustained in both infants and toddlers.

- Vaccine co-administration (i.e. Measles, Rubella, YF, PCV, Rota) interference with the protection offered by Men A conjugate vaccine

  WHO 2011, 2015

  Results:

- Reporting the two double-blind randomized controlled studies of monovalent MenA conjugate vaccine designed to assess safety and immunogenicity of different doses of antigen and different vaccination schedules before 2 years of age in the Ghana and Mali, non-inferiority of each of the monovalent MenA conjugate vaccine groups (monovalent MenA conjugate vaccine with other routinely administered vaccines) to the relevant control group (other routinely administered vaccines alone –diphtheria toxoid, tetanus toxoid, whole cell pertussis, hepatitis B, Haemophilus influenzae type b, oral poliovirus, yellow fever, measles and rubella vaccines) was demonstrated for most of the vaccine comparisons, as shown by the response rate to a given routinely administered vaccine antigen reaching a pre-defined threshold. However, the immunogenicity when co-administered with rotavirus and pneumococcal conjugate vaccines was not evaluated.

iii. Vaccine indirect effects

- Vaccine coverage threshold required with Men. A conjugate vaccine to provide herd immunity

Karachaliou et. al.2015a

Type of study: Mathematical age structured model

Objective:
Investigate the potential impact of a range of immunization strategies through a model of MenA transmission and disease and how best to sustain population protection in the long term with MenA vaccination

Method

- The model is age structured and includes classes of susceptible, carrier, ill, and immune people (who may be vaccinated or unvaccinated);
- Comparison of different vaccination strategies: mass vaccination campaigns targeting 1–29 year-olds alone (1), followed by periodic campaigns targeting 1–4 year-olds (2) or by routine vaccination at 9 months of age with (3) or without (4) an initial catch-up campaign among 1–4 year-olds
- The sensitivity of the results to changes in the age at EPI immunization and the coverage achieved for EPI immunization at 9 months was also investigated.

Results

- The study demonstrated that the strategy with the lowest average annual incidence (introduction into EPI at 9 months, 5 years after the initial mass campaigns, with a catch-up targeting unvaccinated children aged 1–4 years) was achieved with a coverage at 95% in the initial mass campaign among 1- to 29-year-olds and routine and subsequent catch-up for 1-4 years coverage at 80%
- As EPI coverage increased, the incidence of disease decreased. For every 10% increase, the average annual incidence decreases by approximately 1 case per 100 000 population per year. Disease control was better when vaccine effectiveness was higher.
- Routine EPI immunization at 9 months of age resulted in lower average annual incidence than regular mass campaigns of 1- to 4-year-olds provided that EPI coverage was above approximately 60%

- Rate of nasal carriage of Men. A pre and post Men. A vaccination in children?

  Daugla et al. 2014

  Type of study: observational study (before and after)
  Objective: To study the effect of PsA–TT on meningococcal meningitis and carriage in Chad during a serogroup A meningococcal meningitis epidemic.
  Method
  - Incidence of meningitis before and after vaccination from national records between January, 2009, and June, 2012.
  - Meningococcal carriage was studied in an age-stratified sample of residents aged 1–29 years of a rural area roughly 13–15 and 2–4 months before and 4–6 months after

vaccination. Meningococci obtained from cerebrospinal fluid or oropharyngeal swabs were characterised by conventional microbiological and molecular methods

- Assessment of the effect of PsA–TT on carriage of serogroup A meningococci was done by comparing the prevalence of carriage before and after vaccination in Mandelia (rural area) with a logistic regression model adjusted for age.

Results

- 2–4 months before vaccination, 32 of 4278 individuals (0.75%) were carrying an epidemic strain serogroup A
- 4–6 months after the vaccination campaign, only one of 5001 individuals tested was carrying an epidemic strain serogroup A (0.02%), a 98% difference in prevalence. The one serogroup A carrier detected after vaccination was a 15-year-old boy who, according to his vaccination card, had been vaccinated with PsA–TT 4 months before detection.
- The number of individuals carrying serogroup A fell in the unvaccinated age groups went from seven of 1374 before vaccination to zero of 336 individuals after vaccination (p=0·19).

Kristiansen et al 2013

Type of study: cross sectional study
Objectives: Identify the impact of MenAfriVac on NmA carriage after vaccination and the effect of vaccination on herd immunity
Method

- Repeated cross-sectional meningococcal carriage study in a representative portion of the 1–29-year-old population in 3 districts in Burkina Faso before and up to 13 months after vaccination. One district was vaccinated in September 2010, and the other 2 were vaccinated in December 2010.
- They analysed 25,521 oropharyngeal samples, of which 22 ,093 were obtained after vaccination

Results

- While baseline NmA carriage was estimated to be 0.39% in Burkina Faso in 2009, the post vaccination carriage study campaigns S6–S9, conducted simultaneously in all 3 districts in 2011, enrolled an additional 20450 persons, and none were carriers of NmA
- Elimination of NmA after mass vaccination was statistically significant when all 3 districts were considered together as well as when each district was considered separately ($P < .05$)

Ky-Ba et. al. 2016

Type of study: cross-sectional study (repeated before and after MenA vaccination). January 2009 to November 2011.
Objectives: The aim of this study was to evaluate the impact of conjugate vaccine A, MenAfriVac, on the frequency of occurrence of clinical cases of cerebrospinal meningitidis and NmA carriage, and possibly cases associated with other common serogroups in Burkina Faso

Design:

- Case base data of meningococcal meningitis in the three studied health districts were collected through meningitidis epidemiological surveillance of Burkina Faso
- Sampling for meningococcal carriage: A sample representing persons aged 1 to 29 years was obtained by cluster sampling at several levels.

Results:

- The overall carrier rate of Nm before vaccination was 2.84% with that of NmA at 12.1%
- The overall carriage rate Nm after vaccination was 6.42%. However, NmA was isolated in only 0.1% of participants.
- Prior to the vaccination campaign, the prevalence of asymptomatic carriage of serogroup A was 0.11% in the Bogodogo district, 0.18% in the Dande district, and 0.83% in the Kaya district. Post-vaccination, a single NmA carrier was identified in the Bogodogo district; this carrier had not received the MenAfriVac vaccine.

- Following mass campaigns with Men. A vaccine in the country and region has there been an emergence of other epidemic prone serotypes?

Sidikou et al.2016

Type of study: Cross sectional study

Objective: Report the first Neisseria Meningitis epidemic post MenAfriVac introduction in Niger

Method:

- Analysis of nationwide case based surveillance data
- Cases confirmation by culture or direct real-time PCR, or both, of cerebrospinal fluid specimens,

Results

- Before 2015, *Meningitidis* serogroup C (NmC) cases have occasionally been reported in Niger and elsewhere in the meningitis belt.
- From Jan 1 to June 30, 2015, 9367 meningitis cases—1604 (17·1%) confirmed cases, 64 (0·7%) probable cases, and 7699 (82.2%) suspected cases
- 85·0% of suspected cases had their cerebrospinal fluid specimens received by a laboratory performing confirmatory testing and had a case report form available. 37.3% specimens tested positive: 71.5% were positive for NmC; 14·7% NmW; 5·6% undetermined *N. meningitidis*, 0·06% NmX; 7·5% *S pneumoniae*; and 0·5% *H influenzae* serotype b
- At the beginning of the epidemic (weeks 11–14), the proportion of NmC and NmW cases among *N. meningitidis* cases with known serogroup was roughly equal. From week 15 onwards, the proportion of weekly NmC cases predominated 82–90%; This predominance of NmC cases was only observed in the 18 districts that exceeded the alert or epidemic threshold, whereas in districts that remained below the thresholds, the distribution of NmC and NmW cases remained roughly equal (53·6% vs 46·4%.)

Ky-Ba et al. 2016

Type of study: cross-sectional study (repeated before and after MenA vaccination). January 2009 to November 2011.

Objectives: The aim of this study was to evaluate the impact of conjugate vaccine A, MenAfriVac, on the frequency of occurrence of clinical cases of cerebrospinal meningitidis and NmA carriage, and possibly cases associated with other common serogroups in Burkina Faso

Design:

- Case base data of meningococcal meningitis in the three studied health districts were collected through meningitidis epidemiological surveillance of Burkina Faso
- Sampling for meningococcal carriage: A sample representing persons aged 1 to 29 years was obtained by cluster sampling at several levels.

Results:

- From 2009 to 2010 (before the vaccination campaign), 891 cases of suspected bacterial meningitis were reported in the three studied health districts; 10.88% having been confirmed by laboratory analysis. Among the 92 confirmed cases, 43.2% were caused by *N.meningitidis.* The distribution of serogroups of *N. meningitidis* was as follows: 5.15% of NmA, 34.02% of NmX, and 4.12% of NmW

- The MenAfriVac vaccine was introduced in Burkina Faso December 2010; thus, the period from 2011 to 2013 was considered the post-vaccination period. During this period, 965 suspected cases of meningitis were reported in the three studied health districts, 179 (18.54%) of these cases being laboratory-confirmed. Among the confirmed cases, 91 (50.83%) were caused by *N. Meningitidis*. The distribution of N. meningitides serogroups was as follows: 58 cases (32.40%) of NmX, 52 (29.05%) of NmW, one (0.55%) of NmY, and none of NmA.

iv. Vaccine characteristics

- Presentations and formulations is Men A conjugate vaccine available

WHO 2015

- Two licensed formulations of the vaccine are available: (i) MenAfriVac, containing 10 µg of purified Men A polysaccharide antigen conjugated with tetanus toxoid (PsA-TT) per dose for use in those aged 1–29 years, and (ii) MenAfri- Vac 5 µg, containing 5 µg of PsA-TT per dose for use in infants and children aged 3–24 months

WHO website:http://www.who.int/immunization_standards/vaccine_quality/PQ_197_MenAconjugate_10dose_SII/en/

Presentation is a lyophilised 10 dose vial (active) + 10 dose ampoule (diluent). Shelf life 36 months at 2 - 8 °C (active) and 60 months at 25°C (diluent). Cold Chain volume per dose (cm3): 2.6. WHO recommends that opened vials of this vaccine should be discarded 6 hours after opening or at the end of the immunization session, whichever comes first.

The MenAfriVac vaccine can be used in a controlled temperature chain (CTC), for up to four days at ambient temperatures not exceeding 40°C. A CTC is initiated immediately prior to administration, provided that the vaccine has not reached its expiry date and the vaccine vial monitor is still valid.

Unopened vaccine vials should be discarded at the end of the four days at 40°C.
Reconstituted vaccine should be discarded within six hours.
WHO recommends that CTC implementation only occur with appropriate planning, training and guidance.

Figure 1: Pictoral presentation of MenAfriVac vaccine (Serun Insititute of India http://www.seruminstitute.com/product_poly_meningococcal.php

Manufacturer's insert (Serum Insititue of India)

- MenAfriVac is a lyophilized vaccine of purified meningococcal A polysaccharide covalently bound to tetanus toxoid (TT), which acts as a carrier protein. The vaccine consists of purified group-specific bacterial polysaccharide from group A Neisseria meningitidis. The TT is prepared by extraction, ammonium sulfate purification, and formalin inactivation of the toxin from cultures of Clostridium tetani.
  WHO website
  http://www.who.int/immunization_standards/vaccine_quality/pq_197_menAconj_SII_PI_624-2.pdf?ua=1.

- Recommended form of administration and dosage for Men A conjugate vaccine
  WHO 2015
  - The vaccine is for intramuscular use only. MenAfriVac should be administered by deep intramuscular injection, preferably into the deltoid muscle or anterolateral aspect of the thigh. The vaccine must not be administered subcutaneously or intravenously, and must not be mixed with other vaccines in the same syringe. Separate injection sites should be used in case of concomitant administration.

WHO 2015

- MenAfriVac 5 µg should be used for routine immunization of infants and young children from 3 to 24 months of age. MenAfriVac 10 µg should be used for catch-up and periodic campaigns from 12 months of age onwards unless bridging studies have been conducted that show that MenAfriVac 5 µg can be used in older age groups

- Recommended schedule of Men. A conjugate vaccine by WHO?

WHO 2015

- WHO recommends 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.

- The need for a booster dose has not been established

- Any children who miss vaccination at the recommended age should be vaccinated as soon as possible thereafter. If in a specific context there is a compelling reason to vaccinate infants younger than 9 months, a 2-priming dose infant schedule should be used starting at 3 months of age, with doses at least 8 weeks apart, based on evidence from other polysaccharide-protein conjugate.

- Can the schedule of Men. A conjugate vaccine be altered to fit into the current immunization program of Uganda?

  WHO 2015.
  WHO recommends 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. Currently, measles vaccination is routinely administered at 9 months of age. There is therefore opportunity for a shared platform.

- Additional logistical and cold chain requirements of introducing Men. A conjugate vaccine into routine immunization?
  A readiness assessment needs to be done before new vaccine introduction

• The disease

i. Burden of disease

- Incidence, prevalence and case fatality rate of meningococcal disease by serotype, by age and sex in Uganda?

  Lingani et. al. 2014
  Type: Review
  Method: A review of all available data on meningitis cases and outbreaks in Uganda was performed. Data was compiled and a descriptive analysis of the epidemiology of meningococcal meningitis in Uganda was conducted. The District Prioritization Tool was completed with the compiled data to identify districts at high risk for meningitis epidemics.
  For the descriptive analysis of the meningitis epidemiology in Uganda, IDSR case and death counts by district and week were aggregated in order to describe national trends by week, month, and year in Uganda. The outbreak data sources were compiled and an Excel linelist database was created to capture and standardize case-level data. This harmonized data was used to analyze outbreak trends by week, as well as describe the age and geographic distribution of outbreak cases. Aggregate laboratory data was analyzed to ascertain the serogroup distribution during outbreak years, as well as describe the geographic distribution

of outbreak-cases with laboratory confirmation. Population figures were used to calculate incidence as well as estimate number of doses in the target population for vaccination.

Results:

From 2004 to week 22 of 2014, 10,630 cases of suspected meningitis were reported nationally in Uganda through IDSR. Among these, 831 deaths were reported (case-fatality ratio (CFR) of 8%). A large epidemic occurred in 2007 with 4098 cases reported, representing nearly 40% of cases reported during this 10 year period. 2242 cases were recorded during outbreaks from 2006 to week 22 of 2014 in 17 districts (Table 1) Among these, 171 deaths were reported (CFR of 7.6%). Among the 2222 outbreak cases with known sex, 1198 (53.9%) were male and 1024 (46.1%) were female. With the data available in the harmonized outbreak database, 154 cases (6.9%) were classified as confirmed, 69 (3.1%) as probable, and 2012 (90.1%) as suspect cases based on standard WHO definitions.

From 2006-2014, 367 Cerebral Spinal Fluid specimens were received at the Central Public Health Library. Among the 110 Nm cases, 71 were due to serogroup A (64.5%), and the rest due to serogroup W (n=23) and serogroup X (n=16).

Table 1 Number of outbreak cases in harmonized outbreak database by district and year

District	**2006**	**2007**	**2008**	**2009**	**2010**	**2012**	**2013**	**2014**	**Total**
Adjumani	3	353	58	21	0	0	1	107	543
Amuru	0	0	0	0	0	51	0	2	53
Arua	0	48	12	200	0	0	0	75	335
Gulu	49	0	0	0	0	2	0	0	51
Hoima	0	0	11	37	0	0	0	0	48
Kamwenge	2	0	0	0	0	0	0	0	2
Kitgum	5	0	0	0	0	0	0	0	5
Koboko	0	12	0	0	0	0	0	0	12
Kotido	172	76	0	0	0	0	0	0	248
Kumi	1	0	0	0	0	0	0	0	1
Lira	1	0	0	0	0	0	0	0	1
Maracha-Terego	0	0	0	0	112	0	0	0	112
Masindi	0	0	25	29	0	0	0	0	54
Moroto	103	0	0	0	0	0	0	0	103
Moyo	0	147	0	17	0	0	0	0	164
Nakapiripirit	16	0	0	0	0	0	0	0	16
Yumbe	0	450	0	43	0	0	0	1	494
Total	352	1086	106	347	112	53	1	185	2242

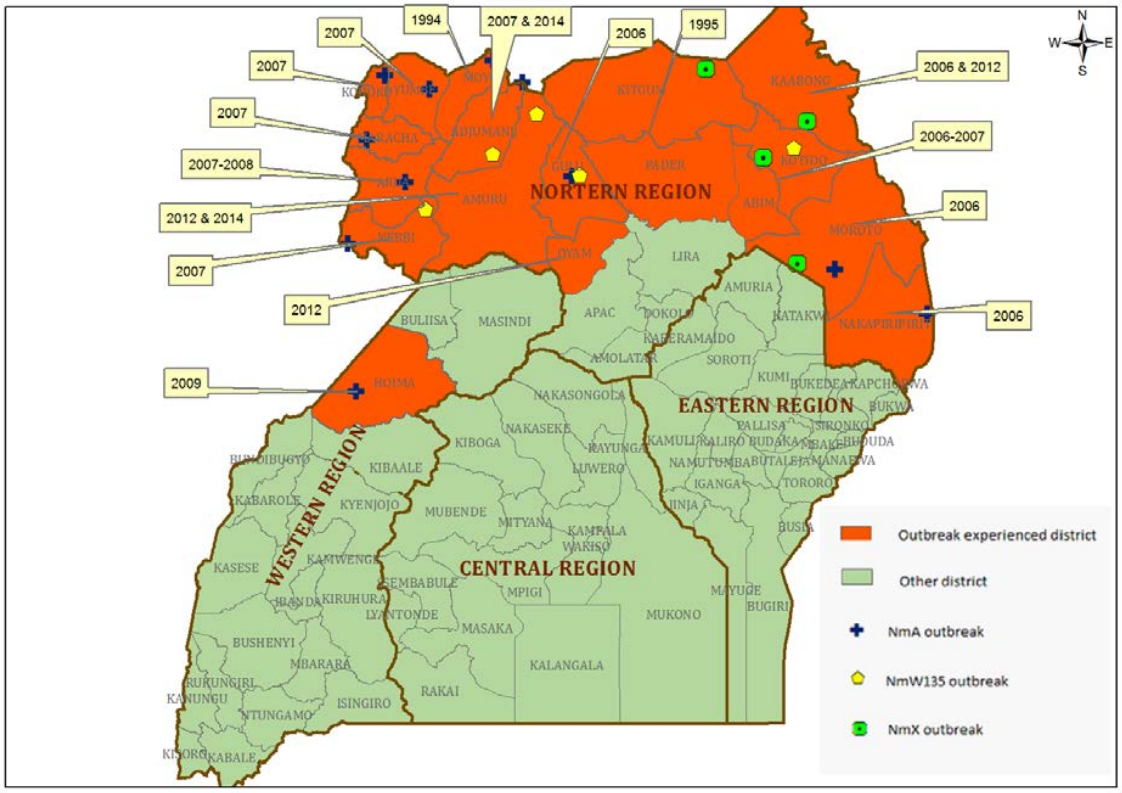


Figure 2: Districts where at least 1 meningitis outbreak reported, 1994-2014.

- How does the Incidence/prevalence of Meningococcal disease in Uganda compare with that of the Ugandan meningococcal belt and the African Meningococcal belt?

  In Uganda: From 2004 to week 22 of 2014, 10,630 cases of suspected meningitis were reported nationally in Uganda through IDSR (Lingani et. al 2014.)

  Lingani et al 2015 DOI 10.1093cidciv597

Table 2: Suspected and confirmed Meningitis cases in 10 Counties in the African Meningitis Belt 2004-2013

Year	Benin	Burkina Faso	Chad	DRC	Ghana	Côte d'Ivoire	Mali	Niger	Nigeria	Togo	Total
2004	377	6252	863	13 367	982	464	1480	4081	659	305	28 830
2005	303	3626	1015	9082	430	527	454	1404	657	333	17 831
2006	316	19 134	1430	6109	371	705	1039	4465	5731	578	39 878
2007	502	26 878	1452	8645	461	760	977	1097	2642	723	44 137
2008	414	10 401	1093	8406	281	1131	1538	3757	6835	428	34 284
2009	416	4723	1505	9150	201	289	335	13 449	56 128	350	86 546
2010	323	6732	3147	8160	1129	151	482	2908	4983	460	28 475
2011	269	3875	5960	5167	773	141	430	1189	1165	440	19 409
2012	1165	6957	3874	10 142	956	500	688	314	1206	408	26 210
2013	833	2917	371	9326	454	255	358	311	871	266	15 962
Total	4918	91 495	20 710	87 554	6038	4923	7781	32 975	80 877	4291	341 562

Abbreviation: DRC, Democratic Republic of Congo.

Occurrence of Meningitis cases over time in the African Meningitis belt

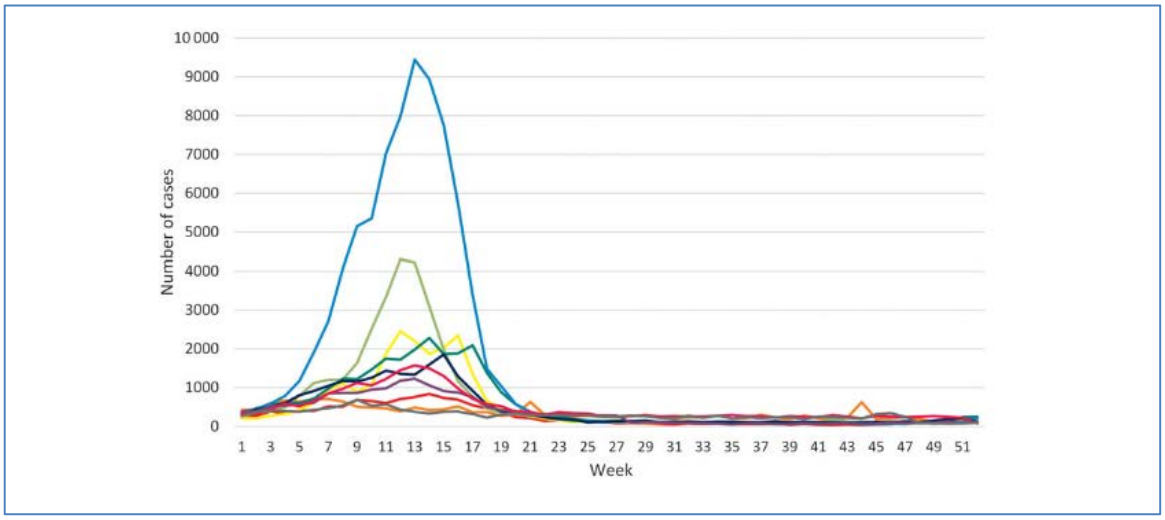


Figure 3: Number of suspected and confirmed meningitis cases by week in the African meningitis belt of 2004 (red), 2005 (orange), 2006 (yellow), 2007 (light green), 2008 (green) 2009 (light blue), 2010 (blue), 2011 (purple), 2012 (pink) and 2013 (grey)

- Seasonality of meningococcal disease occurrence by serotype, age and sex in Uganda?

  The reported outbreaks occurred primarily during the dry season (January-June) (Lingani et al. 2014)

- Populations by age and sex at greater risk of developing meningococcal disease?

  Table 3: Age distribution of outbreak cases 2006- 2014 (week 22)

Age Category	Cases	Proportion
<1	59	2.7%
1-4	172	7.8%
5-14	723	32.9%
15-29	723	32.9%
30+	519	23.6%
Total	2196	100.0%

Among the 2222 outbreak cases with known sex, 1198 (53.9%) were male and 1024 (46.1%) were female. (Lingani et. al. 2014)

WHO 2007

Surveillance studies conducted in Ghana and Niger showed that the incidence of meningococcal meningitis was similar in all age groups under 20 years of age (average annual incidence 30–40 cases per 100 000).

- Meningococcal serotypes that have been identified in outbreaks and epidemics in the country?

Lingani et al 2014

Table 4: Meningococcal serotypes isolated at Central Public Health Laboraory 2006-2014

Year	Central Public Health Laboratory Results							Total cases IDSR	Total cases outbreak linelist
	Number CSF tested	NmA	NmW135	NmX	Spn	Hib	Total CPHL		
2006	63	11	3	10	1	1	26	1441	352
2007	118	32	0	6	0	0	38	4098	1086
2008	41	13	0	0	0	0	13	839	106
2009	33	15	0	0	0	0	15	381	347
2010	2	0	0	0	0	0	0	219	112
2011	2	0	0	0	1	0	1	128	0
2012	29	0	0	0	3	0	3	278	53
2013	2	0	0	0	0	0	0	652	1
2014	77	0	20	0	0	0	20	230	185
Total	367	71	23	16	5	1	116	8266	2242

- Which are the prevalent meningococcal strains in nasal carriage categorized by age both in Uganda and in the meningococcal belt?

Daugla et al; 2014

Type of study: observational study (before and after)
Objective: To study the effect of PsA–TT on meningococcal meningitis and carriage in Chad during a serogroup A meningococcal meningitis epidemic.
Method

- Carriage survey: Between August and October 2011, prevaccination survey between April and June 2012, post vaccination survey in the same community. Four age groups (0–4 years, 5–14 years, 15–29 years, and >30 years) were adequately represented.
- Assessment of the effect of PsA–TT on carriage of serogroup A meningococci was done by comparing the prevalence of carriage before and after vaccination in Mandelia (rural area) with a logistic regression model adjusted for age.

Results

- The prevalence of meningococcal carriage in the rural area of Mandelia varied with age, and was most frequent in individuals aged 1–29 years
- Before vaccination
  - Less than 1 year: Serogroup A
  - 1- 29 years: Serogroup A and X
- After Vaccination
  - Less than 1 year: None
  - 1-29 years: Serogroup X

- How has the epidemiology of meningococcal disease changed over time in Uganda and in the Region i.e. with changes in environment and climate?

  Agier 2017.

  Study type: Systematic review
  Objective:
  Improving bacterial meningitis control by providing a better understanding of the determinants driving the meningitis disease transmission dynamics in the changing context of a reduction in incidence of serogroup A and an increase in incidence of serogroups W and C and of Streptococcus pneumoniae

  Method: The literature was searched to provide a multi-disciplinary overview of the determinants of meningitis transmission dynamics in the African meningitis belt

  Results
  - There is growing evidence that carriage of the epidemic strain is substantially increased during an epidemic. The season and immunization with polysaccharide vaccine appear to have little effect on carriage, but being in contact with a case has.

  - The review revealed that It was hypothesized that the transition to seasonal hyperendemicity , localized epidemics, and larger pluri-annual epidemic waves are distinct phenomena with their own respective mechanisms, which could be explained by an increased risk of invasion given nasopharyngeal colonization (possibly due to a dry and dusty climate), epidemic co-factors increasing meningococcal transmission and colonization during short periods (such as viral respiratory infections), and changing population immunity. For epidemic meningitis in the African meningitis belt, vaccination coverage data were not systematically reported before the introduction of MenAfriVac, and few seroprevalence estimates were available, such that the effect of vaccination on the disease transmission dynamics could not be investigated before 2010

  - At spatially aggregated levels, evidence suggested that humidity/ rainfall was negatively associated with incidence while temperature showed a positive association. Low humidity appeared to prevent acquisition and increase clearance of the non-groupable bacteria, and to be a necessary but not sufficient condition for meningitis outbreaks to occur. Despite a negative association between dust and meningitis in one study, more recent studies have shown a positive correlation between dust and meningitis incidence with a 1- to 2-week delay between dust and meningitis seasonal

ii. Clinical characteristics of the disease in the country

- Signs and symptoms of meningococcal disease in adults and children?

  WHO 2011

  - Signs and symptoms of IMD in infants and young children include fever, poor feeding, irritability, lethargy, nausea, vomiting, diarrhoea, photophobia and convulsions. The

characteristic feature of meningococcal septicaemia is a hemorrhagic (petechial or purpuric) rash that does not blanch under pressure.

- Percentage of patients with meningococcal disease who die?

WHO 2011

  - Most untreated cases of meningococcal meningitis and/ or septicaemia are fatal. Up to 10% of patients die even with appropriate care, typically within 24–48 hours of the onset of symptoms. In the meningitis belt of Africa, fatality from MenA disease has been estimated at 10–15%, although higher rates have been seen in some settings.

- Percentage of the survivors is left with permanent sequelae?

WHO 2011, 2015

Even with appropriate care up, approximately 10% to 20% of survivors of meningococcal meningitis are left with permanent sequelae such as mental retardation, deafness, epilepsy, or other neurological disorders.

Ramakrishnan 2009

Objective: to present a comprehensive review of data on bacterial meningitis sequelae in children from the African continent.

Type of study: systematic review

Methodology: conducted a systematic literature search to identify studies from Africa focusing on children aged between 1 month to 15 years with laboratory-confirmed bacterial meningitis. Study extracted data on neuropsychological sequelae (hearing loss, vision loss, cognitive delay, speech/language disorder, behavioural problems, motor delay/impairment, and seizures) and mortality, by pathogen.

Results: In all, 6 studies including a total of 701 children had data on meningococcal meningitis sequelae with prevalence estimates ranging from 3% to 21% (median 7%, IQR 5% to 10%). Studies found hearing loss in 3% to 9% of subjects (three studies), vision loss in 3% (one study), behavioural problems in 1% (one study), motor impairment in 1% to 2% (three studies), and seizures in 1% (two studies). Among 8 studies following 1,065 children, the CFR for meningococcal meningitis ranged from 1% to 13% (median 4%, IQR 3% to 6%).

- Long term complications of the meningococcal disease?

WHO 2011

  - Even with appropriate care up, approximately 10% to 20% of survivors of meningococcal meningitis are left with permanent sequelae such as mental retardation, deafness, epilepsy, or other neurological disorders.

- What is the standard of care for treatment of meningococcal disease?

WHO 2011, 2007

Empiric therapy with cefotaxime or ceftriaxone should be started while awaiting confirmation of diagnosis.

Alternatively, ceftriaxone may be used for the entire duration of therapy owing to ease of dosing and reports of decreased susceptibility to penicillin in several countries. A single dose of long-acting chloramphenicol or ceftriaxone is used for the treatment of epidemic meningococcal meningitis in sub-Saharan Africa.

iv. Regional and international considerations

- What are the Global and regional recommendations for Men A conjugate vaccine in routine schedules?
  WHO 2011,2015
  WHO recommends 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.
  MenAfriVac 5 µg should be used for routine immunization of infants and young children from 3 to 24 months of age. MenAfriVac 10 µg should be used for catch-up and periodic campaigns from 12 months of age onwards unless bridging studies have been conducted and show that MenAfriVac 5 µg can be used in older age groups. The need for a booster dose has not been established.

- Has there been any spread of Meningococcal disease from neighbouring countries into Uganda and has there been any pandemic in the region in the recent past?
  Source: WHO website:
  http://www.who.int/gho/epidemic_diseases/meningitis/Meningitis_009.gif

  Although no data specific to pandemic spread in Uganda was found, there is a history of pandemic spread in the Men A belt with the disease spreading to epidemic thresholds across countries in 2009. Red – epidemic threshold, Yellow is alert threshold

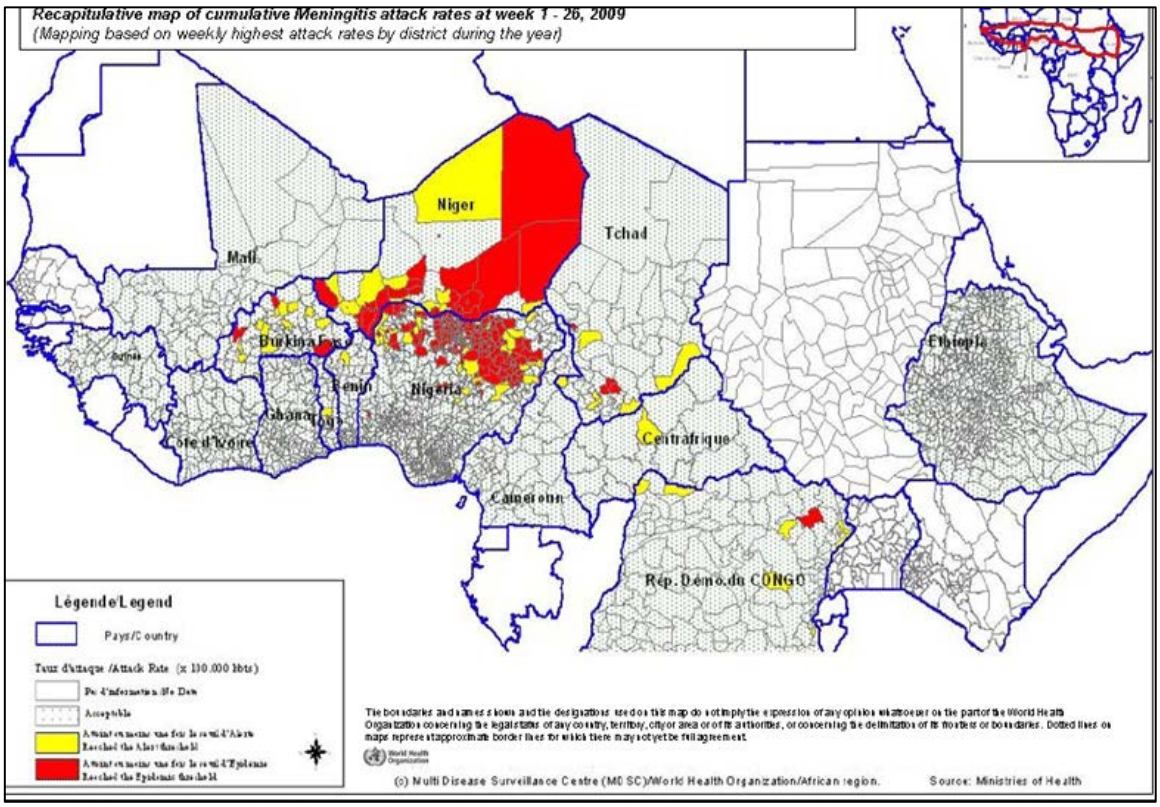


Figure 4: Recaptulative map of cumulative Meningitis attack rates at week 5-26, 2009. Map based on weekly highest attack rates by distict during the year.

• Economic and operational considerations

i. Vaccine related cost and resource use

- Current price of Men A vaccine per dose (5 micrograms)?

  UNICEF Website: https://www.unicef.org/supply/files/Meningitis.pdf
  2017 price for Routine 5 mg in a 10 dose presentation from Serum Institute India is $0.5070 per dose.

- Total (direct and indirect) cost of administering Men A vaccine per child in Uganda?
  It is estimated to cost between $ 2.6-3.4 million per year to introduce Men A vaccine in routine schedule in 217-2021. (Healthnet Consult 2017).

ii. Vaccine availability

- Is there reliable (potential) supply of Men A vaccine to Uganda?
  UNICEF Website:
  https://www.unicef.org/supply/files/Meningitis_Vaccine_Market_Supply_Update.pdf
  UNICEF launched two separate tenders in 2015, to secure quantities of meningococcal A conjugate vaccines for use in pediatric RI programmes mainly in 2016, and for conjugate and polysaccharide vaccines for use in emergency outbreaks also in 2016 and January to June 2017.

iii. Vaccine affordability

- Annual fiscal costs to government of introducing Men. A conjugate vaccine into routine immunization?
  It is estimated to cost between $ 2.6-3.4 million per year to introduce Men A vaccine in routine schedule in 217-2021. (Healthnet Consult 2017). Uganda is eligible for Gavi support to introduce Men A vaccine into its routine schedule, but the government will be expected to make a co-funding.

- Available grant opportunities from partners for introduction of Men. A conjugate vaccine in Uganda's routine immunization schedule.
  Gavi website: www.gavi.org/library/gavi.../supply.../meningococcal-roadmap-public-summary/
  http://www.gavi.org/results/countries-approved-for-support/

  Gavi support to campaign vaccination is planned to end when all 26 target countries will have rolled out routine immunisation and when meningococcal meningitis epidemics are eliminated as a public health problem in Africa. If current epidemiological trends continue, this will occur in 2018 after which routine immunisation is expected to keep MenA disease under control. Thereafter, Gavi funding for meningococcal routine immunisation will continue to be made available to eligible countries requesting such support.

iv. Socio economic and social impact

- Perception of the community in Uganda on Meningitis (Meningococcal disease)?
  No publication was found.

v. Economic impact on the immunization programme

- Cost benefit (O) to the country (P) of introducing Men. A conjugate vaccine intro routine immunization (I) vs. mass campaigns (C)

  A. Colombini et al. 2015

  Type of study: Costing study
  Objective: The study aims to estimate the economic impact of a range of MenAfriVac vaccination strategies in Burkina Faso.
  Method
  - The study is both retrospective (real costs from 2010 to 2014) and prospective from 2015 onward, where future costs are projected
  - Cost-of-illness study comparing 4 different vaccination scenarios in terms of costs to both households and health systems over a 26-year time horizon
  - Scenarios are: (1) reactive vaccination campaign (baseline comparator); (2) preventive vaccination campaign; (3) routine immunization at 9 months; and (4) a combination of routine and an initial catchup campaign of children under 5
  - Costs estimation done from a literature review, which included unpublished programmatic documents and peer-reviewed publications

  Results

- The reactive strategy led to higher total costs both for the health system and for households, regardless of the comparison strategy
- From 2010 to 2014, the total costs associated with the preventive campaign targeting 1- to 29-year-olds with MenAfriVac were similar to the estimated costs of the reactive vaccination strategy (approximately 10 million US dollars [USD]). Between 2015 and 2035, routine immunization with or without a catch-up campaign of 1- to 4-year-olds is cost saving compared to the reactive strategy, both with and without discounting costs and cases.
- All the alternative strategies save money compared to the reactive strategy (Table 5, Figure 1). In total, the savings for the routine and the combination strategy are similar and amount to 32.5 and 32.3 million USD between 2015 and 2035, respectively. Savings are higher overall for the households than for the health system. Between 2010 and 2014, the savings are much lower (about 300 000 USD);
- Ultimately, each dollar invested in routine immunization generates savings of an additional 1.3 USD, and each dollar invested in the combination strategy saves 1.2 USD.

Limitations

- Methodological choices were conservative and, thus, the study may have underestimated the economic benefits of MenAfriVac. The costs to households may be underestimated for several reasons
- Estimates of the epidemiological impact of MenAfriVac from 2015 through 2035 are based on a transmission dynamic model of MenA
- The transmission model predicts a national incidence and does not predict the occurrence of local epidemics that would trigger a reactive vaccination response
- The effectiveness of reactive vaccination has not been systematically reviewed and critically depends on the speed at which reactive vaccination can be implemented. However, it is not thought to be a highly effective strategy, hence the development and introduction of MenAfriVac

- Cost-effectiveness (O) of introducing Men. A conjugate vaccine into routine immunization (I) vs. mass campaigns (C) in the country (P)

Colombini et al. 2015

Type of study: costing study

Objective: The study aims to estimate the economic impact of a range of MenAfriVac vaccination strategies in Burkina Faso.

Method

- The study is both retrospective (real costs from 2010 to 2014) and prospective from 2015 onward, where future costs are projected
- Cost-of-illness study comparing 4 different vaccination scenarios in terms of costs to both households and health systems over a 26-year time horizon
- Scenarios are: (1) reactive vaccination campaign (baseline comparator); (2) preventive vaccination campaign; (3) routine immunization at 9 months; and (4) a combination of routine and an initial catchup campaign of children under 5
- Costs estimation done from a literature review, which included unpublished programmatic documents and peer-reviewed publications
- The future disease burden for each vaccination strategy was predicted using a dynamic transmission model of group A *Neisseria meningitidis.*

Results

- The number of cases of MenA expected in Burkina Faso varies from one strategy to the other. In the absence of preventive vaccination, 122 466 cases are predicted between 2015 and 2035. In contrast, the most effective combination strategy predicts only 3066 cases over the same period. The 3 alternative strategies considerably reduce the number of cases of MenA, preventing at least 100 000 cases compared with the reactive strategy

Limitations

- Estimates of the epidemiological impact of MenAfriVac from 2015 through 2035 are based on a transmission dynamic model of MenA
- The transmission model predicts a national incidence and does not predict the occurrence of local epidemics that would trigger a reactive vaccination response
- The effectiveness of reactive vaccination has not been systematically reviewed and critically depends on the speed at which reactive vaccination can be implemented. However, it is not thought to be a highly effective strategy, hence the development and introduction of MenAfriVac

vi. Interaction with other intervention immunization schedule

Potential impact of introducing Men A vaccine into routine immunization on other vaccines administered at the same time?

(see page 10 - co-administration).

• Health Policy and programmatic issues

i. Equity

- Are immunization services accessible to the unique population groups in Uganda who are most susceptible to Meningococcal disease?

  UNICEF 2016. Uganda Immunization Equity Assessment Report, September 2016; Communities and Districts Affected by Immunisation Inequities Report as of 29/9/2016

'Immunisation equity assessment' was commissioned to support national stakeholders and district stakeholders to get a list of districts with inequities and high risk communities, identify barriers to access and use of immunisation in those communities, then come up with recommendations and actions

This exercise was done in Uganda in September 2016 through a process of collecting views of EPI stakeholders and DHOs by key informant interviews, desk review of documents like UDHS report 2011and EPI Review 2015, analysis of UDHIS2 data, surveillance data and Secondary analysis of GAVI FCE house hold data from 19 districts. This was followed by a consensus building workshop in Iganga

The 36 districts with immunization inequities contribute 53% of the under immunised children for DPT3 for the period 2013 to 2015. On the other hand, the identified 241 sub counties out of 1386 (17.4%) contribute 49% of the under immunised children for the period 2014 – 2015.

The high risk communities / underserved communities identified were: urban poor settlements, migrants, ethnic minorities, some religious sects (especially Muslims, Bisaka sect and triple 6),

upcoming town settlements, fishing communities, Refugee communities, remote rural, Island and mountainous communities

The districts with immunization inequities were: Adjuman, Amudat, Amuria, Arua, Buikwe, Butalejja, Butambala, Buyende, Hoima, Ibanda, Isingiro, Jinja, Kaabong, Kaliro, Kalungu, Kamwenge, Kapchorwa, Kibaale, Kibuku, Kisoro, Kween, Kyankwanzi, Kyenjonjo, Manafa, Masindi, Mayuge, Mbarara, Moyo, Mubende, Nebbi, Pallisa, Rakai, Sembabule, Sheema, Wakiso and Yumbe. However, the Kampala district was considered to be the 37th district with immunization inequities because it had the largest number of under immunized children for DPT3 for the period 2013 to 2015

The social economic factors that cause immunization inequities in Uganda were: religion, tribe, maternal education, wealth quintile, place of child delivery, travel time and transportation costs to service delivery points.

The system factors that were prevalent in districts and sub counties with immunization inequities were: Human resource challenges like DHT teams with weak leadership, absenteeism, non-transparency with funds and poor supervision, and logistics issues like non-distribution of vaccines from district vaccine stores to lower health facilities and gas shortages.

Matrix for high risk communities and barriers

High risk communities	Barrier: HF (supply side)	Barrier: Community (demand side)
Urban Poor Settlements	There are few government facilities	Leaders do not attend immunization planning meetings eas and services are costly in private clinics
Migrants	Fixed Service delivery service points do not match mobility pattern of those communities -Lack of trained Village health teams	Rural Location : Maternal Education (Primary education) - Inadequate mobilization due to limited facilitation to VHTs. -
Ethnic Minorities	- Health workers in such areas are largely non-qualified staff or nursing assistants	Where such communities live, there are impassable roads during the rainy seasons and it is too dusty during the dry spells
Religious groups	Poor Communication & Mobilisation strategies -Inadequate sensitization of the religious leaders	Religious beliefs and Misconceptions on immunisation and on contents of the vaccine
Upcoming town settlements	Attitude as perceived by the parents towards health workers is that they are rude, long waiting time for parents at facilities while the parents have little time	Low maternal education effects in such areas
Fishing Communities	Service delivery time not favouring their working patterns	Majority of the people sell their fish in the morning when

High risk communities	Barrier: HF (supply side)	Barrier: Community (demand side)
	- Difficult to plan, locate and reach the fishing populations - Limited immunization Services/posts	immunisation services are being offered - They are mobile populations
Refugee communities	Failure to communicate due to language barrier	Lack of organised leadership structures in such communities - Lack of awareness on availability of service points
Remote rural, Islanders & mountain living communities	-Irregular and unreliable outreach sessions -Inadequate knowledge of the health workers; inadequate staffing in such areas -Rift valley escapements make transport difficult -Inadequate logistics for immunization -Poor road & building Infrastructure	High cost of travel from community to health centre, -Low education levels of care takers - District councils and sub county Local councils not prioritizing immunization service delivery -Low community awareness of benefits for immunisation

III. Discussion

Disease Burden

a) The northern part of Uganda is located in the Meningococcal Meningitis A belt of Africa, and evidence shows that Meningitis A represents a significant disease burden in the country with high fatalities, considering that in a ten-year period (2004-2014-week 22), 10,630 cases were reported through Integrated Disease Surveillance and Reporting IDSR, with a case fatality ratio of 8%. Neisseria meningitides serogroup A is the most predominant cause identified in 64% of the laboratory confirmed epidemic cases tested at the Central Public Health Laboratory in that time period. (Dr. Immaculate to obtain Men A disease burden data from sentinel sites for bacterial meningitis, and updated data from the Central Public Health Laboratory).

b) The bacterial disease is carried in a non-infectious form in the nasal pharyngeal, and transition to an infection state is associated with low humidity and high temperatures characteristic of the dry season. The disease spreads rapidly through contact with infected nasal drops, and is fatal if untreated. Laboratory diagnosis is done using cerebral spinal fluid (CSF) obtained through lumbar puncture. Treatment is through intravenous antibiotics, although even with treatment, 10% of cases are fatal, and approximately 10% to 20% of survivors are left with permanent sequelae such as mental retardation, deafness, epilepsy, or other neurological disorders.

Vaccine characteristics, safety, efficacy and effectiveness

a) Evidence shows no serious adverse events related to Men A vaccination were reported in individuals aged 9-24 months of age, following large vaccination campaigns in other African countries including Chad, Niger and Mali. Mild reactions such as redness, swelling and pain at the site of injection may occur. This is similar to the safety profile of measles vaccine

administered at 9 months of age. Following campaign introduction of Men A vaccine in early 2017 targeting 1-29 year olds in northern Uganda , no serious Adverse Events Following Immunisation (AEFI) were recorded (pers. comms-*Dr. Immaculate Ampeire MoH UNEPI**)***

b) A single dose of 5 micrograms administered to children aged 9-24 months has a proven protective effect for 27 months. A mathematical model showed that at 60% coverage in routine schedule, the vaccine resulted in significant reduction of Men A cases.

c) Co-administration of Men A with other vaccines has been shown to have no interference effects. The lack of data on co-administration with PCV and Rota is not a limiting factor as the two doses should be administered much earlier in age than Men A.

d) Men A vaccine has been shown to reduce nasal carriage, resulting in reduced transmission and hence reduced cases of disease, in counties with similar settings in Africa's Men A belt.

e) Men A vaccination has no effect on other Meningitis serogroups (B, C, Y, W-135) also known to cause epidemics, although A is the most frequent cause.

Economic Considerations

a) The international cost price of a single dose of Men A vaccine is $0.5. Introduction of Men A in routine schedule is estimated to cost $2.6-3.4 million per year, which is comparable to other new vaccines recently introduced in Uganda.

b) Men A is on the list of new vaccines supported by Gavi for both preventive campaigns and introduction into the routine schedule, however there is need to secure sustainable co-funding ($0.2 per dose) from the government.

c) A study done in Burkina Faso showed that routine immunisation with Men A vaccine is more cost effective in the long run than campaign vaccination. However, it should be observed that campaign introduction in Burkina Faso is nation-wide, as the entire country is in the Men A belt, while in Uganda it is targeted for high risk districts in northern Uganda.

Health Policy and Programmatic aspects

a) According to WHO mapping, Northern Uganda falls within the African Men A belt. WHO recommends that for countries within the Men A belt, Men A vaccine be introduced into the routine schedule for children aged 9-24 months as a single 5 microgram dose administered intra-muscularly within 5 years of conducting a mass campaign. The routine introduction should be complemented by catch up campaigns for children aged 1-4 years.

b) The vaccine may be administered at 9 months of age, coinciding with measles vaccination, as there are no contra-indications for co-administration. A spate injection site is preferable.

c) The most recent cold chain assessment done in 2014 indicated that there is sufficient cold chain storage at central and district level for vaccines including proposed new vaccine introductions till 2021. With the proposed introduction of the bulky rotavirus vaccine in 2017, a re-assessment of cold chain space may need to be done.

d) Historical UNICEF records show that so far there haven't been challenges with Men A vaccine supply, however, there was no evidence to show sustainable future supplies.

e) The surveillance and laboratory capacities in Uganda will be key in measuring the impact of the vaccine after its introduction by reviewing the incidence of Men A disease. The Central Public Health Laboratory was recently refurbished, but detection at clinical level will be vital.

IV. Proposed recommendation (s) /options

1. Introduction of Men A vaccine into routine immunisation schedule at 9 months of age initially for target districts in northern Uganda. This would be recommended if government fiscal space is not sufficient for nation-wide introduction but enough for targeted introduction.
2. Funds permitting, routine immunisation can be expanded to include all children in Uganda at nine months of age with time.
3. Vaccine effectiveness studies should be continued to determine the long term protective effect of Men A Vaccine beyond 27 months, and guide decisions for the need of a booster dose.

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I. Annexes

1. Advise Request Letter from Ministry of Health

Telephone: General Lines: 340874/ 231563/9
Permanent Secretary's Office: 256 - 41 - 340872
Fax: 256 - 41 - 231584

THE REPUBLIC OF UGANDA

Ministry of Health
P.O. Box 7272
Kampala
Uganda

IN ANY CORRESPONDENCE ON THIS SUBJECT PLEASE QUOTE NO: **ADM:215/306/01**

22nd June 2016

Dr. Nelson Sewankambo,
Chairperson for NITAG Uganda,

RE: REQUEST TO NITAG TO ADVICE THE IMMUNIZATION PROGRAM TO PRIORITIZE WHICH NEW VACCINES SHOULD BE INTRODUCED

The goal of immunization program is to ensure that every child and high-risk group is fully vaccinated with high quality and effective vaccines against the target diseases according to recommended strategies through five operational components: vaccine supply and quality, logistics, service delivery, surveillance, advocacy and communication.

SAGE has made several recommendations to countries to introduce new vaccines into their routine immunization program following evidence presented to them to show that they are effective and efficacious. Over the last three years, Uganda has introduced three new vaccines into the routine immunization program and plans to introduce yellow fever vaccine, Measles and Rubella Vaccine including second dose, Men A and Tetanus Diptheria(Td) Vaccine.
However along the way the program has observed some challenges and anticipates more to come as more new vaccines are introduced into the routine immunization program. Among these challenges, includes fulfilling co financing requirements for the recently introduced vaccine affecting the performance of new vaccine introduction

In line with the WHO recommendation, Uganda established the NITAG to provide evidence based advice to the Ministry of Health on immunization.

The purpose of this letter is therefore to request the NITAG to provide guidance on which new vaccine Uganda's immunization program should prioritize in order of importance in the next five years. Your response will highly be appreciated preferably by end of 2016.

Prof. Anthony K. Mbonye
FOR DIRECTOR GENERAL HEALTH SERVICES

Cc: The Permanent Secretary, Ministry of Uganda
Cc: The Director Health Services, Clinical and Community
Cc: Commissioner Health Services, National Disease Control
Cc: The Program Manager, UNEPI

2. Members of Meningitis A Vaccine Working Group

I. Prof. George Kirya(Chair)

II. Dr. Peter Waiswa– Core member, Public Health

III. Dr. Lawrence Kagwa – Core member, Health Systems

IV. Hon. Benson Obua Ogwal – Core member, Sociology

V. Dr. Jesca Nsungwa Sabiiti - Liaison member, Child Health

VI. Dr. Immaculate Ampeire – Liaison member, EPI

VII. Dr. Issa Makumbi– co-opted expert (Epidemiologist/ Health Systems)

3. Evidence search process and results

Excel Sheet with Recommendation Framework.

Uganda Immunization Technical Advisory Group

Recommendation on Measles and Rubella vaccination in the routine immunization programme:

Uganda Immunization Technical Advisory Group

Recommendation on Measles and Rubella vaccination in the routine immunization programme:

AS PART OF ROUTINE IMMUNIZATIONS IN THE 2ND YEAR OF LIFE SHOULD THE UGANDA EPI CONSIDER MEASLES ELIMINATION ONLY OR MEASLES & RUBELLA ELIMINATION?

SEPTEMBER 2017

Contents

Executive summary

The Ministry of Health asked the Uganda National Technical Advisory Group (UNITAG) to make recommnendations on the prioritization of various new vaccines to introduce to the routine immunisation schedule. Challenges to the immunisation program's vaccine introduction efforts such as low coverage and limited financing prompted this request. The five new vaccines proposed for introduction are : Hepatitis B birth dose, Yellow Fever, Meningococcal A, 2nd dose of measles containing vaccine and a switch fro Tetanus Toxoid to Tetanus diphtheria.

The vaccine considered in this dossier is the 2nd dose of measles containing vaccine. Measles disease is a highly contagious infection with symptoms including high fever, cough, coryza, conjunctivitis and a typical maculopapular rash. Severe measles infections can lead to blindness, encephalitis, severe diarrhea, and death. There were 10,730 reported cases of measles in Uganda in 2014. Currently, there is one monovalent measles vaccine given at 9 months with SIAs offered to reach unvaccinated children and offer booster doses. WHO recommends routine immunization programmes include two doses of measles containing vaccine. A systematic review of evidence shows that Uganda continues to face sporadic measles outbreaks with the last large outbreak occurring in 2016. Uganda Demographic Health Surevy 2016 put measles vaccine coverage in Uganda at 80%, hence Uganda has not yet achieved the 92-95% immunity needed to stop measles transmission.

Rubella is a self-limiting disease usually occurring during childhood with symptoms that include: prodromal illness consisting of fever <39.0 C, malaise and mile conjunctivitis. However, rubella infection just before conception or during early conception can cause congenital rubella syndrome (CRS), which can result in many defects that are ophthalmic (e.g. cataracts, microphthalmia, glaucoma, pigmentary retinopathy, and chorioretinitis); auditory (e.g. sensorineural deafness); cardiac (e.g. peripheral pulmonary artery stenosis, patent ductus arteriosus or ventricular septal defects); and craniofacial (e.g. microcephaly).

Between June and July 2014, a cross-sectional study conducted among 626 pregnant women selected randomly from those attending antenatal clinic at Mulago National Referral Hospital found that 95.5% tested positive for rubella IgG (past exposure), which indicated the presence of the virus within the population. There were several cases of CRS found between October 2014 and June 2015, and CRS cases were observed to suffer from congenital heart defects, hearing and vision impairments, mental retardation and other serious conditions. Mulago sentinel site reports show that in 2015, 6 cases of CRS were recorded, of these 73% had congenital heart disease, 61% had cataracts, 12% had glaucoma, , 7% had hearing loss and 20% had pigmentary retinopathy.

WHO recommends that reaching all children with two doses of measles containing vaccine (MCV) should be the standard for all national immunization programmes. WHO also recommends vaccination against Rubella using a Rubella containing vaccine either by focusing exclusively on reducing CRS by immunizing adolescent girls or women of

childbearing age, or a more comprehensive approach focusing on interrupting transmission of rubella virus, thereby eliminating rubella as well as CRS by introducing the vaccine into the routine childhood immunization schedule and combined with the vaccination of older age groups who are susceptible to rubella. A large scale campign coveraing children aged 9 months to 15 years is recommended before introduction of MR vaccines into the routine program. There are various WHO prequalified measles containing vaccines including a monovalent measles vaccine (MV) and combination vaccines e.g. Measles Rubella (MR), Measles-Mumps-Rubella (MMR) and Measles Mumps Rubella and Vericella (MMRV). One dose of rubella vaccine is recommended for children 9- 12 months to effectively control rubella infection, and MMR and MR vaccines are at least 95% effective in preventing measles. All these vaccines have also shown a satisfactory safety profile, although some cases of febrile seizures have been found associated with MMR vaccine.

In terms of costs and delivery models, MV, MR and MMR are all cost effective. Modeling studies show cost benefit figures based on coverage, with routine delivery for both doses comabined with SIAs preferable with lower coverage, but as coverage impoves above 95% for both vaccines, cost benefits are highest for routine delivery for both doses without SIAs. In terms of absolute cost, the weighted average price per dose of MR vaccine is 3x the price of MV vaccine and MMR vaccines are 5x as much. Gavi provides support for large catch up campaigns with the MR vaccine. The Measles Rubella Initiative also provides funding and technical support to countries introducing MR vaccine. The bulk of the funding for routine introduction of MR vaccine would have to be borne by the Government of Uganda.

Based on this evidence, the working group made these following recommendations:

i. Introduce Measles Rubella vaccine at 9 months as Measles Containing Vaccine (MCV1) in routine schedule to control measles and rubella. However, it is important that Government and Immunisation Partners work to increase and sustain MCV 1 coverage in routine to > 95% as recommended by WHO. In addition, prior to introduction into routine, a large scale campaign with MR covering children aged 9 months to 15 years is recommended for 2019.
ii. Introduce a 2nd dose of Measles Rubella vaccine at 15-18 months into the routine program as a cost effective measure to improve overall measles coverage to higher than 95%, reduce burden of measles and rubella epidemics in the country, and reduce the need and frequency of Supplementary Immunisation Activities.

I. Introduction

a. Context of the question

The Ministry of Health requested Uganda National Immunisation Technical Advisory Group (UNITAG) for advice on which new vaccines Uganda should prioritise in the next five years for introduction into the routine immunisation schedule. This was prompted by challenges facing the immunisation program new vaccine introduction efforts including low coverage and limited financing. Five new vaccines were proposed for consideration including: Hepatitis B birth dose, Yellow Fever, Meningococcal A, 2nd dose of measles containing vaccine, and switch from Tetanus Toxoid to Tetanus diphtheria. This dosier looks at possible introduction of a 2nd dose of measles containing vaccine, as a startegy for measles elimination or measles and rubella elimination. (Request letter attached as Annex 1)

b. General information on the issue

Measles disease is caused by the measles virus (*Morbillivirus Paramyxoviridae*), a highly contagious infection whose symptoms include: high fever, cough, coryza, conjunctivitis and a typical maculopapular rash. At the onset of rash, bluish-white Koplik's spots, which are pathognomonic of measles, are seen in the oral mucosa. Patients normally improve by the third day after rash onset and are fully recovered 7–10 days after onset of disease. Severe measles infection can lead to blindness, encephalitis, severe diarrhea, and death. The risk of developing severe or fatal measles increases for those aged <5 years, living in overcrowded conditions, who are malnourished (especially with vitamin A deficiency), and those with immunological disorders, such as advanced HIV infection. In developing countries, case-fatality rates among young children may reach 5–10%. In children, otitis media occurs in 5–15% of cases and pneumonia in 5–10%. In developing countries, persistent diarrhoea with protein-losing enteropathy may ensue, particularly in infants. Post-infectious measles encephalitis occurs in about 1/1000 cases, and subacute sclerosing panencephalitis, a slowly progressing infection of the central nervous system, occurs in about 1/10 000–100 000 cases.

The WHO position paper (2009) estimated that a total of >23 million disability-adjusted life years were lost as a result of measles globally in 2001, with 114900 deaths attributed to measles in 2014. In Uganda, 10,730 cases of measles were reported in 2014 (cMYP 2016-2020).

WHO recommends that reaching all children with two doses of measles containing vaccine (MCV) should be the standard for all national immunization programmes. There are various WHO prequalified measles containing vaccines including a monovalent vaccine and combination vaccines e.g. Measles Rubella (MR), Measles-Mumps-Rubella (MMR) and Measles Mumps Rubella and Vericella (MMRV). Currently in Uganda, one dose of measles

monovalent vaccine is given to children at 9 months in the routine schedule, with supplementary doses administers through Supplementary Immunisation Activities (SIAs) to reach unvaccinated children and offer booster doses. A population immunity of 92% - 95% is considered necessary to stop measles transmission. Uganda had a coverage of 96% in 2014.

WHO, in partnership with UNICEF, US Centers for Disease Control and Prevention, the United National Foundation, and American Red Cross, set a global target for measles eradication in a 2010-2020 strategic plan, which was revised in 2012 to include elimination of Rubella. Rubella is caused by a togavirus of the genus *Rubivirus* that is transmitted by the respiratory route and only found in humans. Rubella usually occurs during childhood in a mild self limiting presentation with symptoms including prodromal illness consisting of fever <39.0ºC, malaise and mild conjunctivitis, which is more common in adults. Postauricular, occipital and posterior cervical lymphadenopathy is characteristic, and typically precedes a maculopapular, erythematous and often pruritic rash by 5–10 days. The disease is of primary concern due to the fact that infection occurring just before conception and during early pregnancy may result in miscarriage, fetal death, or congenital defects a condition known as congenital rubella syndrome (CRS). The defects associated with CRS are: ophthalmic (e.g. cataracts, microphthalmia, glaucoma, pigmentary retinopathy, and chorioretinitis); auditory (e.g. sensorineural deafness); cardiac (e.g. peripheral pulmonary artery stenosis, patent ductus arteriosus or ventricular septal defects); and craniofacial (e.g. microcephaly). CRS can present with neonatal manifestations that include meningoencephalitis, hepatosplenomegaly, hepatitis, thrombocytopenia and radiolucencies in the long bones (a characteristic radiological pattern of CRS). The complications of thrombocytopenia can be fatal. Interstitial pneumonitis may occur in infants with CRS. Those that survive the neonatal period may face serious develop mental disabilities (for example, visual and hearing impairments) and have an increased risk for developmental delay, including autism, type I diabetes mellitus and thyroiditis. A progressive encephalopathy resembling subacute sclerosing panencephalitis has been observed in patients with CRS.

Currently, ELISA is the most frequently used method for rubella antibody screening and diagnosis. Rubella usually occurs in a seasonal pattern, with epidemics every 5–9 years. WHO estimated that in 1996, approximately 22 000 children with CRS were born in Africa. In Uganda, 7878 Rubella cases were reported in 2013 (cMYP 2016-2020).

WHO recommends vaccination against Rubella using a Rubella containing vaccine either by focusing exclusively on reducing CRS by immunizing adolescent girls or women of childbearing age, or a more comprehensive approach focusing on interrupting transmission of rubella virus, thereby eliminating rubella as well as CRS by introducing the vaccine into the routine childhood immunization schedule and combined with the vaccination of older age groups who are susceptible to rubella. Depending on the burden of disease and available resources, countries may choose to accelerate their progress towards elimination by conducting campaigns that target a wide age-range of both males and females.

Rubella vaccines are available either as monovalent formulations or in combinations with other vaccine viruses, as RCVs. Commonly used RCVs are combinations with vaccines against measles (MR), measles and mumps (MMR), or measles, mumps and varicella (MMRV).

A review by the Strategic Advisory Group of Experts (SAGE, November 2010) found that eradication of both measles and rubella was technically feasible and more cost effective than infinite high level control of either of these diseases.

WHO recommends one dose of rubella and two doses of measles vaccine in country routine immunization programmes. The WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommends that:

1. Countries are to introduce or use a rubella - containing combination vaccine such as MR or MMR vaccines as a first dose measles-containing vaccine. A first dose of MR or MMR vaccines will ensure a higher coverage rate for both rubella and measles.

2.Countries that introduce MR or MMR combination vaccines into routine immunization should carry out one-time catch-up campaigns to reach all children between 9 to >15 years of age, according to national epidemiology, to ensure coverage of all susceptible age groups.

3. Countries that use different MCVs for their first and second dose measles vaccine should switch to the same combination vaccine (MR or MMR vaccine) for both routine doses.

This report therefore considers whether to introduce a second monovalent measles containing vaccine or a measles and rubella vaccine in the second year of life in Uganda's routine immunisation schedule.

II. Methodology

a. Establishment of a working group

In line with the UNITAG Internal Procedures Manual, the UNITAG Chair in consultation with the Secretariat commissioned a working group to develop a Recommendation Framework on introduction of a second dose of Measles containing vaccine in Uganda's routine immunisation program, and conduct a systematic review of relevant evidence based on which, recommendations would be proposed. The Working Group was chaired by the Medicine Core-member representative and comprised of the following UNITAG members: Paediatrician, Epidemiologist, Public Health expert, and Health Policy specialist. All members signed a declaration form stating that they had no known conflict of interest on the topic. The working group has met once to develop the Recommendation framework, and once to review the evidence and develop recommendation options. List of members in Annex 2.

b. Recommendation framework

The working group reviewed evidence on Burden of measles and Rubella Diseases in Uganda, efficacy and safety of available measles and rubella containing vaccines, Programmatic and Economic Considerations, Policy issues and Acceptability. A detailed Recommendation Framework is attached as Annex 3.

c. Evidence search and assessment

The Working group followed the steps outlined below in its evidence search and assessment:

•Step 1: Framing questions for the review

For each issue in the recommendation framework, the WG went further in specifying the specific data that is needed. For each data, queries were specified in the form of clear, unambiguous and structured questions before beginning the review work. Queries were categorised as those that required a systematic search in databases and those for which information could be found in reference documents (WHO papers, text books, vaccine manufacturers' websites). These documents were used as source of background information. For systematic search of data, the queries were formulated to specify the specific outcomes of interest from the use of the intervention in the population considered as per UNITAG method of working for issuing evidence-based recommendation (using the PICO approach to search for evidence on the efficacy, effectiveness and safety of an intervention). Queries requiring systematic literature search proceeded to step 2. Grey literature (Ministry of Health Reports, Immunisation partner surveys, websites and unpublished local reports) and reference documents were looked for to answer background data queries.

•Step 2: Identifying relevant peer reviewed articles

Search strategies were developed to ensure that search terms covered all known terms relevant to the question. Multiple journal resources (Pubmed, Scopus, Embase and Cochrane) were searched with English language restriction to generate relevant title-abstracts. Selection criteria were set for each query to flow directly from the review question and was specified a priori. Reasons for inclusion and exclusion were recorded. Articles obtained were screened (titles and abstracts) for relevance to the question. The search strategy and result was recorded, the report is available at the secretariat.

•Step 3: Assessing the quality of articles

Selected title abstracts were extracted in full text and subjected to review and if still relevant to the question, a more refined quality assessment by use of a design-based quality checklists; CASP[1]. These detailed quality assessments were used for exploring for bias or

[1] http://www.casp-uk.net/casp-tools-checklists

flaws of the study by evaluating its methodological quality, certainty of results, and relevance to the question, hence informing decisions regarding suitability of meta-analysis (Step 4). List of articles retrieved and assessed is also indicated in the search strategy and results report.

•Step 4: Summarizing the evidence

Selected full text articles were read and relevant findings under each query were summarised in a standard UNITAG working group outline report. The Working Group organized a one-day workshop for review of the evidence presented on each issue of the recommendation framework.

•Step 5: Interpreting the findings

During the workshop the group worked on the write-up of the discussion section, analysing the findings with the view of joining the pieces together that then lead to the proposed recommendations.

III. Presentation of the evidence

In this section each query indicated in the recommendation framework will be listed and the source of evidence on the same will be indicated alongside. It will be in bullet points to facilitate the reporting but afterwards the working group will write it in a narrative form. Note this section only presents the findings, the discussion (judgment/sense -making in the country context) takes place in the next section. Based on that, recommendations/options are proposed in the subsequent section

1. Vaccine and immunization characteristics

i. Safety

a) Safety profile
   - Safety profile of MR vaccine compared to other vaccines given to children at 9 months and 2nd year of life?
   - How does the safety profile of RCV vaccine compare to Measles vaccines when administered in children under 2 years?

Bennett et. al. 2002.

- Type of study
  - Randomized, controlled trial

- Objectives
  - To compare antibody response and side-effects of aerosolized and injected measles vaccines after re-vaccination of children

- Reported the antibody response to measles in children given measles or measles-rubella vaccines

- Design
  - Measles and measles-rubella vaccines given by aerosol or injection
  - Randomized by school, 79 schools were randomly assigned
  - 1624 children aged 6-8 years old participated in the study, randomized to 6 arms
    - Aerosolized groups total 760 children
      - Low-dose EZ (Edmonston-Zagreb) measles
      - EZ measles
      - EZ measles-rubella (Edmonston-Zagreb with RA27/3)
    - Injected groups total 864 children
      - EZ measles
      - Schwartz measles
      - EZ measles-rubella

- Specific Results in relation with the query (include limitation of the study)
  - Fewer side effects were noted after aerosol vaccine compared to injected vaccine
  - Immunogenicity of the measles vaccine administered by aerosol is superior to that when the vaccine is given by injection
  - The group that received measles-rubella subcutaneously had the lowest point estimate of seronegativity
  - Frequency of seroconversion in the group that received low-dose aerosolized measles vaccine (52%) significantly exceed that for the three groups that received injected vaccine (range 4%-23%)
  - Seroconversion was detected in 57% of children who received aerosolized vaccine and only 11% in the injected groups
  - Antibodies increased nearly 12-fold in the combined aerosolized group vs. only 2-fold in the combined injected group
  - Antibody geometric meant titers 4 months after vaccination were 3x higher in the combined aerosol group
  - AEs recorded that lasted 1 or more days in the 2 weeks after vaccination:
    - Cough
    - Rhinitis
    - Fever
    - Diarrhea
    - Rash
    - Conjunctivitis

- Every symptom occurred less frequently among the aerosolized group compared to the injection, statistically significant except for rhinitis and diarrhea
- Low dose aerosol measles vaccine group had significantly less frequent symptoms than those who received measles-rubella vaccine subcutaneously
- The groups that received standard dose aerosolized measles and measles-rubella had symptoms significantly less frequently than any group that received injected vaccines
- Study results confirmed previous results that showed superior boosting response for aerosol vaccination compared with vaccination by injection
- Mentions that this study and South African study had frequencies of respiratory illnesses after vaccination higher in those given injected vaccines than those receiving aerosolized vaccines
    - Although aerosol vaccine may be less reactogenic than vaccination by injection

- Safety profile of monovalent Measles vaccine compared to other vaccines given to children at 9 months and 2nd year of life?
- Safety of administering multiple doses of MR vaccine as compared to monovalent Measles vaccine?

b) Safety of co-administration

Miller et. al 2011

- Type of study
    - Randomized study with two arms

- Objectives
    - Determine immunogenicity and safety of combined of meningococcal serogroup C (MCC)/*Haemophilus influenzae* type b (Hib) when co-administered with pneumococcal conjugate vaccine (PCV7) and measles, mumps, and rubella (MMR) given to children at 2 years old
        - All three vaccines at the same visit (group B) vs. 12 moths MCC/Hib and PCV7 and MMR at 13 month (group A)

- Design
    - Study in the United Kingdom, introduction of a booster dose of MCC/ Hib at 2 years of age
    - Vaccines: meningococcal serogroup C (MCC)/*Haemophilus influenzae* type b (Hib), pneumococcal conjugate vaccine (PCV7) and measles, mumps, and rubella (MMR)
    - Vaccines were administered into different limbs

  - Two cohorts: group A received the national schedule or group B children randomized to receive MCC/Hib vaccine, PCV7 and MMR vaccine concomitantly
  - Blood samples taken before booster vaccination at 12 moths and again at 13 months
  - Safety assessment included parents to record system and local symptoms in the post-vaccination period
  - Safety analysis comparison between groups A and B was restricted to only children who received MMR vaccine and did not receive extra doses of MMCC vaccine, Hib vaccine, or PCV 7 for primary immunizations

- Specific Results in relation with the query (include limitation of the study)
  - 280 children were recruited, 84% opted for MMR vaccine
  - 123 occasion of concomitantly administration and 157 occasions separate administration
  - No adverse consequences for either safety (reactogenicity) or immunogenicity were demonstrated when MCC/Hib vaccine was given concomitantly with PCV and MMR vaccine at 12 months of age or separately at 12 and 13 months of age
  - Small difference in immunogenicity in the direction of higher response when all three vaccines were given concomitantly, also saw lower proportions of children with post-vaccination fever
  - No additive effect, rather differences between schedules showed benefit from the concomitant administration of all three vaccines
  - Some proportion of parents opted for their children to not receive the MMR vaccine but agreed to MCC/Hib with or before PCV7
  - No difference in proportions achieving protective thresholds for measles, mumps, or rubella virus according to whether MMC/Hib vaccine was given concomitantly or not with MMR vaccine and PCV7
  - Proportion of children with erythema, swelling, or tenderness at the site of injection of MMC/Hib vaccine, PCV7, or MMR vaccine were not significant whether the vaccines were sequential or at the same time
  - Local reactions were mild
  - Recommended in the United Kingdome that vaccines given at 12 months and 13 months can be given on the same visit between 12 and 13 months, to simplify the route childhood immunization schedule

Yetman et. al. 2013

- Type of study
  - Open label, multicenter, randomized, comparative study

- Objectives
    - To evaluate immunogenicity, safety, and tolerability of Hepatitis A vaccine (HAV) concomitantly administered with measles, mumps, rubella, and varicella (MMRV), and 7-valent pneumococcal (PCV7) in children 12 to 23 months of age

- Design
    - Vaccines: Hepatitis A vaccine (HAV), measles, mumps, rubella, and varicella (MMRV), and 7-valent pneumococcal (PCV7)
        - Group 1- HAV/MMRV/PCV7 on Day 1 and second doses of HAV/MMRV at Week 24
        - Group 2- MMRV/PCV7 on Day 1, HAV at Weeks 6 and 30, and MMRV at Week 34
    - April 2006- March 2008, multicenter clinical trial conducted across 39 sites in the United States
    - Group 1 had 330 subjects and group 2 had 323

- Specific Results in relation with the query (include limitation of the study)
    - No statistically significant differences in the incidence of individual AEs were seen in concomitantly vs. non-concomitantly administration
    - Three out of seven serious AEs were considered vaccine-related
        - Dehydration and gastroenteritis (same subject on day 52)
        - Febrile seizure (on day 9)
        - No deaths were reported
    - Most common systemic AEs following vaccination were pyrexia (fever), upper respiratory tract infection, and otitis media
    - Most common vaccine-related AEs following any vaccination were pyrexia (fever) and irritability
    - Serious AEs reported during the 28 day follow up
        - Group 1 – two subjects reported SAEs
            - Cellulitis and perineal abscess
            - Pneumonia
        - Group 2 – six subjects reported SAEs
            - Bronchopneumonia
            - Febrile convulsion
            - Dehydration and gastroenteritis (2 subjects)
            - Gastrointestinal hemorrhage – subject discontinued from the study (not related to the study vaccination)
            - Genital abscess
    - 2.4% of group 1 subjects and 5.3% in group 2 had measles-like symptoms of the vaccine-associated rashes and mumps-like symptoms reported during the

42 day follow up, and varicella-like rashes in 1.8% in group 1 and 2.8% in group 2
    - No statistically significant difference in the incidence of individual AEs between the two groups
    - Antibody response to hepatitis A, varicella, and seven components of the pneumococcal conjugate vaccine were similar whether or not HAV was given along or concomitant with PCV7 and MMRV
    - Administration of two doses of HAV concomitantly or non-concomitantly with MMRV and PCV7 vaccines displayed an acceptable safety profile
    - Type of vaccine-related AEs reported following 2 doses of HAV administered alone or concomitantly with MMRV and PCV7 were consistent with prior studies of these vaccines
    - Limitations
        - Open-label study
        - PCV 7 not 13 was available
        - Immunogenicity results after MMRV dose 1 only are available

Bryant et. al. 2012

- Type of study
    - Pooled analysis

- Objectives
    - Pooled analysis of immune responses to the co-administration of MMR and VAR in HibMenCY-TT group relative to Hib-OMP control group in toddlers 12-15 months of age
        - Used studies with similar designs

- Design
    - 1,257 toddlers who received a fourth dose of *Haemophilus influenzae* type B-*Neisseria meningitis* serogroups C and Y- tetanus toxoid conjugate vaccine (HibMenCY-TT) or Hib conjugate vaccine co-administered with measles-mumps-rubella (MMR) and varicella (VAR)
    - Australia data from phase II randomized controlled study and United States data from phase III randomized controlled study
    - Conditions were established to determine if data could be pooled

- Specific Results in relation with the query (include limitation of the study)
    - Statistical non-inferiority of response to MMR and VAR was demonstrated
    - No statistically significant difference between the HibMenCY-TT group and Hib-OMP group with respect to solicited symptoms specific to the co-administered MMR and VAR

- Most frequently reported symptom during the 43 day follow up was fever, peak incidence around day 9 in both groups
- HibMenCY-TT 4 subjects (0.3%) reported parotid/salivary gland swelling no reports in the HIb-OMP group
    - All reports were from Australia and considered related to vaccination
    - This AE is consistent with a review of various randomized studies involving 3 different MMR vaccines that also showed low incidence of this AE
- Rashes were reported in 25% of HibMenCY-TT and 22.6% in Hib-OMP groups
- Immune response of HibMenCY-TT, MMR, and VAR are not compromised when administered together, although the possibility of interference cannot be completely excluded
- Limitations
    - 1/3 of the US infants enrolled in the immunogenicity cohort were excluded because of noncompliant with blood samples
    - Most subjects were white/Caucasian
    - Lack of blinding study personnel, which could have influenced the assessment of reactogenicity
- 4 dose HibMenCY-TT series can be administered with an acceptable safety profile without diminishing the immune response to MMR and VAR

Nolan et al 2014

- Type of study
    - Randomized study

- Objectives
    - Evaluated the immunogenicity and safety of a 4-dose infant/toddler regimen of MenACWY-CRM given at 2, 4, 6, and 12 months of age concomitantly with pentavalent diphtheria, tetanus, acellular pertussis-*Haemophilus influenzae* type b-inactivated poliovirus-combintion vaccine (DTaP-IPV/Hib) , hepatitis B vaccine (HBV) 7 or 13-valent conjugate pneumococcal (PCV) and measles, mumps, and rubella vaccine (MMR)

- Design
    - Phase 3 randomized, open-labeled, controlled, multicenter study conducted at 42 sites in the United States, 3 sites in Australia, and 1 site in Canada
    - From November 2009-November 2011
    - 2 month old infants randomized to receive MenACWY-CRM with routine vaccines or routine vaccines alone

  - 529 enrolled infants, 258 randomized to MenACWY-CRM and routine vaccines (only 213 completed) and 271 randomized to routine vaccines only (only 201 completed)
  - During the study there was the transition from PCV7 to PCV13
  - AE rates were similar between groups, with low rates of "possible vaccine-related"
  - Most commonly reported AE was upper respiratory infection
    - 56% MenACWY-CRM and routine vs. 57% in routine only
  - Serious AEs were reported in 8% MenACWY-CRM and routine and 7% routine only, but were not consider vaccine-related
  - Immune response to routine infant vaccinations was not affected when administered concomitantly with MenACWY-CRM
  - Safety profile was not affected when MenACWY-CRM was included and all vaccines were well tolerated
  - Limitations:
    - Majority of enrollees were Caucasian
    - High withdrawal rate, 22% of enrolled population withdrew from study early
      - Higher than expected drop-out rate decreased the power to conclude non-inferiority for routine vaccinations
    - Study was conducted during the PCV7 to PCV13 transition and subjects might have received a mix of the two vaccines and therefore the data evaluated only included the serogroups common to both vaccines

- Specific Results in relation with the query (include limitation of the study)
  - Responses to route vaccines administered with MenACWY-CRM were non-inferior to route vaccinations alone, except for seroresponse to the pertussis antigen fimbriae
  - Reactogenicity profile was not affected when MenACWY-CRM was administered concomitantly with route vaccines

Madhi et al 2013

- Type of study
  - Phase 3, open-label 2-center trial in infants

- Objectives
  - To asses antibody persistence and booster immunogenicity and safety of a new, fully liquid, hexavalent DTaP-IPV-Hep B-PRP-T vaccine

- Design
    - South Africa study from January 2008- February 2009 and included 602 participants. Only 567 returned for the booster regiment of the trial
    - Phase 3, open-label 2-center trial in infants previously primed at 6, 10, 14 weeks of age with DTaP-IPV-Hep B-PRP-T or Hep B at birth or control DTwP-Hib, Hep B, and oral polio vaccines at 15-18 months of age, co-administered with MMR plus varicella vaccine
    - All participants received measles vaccine at 9 months of age
    - Group 1- primary series of DTaP-IPV-Hep B-PRP-T no Hep B vaccination at birth (218 infants)
    - Group 2-primary series of DTwP-Hib, Hep B, OPV, no Hep B vaccination at birth (219 infants)
    - Group 3- primary series of DTaP-IPV-Hep B-PRP-T with Hep B vaccination at birth (130 infants)
    - Measles, mumps, rubella (MMR) and a separate varicella vaccine (V) were co-administered with the booster vaccine to all participants at 15-18 months of age
        - Participants had all received the measles vaccine at 40 weeks
- Specific Results in relation with the query (include limitation of the study)
    - Response to MMR + V was similar in all groups
    - All vaccines were well tolerated
    - Seroresponse to the MMR and V vaccines was the same in all groups
    - Incidence of injection site reactions for the investigational or control vaccine was similar and higher than the incidence after the MMR and V caccine
    - The incidence after the MMR and V vaccine was similar between groups
        - Most injection site reactions were rated as grade 1 or 2
    - AEs reported were not considered related to vaccination and were low grade (1 or 2)
        - At least 1 unsolicited AE reported in the 7 days and 28 days post vaccination, similar in each group
    - 3 participants experienced non-fatal serious adverse event within 28 days after the booster, none considered related to vaccination
        - Failure to thrive (group 1)
        - Dysentery (group 3)
        - Gastroenteritis (group 3)
    - Long term persistence data will be collected at 3.5 and 4.5 years (to be published later)
    - First trial of investigational vaccine co-administered with MMR and V vaccine and the first trial on varicella in South African children
    - The co-administration did not affect the expected booster response

- Demonstrated strong MMR response after co-administration with investigational vaccine and control vaccine
- Varicella response had no different between groups, although the response in both groups was lower than would be expected after a single dose (72.5% to 75% in the current study compared to 95% reported for the marketed varicella vaccine)
- Safety profile was good and was reactogenicity was not affected by co-administration of MMR and V vaccines
- MMR and V vaccine immunogenicity was good and similar after co-administration with the fourth dose of the hexavalent investigational vaccine or control vaccine
- Robust and anamnestic response (immune response) in all groups as well
- Limitations:
  - Sample size is small for some analysis

Leonardi et al 2011

- Type of study
  - Randomized study

- Objectives
  - Assessed immunogenicity and safety of a combination of Measles, mumps, rubella and (MMRV) administered to healthy children concomitantly with pneumococcal 7-valent conjugate vaccine (PCV7)

- Design
  - 1,027 enrolled 12-15 months old children who lacked vaccination or clinical histories of measles, mumps, rubella, varicella or zoster but had 3-dose primary series of PCV7
  - 24 centers in the United States from March 2006-Septmeber 2007
  - Group 1- MMRV and PCV7 (510 subjects)
  - Group 2- PCV7 followed 6 weeks later by MMRV (258 subjects)
  - Group 3- MMRV followed 6 weeks later by PCV7 (259 subjects)
  - Safety analysis for 56 days (28 days after each visit) and immunogenicity evaluated at 6 weeks after each vaccination

- Specific Results in relation with the query (include limitation of the study)
  - MMRV and PCV7 vaccines can be administered concomitantly in healthy children 12-15 months of age without affecting the safety or antibody response to any of the components of either vaccine
  - Immune response to all antigens present in the MMRV and PCV7 vaccines were similar whether administered concomitantly or sequentially

- Concomitant administration of MMRV and PCV7 was highly immunogenic and well tolerated
- Antibody response rates to measles, mumps, rubella, and varicella were similar when MMRV was administered concomitantly with PCV7 or MMRV was administered alone
- No vaccine-related serious AEs
    - Rate of serious AEs for all three groups was not significantly different
    - One SAE was reported in group 3- stage IV neuroblastoma diagnosed 8 days after MMRV vaccine, subject died 218 days later but SAE was not relate to vaccine
- AEs were comparable among the three groups when looking at
    - 1 or more AEs
    - Systemic AEs
    - Injection site AEs
- Most commonly reported AEs were
    - Pyrexia (fever), reported in 22% of subjects and most common systemic AE related to vaccine
    - Otitis media
    - Upper respiratory infection
    - Nasopharyngitis and insomnia reported lower in group 1 compared to groups 2 and 3 combined
- Rate of vaccine-associated rashes and mumps-like symptoms were comparable among the groups
    - Only 5% subjects reported measles-like rash
- Rate of injection site related AEs was reported higher for PCV7 vaccine compared to MMRV for all three groups (mild and short duration)
    - Redness
    - Swelling
    - Pain
- No clinically significant differences in safety profiles among the groups
- Limitations:
    - Majority of subjects were white
    - Requirement of parents to fill out the diary card for 28 days could have led to fatigue over time

Black et al 2006

- Type of study
    - Open label, randomized study

- Objectives

  - To evaluate the immune response to MMR, varicella, and Hib vaccines when administered concurrently with a 4th dose of PCV7

- Design
  - Study conducted in 4 Kaiser California sites from May 2001 to May 2002
  - 694 children enrolled 12-15 months of age received Hib vaccine and varicella and either
    - Group 1- MMR with PCV7 (347 subjects)
    - Group 2- MMR without PCV7, PCV7 6-9 weeks after MMR (347 subjects)

- Specific Results in relation with the query (include limitation of the study)
  - Immune response to MMR, Hib, and varicella vaccine when administered concurrently with a 4th dose of PCV was noninferior to that of these vaccines when given without PCV7
  - Results support concomitant administration of PCV7 and MMR, varicella, and Hib
  - Febrile seizure was reported following MMR in one subject 7 days later
  - There were no differences between the two groups in the proportion of subjects reporting 1 or more injection site reactions
  - Rate of redness, induration, and pain at the injection sites were similar in both groups
    - Tenderness at the Hib injection site
  - There was a trend toward statistically significance with regard to fever in group 1 compared to group 2
  - 37 AEs reported within 14 days after visit
    - Otitis media (group 1 24 subjects and group 2 11 subjects)
    - Febrile seizures in 1 subject in group 2
    - Upper respiratory infections, 46 reports, followed by otitis media (35 reports) and rash (25 reports)
  - Response rates for MMR given concomitantly are consistent with previous published results
  - Immunogenicity and safety reported in this study support the concomitant administration of the 4th dose of PCV7 with MMR, varicella, and Hib at 12-15 months of age

Vesikari et al. 2010

- Type of study
  - Phase 3, open, randomized, controlled study

- Objectives

  - To study the safety, reactogenicity, and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) when co-administered with MMRV vaccine

- Design
  - Study carried out from October 2006 and March 2007 in 8 centers in Finland
  - 325 healthy children 12-14 months were enrolled and randomized to three groups
  - Group 1- PHiD-CV and MMRV vaccine followed by 6-8 weeks later by MMRV and DTPa-HBV-IPV/Hib vaccines
  - Group 2- DTPa-HBV-IPV-Hib and MMRV vaccine followed 6-8 weeks later by PHiD-CV and MMRV vaccine
  - Group 3- PHiD-CV and DTPa-HBV-IPV/Hib vaccine during 1 vaccination visit

- Specific Results in relation with the query (include limitation of the study)
  - Two fever peaks were observed at
    - Days 0 - 2 related to PHiD-CV and DTPa-HBV-IPV/Hib vaccination
    - Days 4 – 12 related to MMRV vaccination
  - Fever partners in the two MMRV groups was similar
  - Group that did not receive MMRV only had one fever peak between days 0 and 2, but the peak was higher than the MMRV groups
  - Incidence of grade 3 fever was low in all three groups postdose 1
  - Postdose 2, only 1 grade 3 fever case was reported (Hx-MV group)
  - Irritability was the most frequently reported solicited AE in the 4day period after each dose in all three groups
  - Low incidence of grade 3 vaccine-related AE reported
  - No increase incidence of AEs reported when comparing dose 1 and dose 2 in the MMRV containing groups
  - Measles/rubella-like rash reported in 3.7%-8.9% of children
  - 1 febrile convulsion was reported after 36 post vaccination and not considered to be related to vaccine
  - Local pain, redness, and swelling were higher in the PHiD-CV and DTPa-HBV-IPV/Hib group than MMRV injection sites, in both dose 1 and dose 2, lower incidences after dose 2
  - Redness was common among all three groups
  - No larger swelling reactions were reported at the MMRV injection site, 8 subjects reported large swelling reactions at injection site for the other vaccines
  - Most common unsolicited AEs were
    - Otitis media
    - Upper respiratory tract infection

        - Rhinitis
    - 2 serious AEs were reported, not related to vaccination
        - Skin infection and adenovirus infection in the 10Pn-MV group
        - Obstructive bronchitis in 10Pn-Hx group
    - Seroconversion for all MMRV vaccine components were high
        - Seroconversion rate for measles, rubella and varicella after 1st dose was ≥97.6% and ≥99% for 2nd dose of MMRV
        - Seroconversion rate for mumps after 1st dose was ≥89.8% and ≥97.1% for 2nd dose of MMRV
    - PHiD-CV and MMRV can be co-administered without compromising the safety and immunogenicity profiles of either vaccines
        - Results similar to other study looking at MMRV and DTPa-HBV-IPV/Hib vaccine
    - Limitations:
        - Relative small sample size and lack of investigator blinding
        - Ethic homogeneity of the population in Finland

Collaborative Group 2007

- Type of study
    - Randomized, double-blind, multicenter prospective study

- Objectives
    - To assess the effect of simultaneous administration of yellow fever and the measles, mumps, rubella vaccine

- Design
    - Study conducted in four Brazil states in healthy children ages 9-23 months old
    - Children were randomized to:
        - 17D or 17DD yellow fever vaccine
        - 17D or WHO17D-213/77 yellow fever vaccine but also receive
            - MMR simultaneously or
            - MMR at a 30-day interval

- Specific Results in relation with the query (include limitation of the study)
    - Interaction between yellow fever vaccine and MMR vaccine was assessed by comparing seroconversion rates for yellow fever in the same age groups
    - **This article did not mention any of the results, only explained the methods**

Vesikari et al 2011

- Type of study
    - Open, randomized controlled trial

- Objectives
    - To assess the immunogenicity and safety of meningococcal ACWY-tetanus toxoid conjugate vaccine (ACWY-TT) when co-administered with MMRV vaccine during the second year of life

- Design
    - 1,000 12-23 month old children randomized to receive
        - Co-administered ACWY-TT and MMRV (375 subjects)
        - Single dose of ACWY-TT, MMRV, or MenC-CRM (374 subjects ACWY-TT; 126 subjects MMRV; 125 subjects MenC)
    - Out of the 1,000 37 withdrew from study and 38 during follow up phase

- Specific Results in relation with the query (include limitation of the study)
    - Non-inferior co-administration of ACWY-TT and MMRV compared to MMRV alone and ACWY-TT alone
    - Exploratory analysis did not detect any statistically significant difference between ACWY and MMRV and ACWY-TT for antibody response
    - 42 days after first MMRV dose 100% subjects in the ACWY-MMRV and MMRV groups had seroconverted for antibodies against measles and rubella, for mumps (87.7% and 83.6% for each group respectively), and varicella (97.9% and 94.6% in each group respectively)
    - Exploratory analysis did not detect any statistically significant differences between ACWY+MMRV and MMRV groups 42 days post-vaccination
        - Exception for the anti-rubella geometric mean antibody concentration, statistically significantly lower in the ACYW+MMRV group compared to the MMRV group
    - Serious AEs
        - 5 subjects reported SAEs during 43-day post-vaccination period after dose 1, none considered due to vaccine
            - 3 from ACWY+MMRV group
            - 2 from ACWY-TT
        - 23 subjects reported SAEs 42 days post-dose 1 up to the end of the extended follow up, none of the events related to vaccination
    - Unsolicited symptoms reported within 43 days of first vaccination were
        - 64.8% in the ACWY+MMRV group
        - 60.2% in the ACWY-TT group
        - 68.3% in MMRV group
        - 54.4% in the MenC group

- The most common unsolicited AE related to vaccination was irritability (ACWY+MMRV 8.8% and MMRV 7.9%) and diarrhea (ACWY-TT 4.5% subjects and MenC 8.8%)
- Redness at the injection site was the most frequent reported local symptom
- No grade 3 local reactions were reported after MMRV
- Fever was reported by 1 subject 3 days post-vaccination in the MMRV group
- ACWY+MMRV and MMRV groups had fever as the AE most prevalent between days 4-10, peaking at day 8
    - In line with the known timing of fever associated with MMRV vaccines
    - Higher proportion of children reported fever than previously reported after MMR, indicating a possibility for the higher incidence due to MMRV
- Measles/rubella like rash was reported in 3.7% of subjects in ACWY+MMRV group and 3.2% in the MMRV group, none in the other non-MMRV groups
- One subject reported febrile seizure 26 days post-vaccination with ACWY+MMRV
- Limitations:
    - Open study design
    - Bias in safety reporting, could be in favor of licensed vaccines vs. investigational vaccines
    - Higher drop-out rate in the ACWY-TT groups than in the other groups
    - MenC conjugated to TT was not used as a control (limited supply), but did use a valid control (MenC-CRM)
- Overall, this study demonstrates that ACWY-TT can be co-administered with MMRV between 12-23 months of age without affecting the immunogenicity or safety profile of either vaccine

Klein et al 2012

- Type of study
    - Phase 3 study, open-label, randomized, multicenter study

- Objectives
    - Study to assess the safety and immune response to MenACWY-CRM at alternative visits in older infants and concomitant use with measles, mumps, rubella, varicella vaccine (MMRV) at 12 months of age

- Design
    - Conducted in 90 centers in the United States
    - 1,630 children 7-9 months of age received 2 doses of MenACWY-CRM at 7-9 months and 12 months and were randomized to receive MenACWY-CRM with

or without MMRV at 12 months, and 12 months infants who received MMRV only at 12 months

- 1014 subjects randomized 1:1 to
  - MenACWY-CRM+MMRV
  - MenACWY-CRM alone
- MMRV only (616 subjects)

- Specific Results in relation with the query (include limitation of the study)
  - Concomitant administration of MMRV with MenACWY-CRM did not affect the immune response to either vaccine, was well tolerated and without safety concerns
  - No increased reactogenicity was observed with MenACWY-CRM+MMRV compared with MMRV alone and no study-related SAEs
  - Seroconversion rates for MMR and varicella were similar among the groups
  - MMRV response was non-inferior between MMRV alone or concomitantly administered with MenACWY-CRM
  - Immune response to all MMRV antigens measured were also non-inferior comparing MenACWY-CRM+MMRV with MMRV alone
  - Local reactogenicity was similar between subjects in both groups MenACWY-CRM+MMRV compared to MMRV alone
  - Most common AE were
    - Otitis media
    - Upper respiratory infections
    - Teething
    - Fever
    - Rash
    - Irritability
    - Diaper rash
    - Viral infections
  - MenACWY-CRM-MMRV experienced higher rates of severe systemic reactions, including fever, compared with MenACWY-CRM alone during 7 day period follow up
  - Febrile seizures were reported in MenACWY-CRM (5 subjects) alone and MMRV alone (2 subjects) 41-122 days post-vaccination (none in the MenACWY-CRM+MMRV group)
    - One reported 10 days after MMRV vaccine
  - Study demonstrated that MenACWY-CRM can be administered concomitantly with MMRV-containing vaccines that are routinely used in this age group without negatively impacting the safety or immunogenicity of either vaccine

c) Is it safe to co-administer RCV vaccine with other vaccines administered in children under 2 years? (i.e. YF, Men. A)

- Nolan et al 2014
- STUDY DESIGN: phase 3 study randomized, open-label, controlled, multi-center study was conducted at 42 sites in the United States, 3 sites in Australia, and 1 site in Canada from November 2009–November 2011 in healthy infants to assess the immunogenicity and safety of DTaP-IPV/Hib, PCV, and HBV, and the safety of MMR when co-administered with MenACWY-CRM
- METHODS: A total of 529 healthy 2 month old infants were randomized 1:1 to receive 4 doses of MenACWY-CRM coadministered with routine vaccines (MenACWY-CRM + Routine; n = 258) at 2, 4, 6, and 12 mo of age or routine vaccines alone (Routine Only; n = 271)
- RESULTS
- In group MenACWY-CRM + Routine 213 infants completed the study and in group routine Only 201 completed the study
- *Responses to co-administered antigens:* Following the 3-dose infant series, non-inferiority criteria for the difference in seroresponse rates were met for all of the antigens except pertussis antigens pertussis toxin (PT) (LL95%CI: –12.1%)
- *Reactogenicity and Safety:* Of 529 enrolled participants, 525 (99%) were exposed to ≥1 study vaccination and contributed to the safety analyses. Adverse event (AE) rates were similar between groups, with low rates of "possibly vaccine-related" events. Noting that there was no placebo control group, the most commonly reported AE by preferred term was upper respiratory infection (56% MenACWYCRM + Routine, 57% Routine Only), followed by otitis media (39% both groups), and conjunctivitis (23% MenACWY-CRM + Routine, 19% Routine Only). Overall, serious AEs (SAEs) were reported in 21 participants (8%) receiving MenACWY-CRM + Routine vaccines and in 20 participants (7%) receiving Routine Only. No SAEs were considered vaccine-related. There were no deaths
- Overall, routine co administration of MenACWY-CRM, pentavalent DTaP-IPV/ Hib, HBV, and PCV vaccines at 2, 4, and 6 mo and with PCV and MMR vaccines at 12 mo of age was well tolerated; non-inferiority criteria for the difference in seroresponse rates were met for all of the antigens
- This study has some limitations, including a high withdrawal rate. In total 115 subjects (22% of enrolled population) withdrew from the study early.

d) Risk factors that can lead to adverse events of MR vaccine and monovalent Measles vaccine?

- ✓ A systematic review and meta-analysis of the safety and immunogenicity of measles vaccine in HIV-infected children commissioned by WHO's Global Advisory Committee on Vaccine Safety (GACVS) did not show an increased risk of serious adverse events among HIV-positive children when compared with uninfected children.(WHO 2009)

e) Contraindications to administering MR vaccine and monovalent Measles vaccine?

- ✓ measles vaccine is contraindicated in people who are severely immunocompromised (WHO, 2009)
- ✓ there are no contraindications to vaccination against rubella, except for a history of an anaphylactic reaction to components of the vaccine, pregnancy and severe immunodeficiency (WHO 2011)
- ✓ Anaphylactic or anaphylactoid reactions to neomycin, history of anaphylactic or anaphylactoid reactions are absolute contraindications. (Serum Institute of India Ltd. Manufacturers insert)

f) Is it safe to administer multiple doses of MR vaccine as comapred to monovalent Measles vaccine?

Esteghamati et al 2011.

The MMR vaccine was introduced into the routine infant immunization schedule in 2003, followed by a second dose of vaccine at school-entry for children 4 to 6 years of age. The objective of this study was to characterize adverse reactions following MMR vaccination in Iran.

Method and Materials

Between August through October 2006, trained providers examined 43,447 MMR vaccine recipients weekly for four weeks to detect any fevers, encephalopathy and anaphylactic reactions. Vaccine recipients were selected for the detection of well-known AEFIs, including: parotitis, fever and convulsions without fever, encephalopathy, and anaphylactic reactions. All health workers and staff from health centers and health houses in the study fields were trained to recognize AEFIs, complete data collection forms and refer patients to collaborating physicians. The collaborating physicians (three physicians in each area) examined patients with suspected AEFIs and verifed or disproved the adverse event. the time period determined for patients to be at risk for adverse reactions was considered as two to three weeks (three weeks for parotitis and two weeks for other adverse reactions).The incidence of AEFIs was calculated by dividing the number of events to the total number of evaluated children in each region.

Results

Overall, 14,109 children aged 12 months (32.5%) and 29,338 children aged 4 to 6 years (67.5%) were vaccinated and monitored during the study period. Seven hundred and ninety-two AEFIs were reported. Parotitis, the most common AEFI, occurred in 1.8% of vaccine recipients.

In all of the regions, the occurrence of parotitis among children 4 – 6 years old was twice that of children aged 12 months while the incidence of febrile seizures was 3.5 times higher among 12 month old vaccine recipients when compared to those aged 4 to 6 years old.

The incidence of parotitis, fever and convulsions, and anaphylactic reactions in children in this study was in the range declared by WHO, however, the incidence of encephalopathy in our study was higher than the WHO range.

Demicheli et al 2012

Despite its worldwide use, no systematic reviews studying the effectiveness and safety of MMR vaccines are available. This systematic review was to assess the effectiveness and adverse effects associated with the MMR vaccine in children up to 15 years of age. Main objectives were (1) To review the existing evidence on the absolute effectiveness of the MMR vaccine in children (by the effect of the vaccine on the incidence of clinical cases of measles, mumps and rubella). (2) To assess the worldwide occurrence of adverse events, including those that are common, rare, short-term and long term, following exposure to the MMR vaccine in children.

Search methods and Data collection and analysis

For this update authors searched the Cochrane Central Register of Controlled Trials which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, PubMed (July 2004 to May week 2, 2011) and Embase.com (July 2004 to May 2011). They used comparative prospective or retrospective trials assessing the effects of the MMR vaccine compared to placebo, do nothing or a combination of measles, mumps and rubella antigens on healthy individuals up to 15 years of age. Two review authors independently extracted data and assessed methodological quality of the included studies. One review author arbitrated in case of disagreement. In total five randomised controlled trials (RCTs), one controlled clinical trial (CCT), 27 cohort studies, 17 case-control studies, five time-series trials, one case cross-over trial, two ecological studies, six self-controlled case series studies were retrieved involving in all about 14,700,000 children and assessing effectiveness and safety of MMR vaccine.

Results

One MMR vaccine dose is at least 95% effective in preventing clinical measles and 92% effective in preventing secondary cases among household contacts. Effectiveness of at least

one dose of MMR in preventing clinical mumps in children is estimated to be between 69% and 81% for the vaccine prepared with Jeryl Lynn mumps strain and between 70% and 75% for the vaccine containing the Urabe strain. Vaccination with MMR containing the Urabe strain has demonstrated to be 73% effective in preventing secondary mumps cases.
Effectiveness of Jeryl Lynn containing MMR in preventing laboratory-confirmed mumps cases in children and adolescents was estimated to be between 64% to 66% for one dose and 83% to 88% for two vaccine doses. Authors did not identify any studies assessing the effectiveness of MMR in preventing rubella.
The highest risk of association with aseptic meningitis was observed within the third week after immunisation with Urabe-containing MMR (risk ratio (RR) 14.28; 95% confidence interval (CI) from 7.93 to 25.71) and within the third (RR 22.5; 95% CI 11.8 to 42.9) or fifth (RR 15.6; 95% CI 10.3 to 24.2) weeks after immunisation with the vaccine prepared with the Leningrad-Zagreb strain. (5.38; 95% CI 2.72 to 10.62).
Due to the results of a well conducted, very large person-time cohort study involving 537,171 children between three months and five year of age, febrile seizure (as first or as recurrent episode) has been found to be associated with MMR vaccine (prepared with Moraten, Jeryl Lynn and Wistar RA) within two weeks after administration in preschool Danish children.
Based on the identified studies, no significant association could be assessed between MMR immunisation and the following conditions: autism, asthma, leukaemia, hay fever, type 1 diabetes, gait disturbance, Crohn's disease, demyelinating diseases, bacterial or viral infections.

LeBaron et. al. 2006

With measles and rubella eliminated from the United States, measles-mumps-rubella vaccine adverse events have come under scrutiny, but no study has compared the reactogenicity of the first and second measles-mumps-rubella vaccines doses at the most common ages of administration in the United States. The primary purpose of this work was to evaluate rates and patterns of potentially common adverse events occurring within a month after receipt of the first and second doses of MMR vaccine, when administered to healthy children at the commonly recommended ages for school entry in the United States in a setting where wild disease exposure and boosting were unlikely to have occurred before vaccination. Secondly, the study compare adverse event rates for MMR1 and MMR2 doses of vaccine and at the 2 ages when it has been most commonly administered: 4 to 6 years versus 10 to 12 years.

Methods
Three groups of children were recruited: (1) toddlers aged 12 to 24 months receiving measles-mumps-rubella vaccine dose 1; (2) kindergartners aged 4 to 6 years receiving measles-mumps-rubella vaccine dose 2; and (3) middle schoolers aged 10 to 12 years receiving measles-mumps-rubella vaccine dose 2. From 2 weeks before measles-mumps-rubella vaccine

administration until 4 weeks afterward, families recorded in diaries the occurrence of potentially common symptoms. Postvaccination symptom rates were compared with the prevaccination baseline, with significance assessed by testing incidence rate ratios estimated by Poisson regression.
Because study vaccinations were required by law for school attendance, it was not considered possible or ethical to recruit a separate control group from whom vaccines were withheld. Instead, within the study population, a designated period preceding vaccination was treated as a baseline for rates of specified health events to which rates in the postvaccination period were compared. Specifically, 2 weeks before vaccination, the family of each participant was prospectively provided with a prevaccination diary on which to record daily by check mark the occurrence of 13 symptoms identified in the literature as potentially associated with MMR vaccination. Both prevaccination and postvaccination diaries were reviewed by study nurses.

Results
Overall vaccination-associated adverse events occur in 1 of every 6 toddlers receiving measles-mumps-rubella vaccine dose 1, with high fever occurring in 1 of 20. Adverse events are infrequent for measles-mumps-rubella vaccine dose 2 administered to school-aged children. Postvaccination data compared with prevaccination baseline show rates of fever, diarrhea, and rash were significantly elevated among 535 toddlers receiving measles-mumps-rubella vaccine dose 1. An estimated 18% experienced measles-mumps-rubella vaccine-associated events with high fever (temperature _39.5°C) occurring in 6%. None required medical attention. For 633 kindergartners and 632 middle schoolers, symptom rates were not significantly elevated after measles-mumps-rubella vaccine dose 2 compared with baseline. Data from this study suggest that MMR2 reactogenicity may be quite low, even in a context where the first dose had been administered as long as 10 years prior, and wild disease boosting is unlikely to have occurred in the interval.

Virtanen et. al. 2000

The measles components used in various measles-mumps-rubella (MMR) vaccines have been associated with various short-term and long-term adverse events. This is also true to a lesser extent for the rubella antigen, whereas the mumps component (particularly the Jeryl Lynn strain) is deemed virtually harmless.8 Controlled studies on vaccine reactogenicity are rare, and uncontrolled studies exaggerate findings because of a temporal rather than a causal association with vaccination. Very little is known about factors modifying adverse reactions. Authors performed a randomized, double-blind, placebo- controlled, and crossover vaccination trial in twins using the MMR vaccine to assess day-to-day symptoms and signs in 2 age groups with or without previous measles vaccination, and we examine the role of other factors in relation to reactogenicity.

Methods

The study comprised 1162 monozygous and heterozygous twins, each of whom randomly received placebo and then vaccine, or vice versa, 3 weeks apart, at 14 to 83 months of age. Most of the oldest children had previously been vaccinated against measles, and one half of the remainder of children had had the disease. Symptoms and signs were recorded daily on structured forms. The following items were monitored: local reactions (redness with a diameter exceeding 1 inch, soreness, swelling), rectal temperature (mild fever: ,101.5°F/38.6°C; moderate fever: between 101.5°F/38.6°C and 103.1°F/39.5°C; high fever: further elevated), rhinorrhea or cough, nausea or vomiting, diarrhea, rash, arthralgia, conjunctivitis, staying in bed, drowsiness, irritability, and other potential symptoms. Statistical methods included a complex analysis of the vaccine attributability of the symptoms and conditional logistic regression. The possible effects of gender and zygocity were analysed.

Results

Local reactions were attributable to mechanical trauma, because there was no difference between vaccinees and placebo recipients. Regarding systemic reactions, fever was the sign most uniformly caused by MMR vaccination. All MMR-related events in placebo recipients suggest that low reactogenicity in the older children was attributable primarily to measles immunity. Authors deem the second MMR vaccination to be virtually harmless, at least when the interval between doses does not exceed 5 years.

Reactions after the First and Second Injections: For all symptoms and signs checked, although especially for rash, irritability, and conjunctivitis, the difference between vaccinees and placebo recipients was slightly greater in the subset of twins who received vaccine before placebo. However, conditional logistic regression analysis did not show significant effect of the order of injections.

Effect of Previous Measles Vaccination and Age: 1% of the 14- to 18-month-olds and 89% of the 6-year-olds had received measles vaccination before MMR. The previously vaccinated children experienced 16 times less symptoms and signs than did nonvaccinees. Whether this major difference in reactogenicity was attributable to immunologic reasons (previous measles, vaccination, or measles contact), to age only, or to both factors could not be assessed, although immunology seems more likely

Effect of Zygocity: 41% of the 487 heterozygotic pairs were of different gender and, thus, certainly heterozygotic. The symptom score difference for any fever was higher among heterozygotics, but for other variables there were no differences between homozygotics and heterozygotics.

Dubey and Banerjee 2003.

During recent years, public concern has been caused by the attribution of causation of several disorders, including Autistic spectrum disorders (ASD), meningitis, inflammatory bowel

disease, and Guillain Barre Syndrome (GBS) to MMR vaccination. As a result of the concern surrounding the MMR vaccine, there was a documented decrease in immunization rates in the United Kingdom and Ireland. This led to an upsurge in the annual rates of measles infection. This article reports Controversies about side effects of MMR vaccine.

MMR VACCINE AND AUTISTIC SPECTRUM DISORDERS

Finding a temporal association in a selected population for a disorder with wide individual variation in timing of onset provides weak evidence for an association, especially since the broad age range for recognized onset of symptoms of ASD overlaps with the age when MMR vaccine is routinely administered. Thus, some temporal associations are expected. Increased reporting of ASD in recent years does not correlate with the introduction and widespread use of MMR vaccine. Studies were conducted by the Institute of Medicine in the USA and the Medical Research Council in the UK. Their conclusions were that although the epidemiological studies so far do not support a link between MMR and autism, they have been too imprecise to rule out the prospect completely and there is need for further research.

MMR VACCINE AND INFLAMMATORY BOWEL DISEASE (IBD)

Current evidence regarding the association between measles vaccination and inflammatory bowel disease (IBD) comprises analytic epidemiological studies, a case series report and ecological studies. The first of these, a 1995 cohort study, found an association between measles vaccination and Crohn's disease and ulcerative colitis, but was widely questioned on methodological grounds. This

was followed by a 1997 case-control study showing no association between measles vaccination and IBD. Two additional studies, one case-control and one cohort, then followed and neither found an association with measles vaccination. Of three recent cohort studies, two showed no relationship between infection with early measles exposure and risk for IBD, while one found an approximate 3-fold elevation in risk. To summarize, available evidence does not support an association between measles-containing vaccines and risk of IBD, nor between measles infection and IBD. While further research is necessary into the causal factors underlying Crohn's disease and ulcerative colitis, continued public education efforts are needed to reassure the public about vaccine safety and to prevent declines in vaccine coverage.

MMR VACCINE AND NEUROLOGIC CONDITIONS

Vaccines prepared from live attenuated viruses can occasionally cause symptomatic viral infections of the nervous system e.g., measles encephalitis, rubella neuritis and paralytic poliomyelitis. Although neurologic complications can occur after administration of live, attenuated vaccine, it

must be stressed that the incidence of acute encephalitis and subacute sclerosing panencephalitis after natural measles infection is far higher than after vaccination. Because most vaccinations of children are performed with MMR vaccine, there can be obvious difficulty in attributing a neurologic reaction to the measles component of the vaccine.

However, according to certain authors neurologic complications are not seen with mumps immunization and only rarely with rubella.

HYPERSENSITIVITY REACTIONS

It is recommended that patients with a history ofsevere hypersensitivity reaction to a gelatin-containing vaccine should seek an allergy evaluation (including antigelatin IgE testing) before being administered a subsequent dose of any gelatin-containing vaccine. Efforts should continue to identify less allergenic substitutes for the gelatin currently used by vaccine manufacturers. Persons who have experienced anaphylactic reactions to topically or systemically administered neomycin should receive measles vaccine only in settings where such reactions could be managed and after consultation with an allergist or immunoiogist.

CONTROVERSIES REGARDING THE REQUIREMENT OF A SECOND DOSE

In developing countries, the average age of infection is much lower, possibly due to poor nutrition, rapid loss of maternal antibodies and prolonged excretion of the virus in malnourished children. Basic strategy for control of measles in such a milieu is to sustain high levels of immunization coverage and supplementing it by strategies evolved in response to the changes in epidemiology induced by immunization. Approximately 90%-95% of recipients of a single dose of a parenterally administered live vaccine at the recommended age MMR varicella, and yellow fever), develop protective antibody within 2 weeks of the dose. However, because a limited proportion of recipients
(<5%) of MMR vaccine fail to respond to one dose, a second dose is recommended to provide another opportunity to develop immunity. The majority of persons who fail to respond to the first dose of MMR, respond to a second dose.

Slater et al 1996

Introduction and Methods

The updated communicable disease targetsof WHO European Region include the elimination of indigenous congenital rubella by end of 2000. Israel has made substancial strides towards the achievement of this goal. This review aim to summarize progress made and to address MoH plans for improved control of rubella in the future. Testing results and vaccination compliance rates were submitted by 15 public health office, allowing compilation of national program data.

Results

The decision of MoH to immunize all one year old children against rubella beginning in 1989 was well founded and by itself could have been expected to lead to the elimination of indigenous rubella and CRS within 40 years.

By the year 2000, 90% of children eaching their 12th birthday will have been vaccinated against rubella at age one, and the 2005,nearly 90% of children reaching the age of 12 years will already have been twice immunozed against rubella, at which time consideration can be given to discontinuing the routine vaccination of 12 years old.
Even if all program activities are carried out as planned, authors are however skeptical that congenital rubella will be eliminated in the four years remaining till the target year 2000, as there is little chance that endemic rubella transmission will have been interrupted by then. Nevertheless the authors believe that in the next decade rubella containment in Israel, and the ultimate goal of eliminating CSR, will be much closer to reality.

ii. Efficacy and effectiveness

a) Immune response:
   - Immune response of MR vaccine against **Rubella** when administered to children at 9 months and in the 2nd year of life?

In clinical trials, all licensed rubella vaccines induce in 95–100% of susceptible persons aged 12 months and older a seroconversion rates of approximately 95% or higher after a single dose. The effectiveness of 1 dose of an RCV is ≥95% even at age 9 months, the immune responses to rubella antigens are not affected by the other components of the vaccine in the combinations MR, MMR or MMRV(WHO 2011)

Ceyhan et al 2001.

[Article selected (from developing country) as no article from East Africa was retrieved from the literature search.]

The purpose of this study was to investigate the immunogenicity and protection rate of revaccination with MMR vaccine at 15 months of age after initial vaccination at 9 months of age in comparison with children who received single dose of MMR vaccine at 12 months of age.

Materials and methods

Subjects Study subjects were 1000 healthy infants aged 9 months (38–40 weeks) who had been given primary health care in five different maternity and child health are centers in Ankara, Turkey. In Group A, 442 infants completed the study and 58 infants were excluded from the study (four immigration, four parental decision change, 50 due to the use of a different batch of vaccine). In Group B, 495 infants completed the study and five were excluded (three immigration, two parental decision change).

Study plan Infants in Group A received MV at 9 months of age and MMR at 15 months of age. Blood samples were collected just before measles vaccination and 6 weeks after MMR vaccination. Subjects in Group B received MMR at 12 months of age. Blood samples were collected just before and 6 weeks after the vaccination

Serological tests: Total specific levels of measles, mumps, and rubella Ig Gs were determined by commercial ELISA

Results: *Prevaccination measles GMT* was higher in Group A (MV at 9 months of age and MMR at 15 months of age) in which children were younger (9-month-old) during the blood sample collection (*P*_0.0001). Postvaccination antibody titers were higher in Group B (MMR at 12 months of age) (*P*_0.0001).

No difference was detected between the two groups for *pre- and postvaccination mumps and rubella antibodies* (*P*=0.27 and 0.38, respectively, for prevaccination and 0.19 and 0.36, respectively, for post vaccination).

Although serologic testing was not done in the end of the study for all subjects, and theoretically few cases could be missed, subjects were followed-up for 60 months and authors observed that one dose MMR was apparently more protective than early vaccination/revaccination (zero versus 12 cases).

- Immune response of MR vaccine compared to monovalent Measles vaccine against **Measles** when administered to children both at 9 months and in the 2nd year of life?

b) Duration of Protection:
   - Duration of protection of MR vaccine against Rubella when administered as a single dose in children at 9 months compared to in the 2nd year of life?

   - Duration of protection of MR vaccine against Measles compared to monovalent Measles vaccine when administered as two doses to children at 9 months and in the 2nd year of life?

Helfand et al 2008

OBJECTIVES: The study was conducted in a densely populated area in Blantyre, Malawi. Malawi has a high prevalence of HIV infection in women of childbearing age (15%–33%) and a very low incidence of measles— following the implementation of measles-elimination strategies. The study compared measles antibody responses to a 2-dose schedule administered at 6 and 9 months of age in HIV-infected and HIV uninfected children (both exposed and unexposed) with responses in a control group of HIV-unexposed children

vaccinated only at 9 months of age to help assess the optimal vaccination schedules for areas with a high prevalence of HIV infection.

METHODS: All children of HIV-infected mothers were assigned to be vaccinated at 6 and 9 months of age. Block randomization was used to assign the children of HIV-uninfected mothers to 1 of 3 groups (at a ratio of 4:5:3, respectively):MVat 6 and 9 months;MVat 9 months only; or routine MV without follow-up. Children followed up in the study were given appointments at 6, 9, 12, 16– 18, and 20–24 months, and, for a subset of children, at 30–36 months of age. This manuscript focuses on results observed through 12 months of age. Study children who were vaccinated in the SIA or outside the study before 12 months old were censored from further analyses

Specimen processing, HIV tests, and related tests. HIV infection status was determined from analysis of whole blood in Malawi by using 2 commercially available, rapid HIV-1 antibody Tests. After study completion, an in-house, semi quantitative, HIV-1 real-time reverse-transcriptase polymerase chain reaction (RTPCR) was performed on samples from every study visit (to determine the timing of HIV infection) if the child's HIV antibody test results from samples collected on or after 18 months of age were unavailable or positive. Children who became HIV infected after 12 months of age (presumably through breastfeeding) were excluded from analyses

Measles serology. Serum or plasma samples from mothers and from children through 12 months of age were tested in the same run for measles antibody by using a commercially available indirect IgG EIA

Sample size and statistical analysis. Sample size determinations were made with the aim of having 80% power to detect differences of_15% between HIV-infected and HIV-uninfected children vaccinated at 6 and 9 months old and _10% between HIV-unexposed children vaccinated at 6 and 9 months and HIV-unexposed children vaccinated at 9 months old. The sample size of 2200 was selected with the goal of enrolling _60 HIV-infected children , _200 HIV-exposed but uninfected children, and _400 children of HIV-uninfected mothers randomized to be vaccinated either at both 6 and 9 months or only at 9 months of age.

RESULTS

Enrollment figures and demographic characteristics. Of 2173 mothers screened for HIV, 421 (19%) were HIV infected. Twenty-two hundred children were enrolled (including 27 sets of twins); 1756 children were followed up prospectively (444 children were randomized to the "no follow-up" group).

Measles antibody prevalence before and after vaccination. Nearly all mothers in the study population had detectable levels of measles antibody (95% of mothers in all groups).

At the 9-month visit, 59%–68% of children vaccinated at 6 months were measles seropositive. At 12 months of age, HIV-infected children who received a second dose of measles vaccine at 9 months were significantly less likely to be measles seropositive than HIV-uninfected children (whether HIVexposed or unexposed) who received a second dose at 9 months (29 [64%] of 45 versus 189 [94%] of 202 and 385 [92%] of 417;*P* _ .001). Of 521 HIV-unexposed children vaccinated at 9 months only, 398 (76%) were measles seropositive at 12 months of age;

Forty-four HIV-infected children had blood samples available for both the 9- and 12-month visits. Of these 44 children, 10 (23%) remained measles seronegative at both 9 and 12 months, 19 (43%) remained measles seropositive at both visits, 6 (14%) went from measles seropositive to seronegative, and 9 (20%) went from measles seronegative to seropositive.

Overall results: At 12 months of age, HIV-infected children vaccinated at both 6 and 9 months were less likely to have detectable levels of measles antibodies than HIV-uninfected children who received 2 doses of measles vaccine at 6 and 9 months of age or 1 dose at 9 months of age. HIV-infected children showed little increase in overall measles seropositivity rates after the second dose, in contrast to HIV uninfected children. The proportion of HIV-infected children who were measles seropositive after 2 doses of measles vaccine in this study was 64%. Among HIV-uninfected children, measles antibody prevalence was lower among 1- than 2-dose MV recipients.

Fowlkes et al 2011.

This is a supplementary article of the above study where authors report the results through age 24 months.

METHODS: Children were followed through age 24 months.

Measles and HIV Testing: Measles immunoglobulin G (IgG) level was measured by enzyme immunoassay (EIA) and by plaque reduction neutralization (PRN) on a subset including a random sample of children with follow-up through at least the 12 and 24 month study visits, respectively, to avoid any potential bias of only children who remained in the study to the end of follow-up. The sample sizes for the children in each of these three subsets were: 250 HIV uninfected children vaccinated at 6 and 9 months, regardless of maternal HIV status, 250 HIV-uninfected children vaccinated at 9 months only (born to HIV-uninfected mothers), and all HIV-infected children (n 5 72).

Statistical Analysis All single-dose recipients were HIV-uninfected. Among 2- dose recipients, children were classified in 3 groups: HIV uninfected, HIV-exposed but uninfected, and HIV-infected children. C

RESULTS

Study Population: Of 2200 children enrolled and 1756 (80%) followed, a total of 1185 (66%) children remained in the study until the 12- month visit. The characteristics of children remaining in the study through ages 12 and 20 months did not differ significantly

Measles EIA Antibody. By age 20 months, there were no statistically significant differences between HIV uninfected groups; _81% of single-dose recipients and 77%– 83% of 2-dose recipients among HIV-exposed and unexposed, respectively, were measles seropositive. Among HIV-infected children, only 44% of 23 children (95% CI, 23%–63%) were measles positive at age 20 months. Measles seropositivity at age 24 months was slightly lower than at age 20 months among HIV-unexposed children (84% and 90%, respectively), while among HIV-exposed but uninfected children it had fallen from 83%of 114 to 69%of 42 children.

Measles PRN Antibody GMCs

Among HIV-uninfected children, there were differences between groups in the GMCs at age 12 months but these differences narrowed substantially by the 20 and 24 month specimens. After all study children had received 1 or 2 doses of MV, at the 20-month visit, the GMC among single-dose recipients had increased to 511 mIU/mL, higher than all other study groups. By the 24-month visit, there appeared to be a decrease in antibody levels for all of the vaccine groups, though not statistically significant. Regardless of vaccination schedule, all HIV-uninfected children at the 24-month visit demonstrated a GMC within a comparable range (318–401 mIU/mL) with no statistical differences between groups.

Overall results: In HIV-uninfected children, early 2-dose measles vaccination at age 6 and 9 months provided some protection under age 9 months while achieving a similar rate of protection at age 24 months as a single dose administered at age 9-months. In this study, by age 24 months, 84% and 87% of HIV-uninfected children vaccinated at age 9 months and at age 6 and 9 months, respectively, demonstrated protective levels of measles antibodies by PRN. Among HIV-infected children, however, the early 2-dose schedule did not provide lasting immunity.

c) Efficacy of vaccine:
    - Efficacy of MR vaccine in Rubella elimination when administered in children as a single dose at 9 months compared to a single dose in the 2nd year of life?
        - ✓ only 1 dose of rubella vaccine is required to achieve rubella elimination if high coverage is achieved. (WHO 2011)

Cameron et al 2012

This article briefly reviews the history and epidemiology of measles, mumps and rubella disease and the case for introducing combination measles–mumps–rubella (MMR) vaccine into the national childhood immunization schedule in South Africa. In South Africa, it has been estimated that of the million or so children born in 2005, 654 or 16 to 69/100 000 live births were affected to some degree by congenital rubella infection. The authors report from a previous study recommended that the introduction be preceded by a targeted programme especially for schoolgirls, supported by serosurveillance and be repeated annually for least for the 5 years. The review states that once measles vaccine coverage over 85% uniformly in all provinces has been verified for a period long enough to be considered sustainable, measles vaccine should be replaced with MMR vaccine in the childhood immunization schedule at 9 and 18 months, preceded by the kind of process shown to be successful in South America. While efforts to achieve a uniformly high sustained coverage of measles and other vaccines in South Africa should be continued to be implemented, the following actions should be considered:

- ✓ That a surveillance system for congenital rubella syndrome (CRS) is setup in South Africa, along the lines recommended by WHO
- ✓ That the Southern African Development Community (SADC) should continue strengthen measles control efforts so that the Region can, sooner rather than later, move to a strategy to eliminate the endogenous spread of measles and rubella and mumps based on the South American model.
- ✓ That the education, information and communication efforts around measles, rubella and mumps be strengthened and sustained, especially the information that families using private sector health care maybe more susceptible to congenital rubella—needs to be more clearly and effectively communicated
- ✓ That consideration should be given to adding a MMR vaccine to the national immunization schedule around entry to high school, regardless whether MMR or measles vaccine was given as an infant.
- ✓ That tertiary educational institutions where large numbers of young people gather, one dose of MMR vaccine should be strongly encouraged for all students irrespective of immunization history.

Martinez et al 2015

The article is a review of publications in PubMed on rubella and CRS (systematic reviews, country experiences, and position papers from the World Health Organization (WHO) and other intergovernmental organizations to identify the key factors required for CRS elimination (prevalence reduction, vaccination strategies, and surveillance methods)

Vaccination programs

Strategies.

- ✓ Rubella vaccine incorporated into routine childhood vaccination schedules:
  - This strategy is a cost-beneficial and cost-effective means of preventing congenital rubella infection and CRS.
  - Countries should only consider this strategy if they are able to achieve and maintain 80% or higher coverage with their regular childhood measles vaccination campaigns. Including an RCV in regular childhood measles vaccination campaigns that cover less than 80% of the child population could result in decreased rubella virus circulation, which could increase the average age of rubella infection for females from childhood to the childbearing years.
  - In cases where regular childhood measles vaccination coverage is less than 80%, to protect women of childbearing age from giving birth to babies with CRS, mass immunization of everyone < 40 years old with the measles-rubella (MR) vaccine is recommended.
- ✓ Systematic review of rubella vaccination strategies implemented in the Americas found that a combination of the two types of mass vaccination programs (routine childhood vaccination and mass immunization of all males and females aged 5–39+ years) led to the interruption of rubella virus circulation, the elimination of endemic disease, and the prevention of CRS, in a shorter period of time than expected, compared with routine childhood vaccination alone or in combination with risk-reduction approaches for the adult population such as postpartum vaccination and screening programs for immunity.

Vaccine formulations, dosage and schedules.

One dose of either type of vaccine (monovalent formulations or in combination with other vaccine) is recommended for persons ≥ 12 months old to prevent rubella. Follow-up studies indicate that one dose of rubella vaccine can provide long-lasting immunity and that an RCV provides safety from the infection (low susceptibility to rubella disease), with antibody levels decreasing over time. Despite these findings, most countries currently have a two-dose vaccine schedule (with the first dose administered at age 12–15 months and the second at age 3–5 years) using an RCV—the combined measles-mumps-rubella (MMR) vaccine.

Rubella elimination

Strategies. Review found that strategies for rubella elimination can be divided into : 1) countries that introduced an RCV more than 20 years ago in a routine childhood vaccination programs; 2) countries that have conducted a mass rubella immunization campaigns (targeting both males and females ages 5–39+ years); 3) countries that have conducted partial rubella immunization activities (by cohort, sex, risk group, or geographic area); and 4) countries that have not yet introduced an RCV in their childhood vaccination programs.

Overall findings

Based on the results of the review,there are two types of mass rubella vaccination campaigns that are implemented to eliminate rubella and CRS in endemic areas and reduce re-emergence in previously disease-free areas*:* 1) one single mass national immunization campaign targeting all men and women 5–39+ years old (with the upper age limit depending on the year in which the rubella-containing vaccine was introduced and the epidemiology of rubella in the country) and 2) incorporation of an rubella-containing vaccine in routine childhood immunization programs, including regular vaccination campaigns for 12-month-olds and measles follow-up campaigns. In addition to mass rubella immunization campaigns and routine childhood vaccination programs, the following measures are taken to help fight rubella and CRS: 1) surveillance of the number of susceptible women of childbearing age, and the emergence of imported cases; 2) coverage of susceptible populations with "second-chance" ("catch-up") campaigns (vaccination of older children and adults who may have missed earlier immunization programs); 3) rapid response to outbreaks; 4) strengthening of CRS surveillance.

- Efficacy of MCV in the control and elimination of Measles when given to children under two years as two doses compared to a single dose?

Verguet et. al. 2015

Objective: explored the frequency of SIAs in order to achieve measles control in selected countries and two Indian states with high measles burden. Specifically, computed the maximum allowable time period betweentwo consecutive SIAs to achieve measles control.

Method: mathematical model using numerial simulain and mathematical analysis: DynaMICE (Dynamic Measles Immunization Calculation Engine), an age-stratified model of measles infection transmission in vaccinated and unvaccinated individuals. Using data from selected countries. The selected countries with high measles mortality burden were: India, Ethiopia, Nigeria, Indonesia, Mali, Afghanistan, Niger, Madagascar, and Burkina Faso. These countries were selected among the ten countries with the highest estimated burden of measles from each of two sources of estimates: the Child Health Epidemiology Reference Group of WHO and UNICEF and the Institute for Health Metrics and Evaluation.

Assumptions:

Vaccinated individuals are assumed to have a reduced risk of measles infection. Vaccine effectiveness is assumed to be 85% for the first dose when vaccinating before one year of age, 95% after one year of age and 98% for two doses, as suggested by a recent meta-analysis

Vaccines offer 100% protection and that vaccination gives lifetime protection if it successfully elicits an immune response, and that vaccinating already infected individuals does not increase the rate of infection clearance.

Input data

Infection transmission require data on age-dependent contact patterns in the population. We used well established contact survey data from Great Britain [19] corresponding to a probability of transmission per contact of about 3%, and in a sensitivity analysis, used mixing patterns from Vietnam

The probability of an infected individual transmitting measles to a susceptible individual following an effective contact was set to be consistent with a basic reproduction number (R0, the number of people infected by a single infected person in a completely susceptible population) for measles of 16.

Results

Table 1:

Inter-SIA period required to achieve measles control with 90% SIA coverage and R_0 of 16, as a function of routine immunization coverage for the first dose of measles vaccine and crude birth rate, for selected countries with high measles burden, and two Indian states.

Country	Routine coverage for 1st dose of measles vaccine (%)	Crude birth rate (per 1000 population)	SIA period (years) (computational model)	SIA period (years) (analytical model)
Afghanistan	68	36	2	2
Burkina Faso	87	43	3	3
Ethiopia	66	35	2	2
India	74	23	3	3
State of Bihar	*58*	*29*	*2*	*3*
State of Uttar Pradesh	*53*	*29*	*2*	*2*
Indonesia	80	21	3	4
Madagascar	69	36	2	2
Mali	59	49	2	2
Niger	73	51	2	2
Nigeria	42	43	2	2

Table 2

Supplemental immunization activity (SIA) period required to achieve measles control with 90% SIA coverage and R_0 of 12, for selected countries with high measles burden, and two Indian states.

Country	SIA period (years) (computational model)	SIA period (years) (analytical model)
Afghanistan	3	3
Burkina Faso	5	5
Ethiopia	3	3
India	3	4
State of Bihar	*3*	*4*
State of Uttar Pradesh	*2*	*3*
Indonesia	4	6
Madagascar	3	3
Mali	3	3
Niger	3	3
Nigeria	2	3

Limitations

The study used an average estimate of the basic reproduction number of measles, and hence did not capture local variations in the intensity of measles transmission.

Second, due to lack of data, the model does not take into account potential correlation between MCV1 and SIA coverage, and the fact that often children with better access to health systems and hence more likely to have received MCV1 can be easier to reach through SIA. Neither does it account for changes in immunization and birth rates into the future, as these are largely uncertain to forecast. Finally, though the model captures the conditions necessary for measles control, it is not intended to realistically model measles elimination (i.e. zero indigenous transmission events).

Baliraine et al 2011

Objective: To determine what measles virus genotype(s) circulated in Uganda after strategic interventions aimed at controlling/eliminating measles.

Methodology

As part of routine measles case investigations, urine samples and throat swab specimens for virus isolation were collected along with serum samples (0–12 days after rash onset) from patients across Uganda during 2006 through 2009. Infections were confi rmed serologically or by virus isolation.

Results

Of the serum samples tested, 1,053 (15%) of 6,999 were positive for measles immunoglobulin (Ig) M; most were collected during 2006 Twentytwo isolates (37%) were obtained from 59 samples from patients who had IgM against measles virus; 1 isolate was obtained from a patient who did not have IgM against measles virus; and another isolate was obtained from a patient who did not have serologic testing. Virus isolation was successful only in specimens collected within 5 days of rash onset.

All isolates belonged to genotype B3.1, which had not been previously detected in Uganda. Twelve (57%) of 21 sequences obtained were identical (Table) and also identical to isolates from the 2005 measles outbreak in Kenya. However, 9 (43%) of 21 showed neither 100% similarity with the other 12 Ugandan isolates (Table) nor with any other isolate available in GenBank.

Conclusion

These data provide molecular evidence that Uganda's 2002–2006 vaccination strategy was successful in interrupting indigenous measles transmission, but immunity gaps in the population allowed the establishment of an imported virus that was previously confined to western and central Africa. If national immunization programs across the region

synchronized their vaccination strategies to eliminate sources of reintroduction, measles could be quickly eliminated from the entire continent.

Mbabazi et al 2009.

Objective: This study examines the impact of the 2002–06 measles control strategy for Uganda that was implemented to strengthen routine immunization, undertake large-scale catch-up and follow-up vaccination campaigns, and to initiate nationwide case-based, laboratory-backed measles surveillance on the epidemiology of measles in Uganda, and the lessons learnt.

Methodology:
Number of measles cases and routine measles vaccination coverage reported by each district were obtained from the National Health Management Information System reports of 1997 to 2007. The immunization coverage by district in a given year was calculated by dividing the number of children immunized by the projected population in the same age category. Annual measles incidence for each year was derived by dividing the number of cases in a year by the mid-year projected opulation. Commercial measles IgM enzyme-linked immunoassay kits were used to confirm measles cases.

Results:
Routine measles immunization coverage increased from 64% in 1997 to 90% in 2004, then stabilized around 87%. The 2003 national measles catch-up and 2006 follow-up campaigns reached 100% of children targeted with a measles supplemental dose. Over 80% coverage was also achieved with other child survival interventions. Case-based measles surveillance was rolled out nationwide to provide continuous epidemiological monitoring of measles occurrence. Following a 93% decline in measles incidence and no measles deaths, epidemic resurgence of measles occurred 3 years after a measles campaign targeting a wide age group, but no indigenous measles virus (D10) was isolated.
Recurrence was delayed in regions where children were offered an early second opportunity for measles vaccination.

Santos et al. 2004
Objective: This article summarizes the epidemiology of measles and the evolution of measles control strategies used in Mexico, as well as the impact of these strategies on measles morbidity and mortality and on the elimination of endemic measles.

Methodology: Literature review
Results:

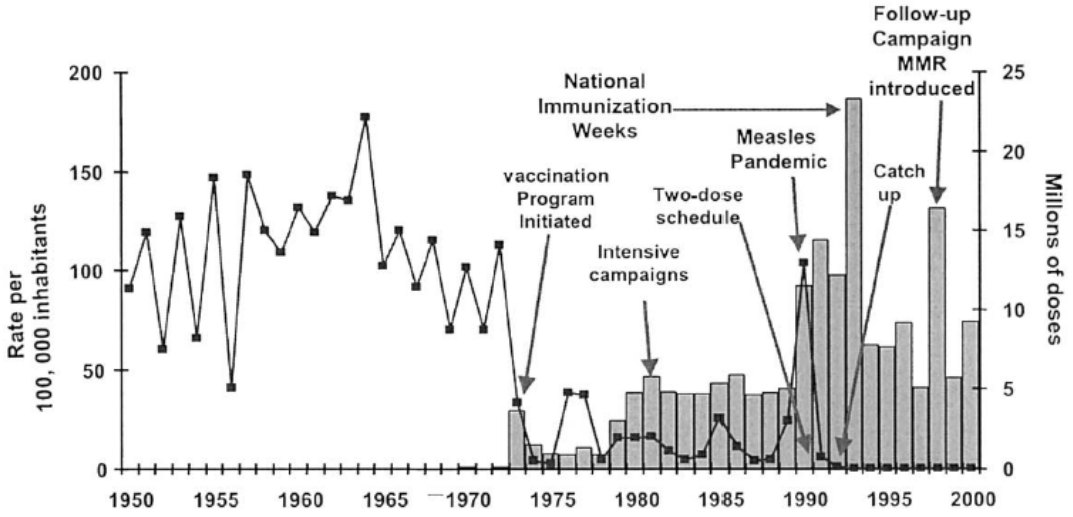


Figure 1. Measles morbidity vs. vaccine doses applied in Mexico, 1950–2000. "Catch-up," immunization of 5- to 14-year-old children regardless of prior vaccination or measles history. MMR, measles-mumps-rubella vaccine. Source: General Directorate of Epidemiology, Ministry of Health. Measles-rubella vaccine was introduced in 2000. Source: CONAVA (National Vaccination Council).

Table 3: Measles elimination strategies in Mexico

Strategy	Year(s)
Immunization program	
Medical units (1 dose)	1973
Household	1991
Booster dose added	1991
MMR supplants monovalent measles vaccine	1998
MR added for adolescents and adults	2000
Intensive campaigns	
<5 years old (1 dose)	1981
School-aged, 6–7 years old (2 doses)	1994
Nationwide house-to-house campaigns	1991–1992
Focalized blockades in areas with EFI cases	1992
Follow-up campaign	1998
Mass immunization	
Catch-up	
Schoolchildren 6–14 years old (2 doses)	1991, 1993
Children <5 years old in areas with low coverage	1995–1996
Municipalities with coverage <95%	1998
Introduction of MR vaccine for health care workers, school teachers	2000
Immunization schedule for adolescents with MR, Td, and hepatitis B virus	2001

Conclusion

The high immunization coverage with MMR vaccine, the introduction of MR vaccine for at-risk adolescents and adults, the analysis of febrile rash illness surveillance indicators, and the fact that from 1996 until the year 2000 no indigenous cases of measles were reported allow

us to conclude that the specific strategies adopted for measles elimination have enabled Mexico to eliminate the endemic transmission of measles.
Finally, in addition to the development and implementation of novel strategies for vaccine delivery, including aerosolized vaccine, collective efforts toward guaranteeing the timely purchase of quality vaccines, sustained high immunization coverage, and field and laboratory surveillance by countries in the region are the key elements for measles elimination in the Americas

Irons and Dobbins, 2011

Objective: To document the Caribbean subregion of the Americas successful strategy to eliminate measles. From 1991 through 2010, the 21 countries of the subregion were remarkably successful in maintaining their measles-free status despite importations of the virus from areas where it continues to circulate.

Methodology: desk review

Results

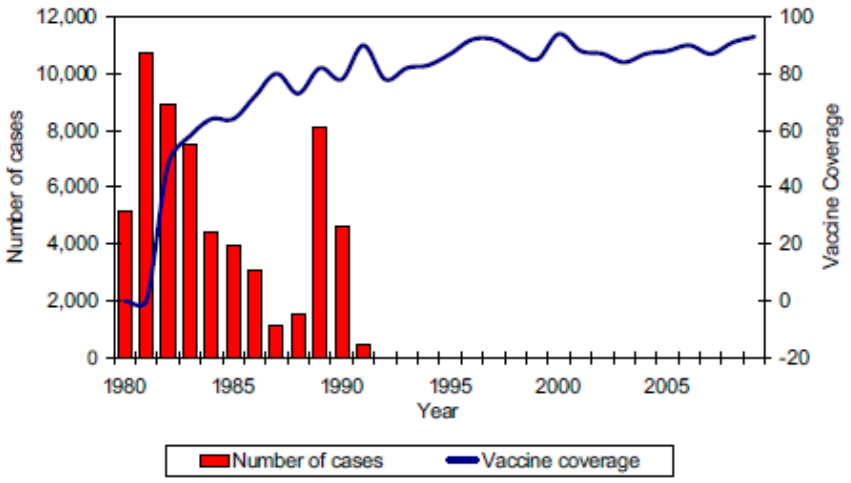


Figure 2: MMR-1 Vaccine Coverage and reported cases of indigenous measles, CAREC-member countries, 1970 -2009

This task has been accomplished by ensuring that each country in the subregion maintains measles vaccine coverage of R95%. The absence of measles is the result of a collaboration between the various national authorities and the Pan American Health Organization in ensuring vaccination campaigns to deliver the second dose of a measles-containing vaccine, estimating and validating vaccine coverage for both the first and second doses of measles vaccine for all local populations; developing detailed plans of action to improve coverage in those populations where coverage is, 95%; providing technical assistance for the implementation of the plan; and performing follow-up to confirm that all aspects of the plans were in fact implemented and that the target vaccination level was achieved.

Conclusion:
The absence of indigenous measles in the Caribbean for the past 18 years has been the result of a collaboration between the various national authorities and PAHO in maintaining and validating vaccine coverage for both MMR-1 andMMR-2 for all local populations; developing detailed plans of action to improve coverage in those populations where coverage is 95%; providing technical assistance for the implementation of the plan; and performing follow-up to confirm that all aspects of the plans were in fact implemented and that the target immunization level was achieved.

Khetsuriani et al 2011

Objective: To assess impact of SIAs on measles incidence in the World Health Organization European Region and their role at the final stages of measles elimination efforts in Europe.

Methodology:
Reviewed information on SIAs, measles surveillance, and routine vaccination coverage during 2000–2009**.** In most SIAs in the European Region, combined vaccines containing both measles and rubella components were used.

Results:
During 2000–2009, >57 million persons received MCV through SIAs in 16 countries. The Region primarily focused on catch-up campaigns with wider target age groups than in other regions and subsequently relied on routine vaccination rather than periodic follow-up SIAs for the secondMCV dose. In addition, the concept of SIAs has been expanded from short-term (>30 days) mass campaigns implemented in other regions to incorporate vaccination efforts over longer periods and outbreak response vaccination. In 2009, 14 of 16 countries that conducted SIAs reported no measles cases or <1 case per 1,000,000 population, reflecting the post-SIA decrease in incidence.

A substantial decrease in measles incidence has occurred in most countries after implementation of SIAs. This decrease was usually sustained for several years, but in some countries (Albania, yrgyzstan, the Republic of Moldova, Serbia, and Croatia), a modest increase in measles cases occurred 2–4 years after an SIA. The peak incidence during these increases was much lower than the incidence before the SIAs, and the cases were often imported. In 2009, overall measles incidence in the countrieswhere SIAs were implemented was at an all-time low, with 13 countries reporting no measles cases or <1 case per 1,000,000 population (Albania, Armenia, Kazakhstan, Kyrgyzstan, Republic of Moldova, Tajikistan, Turkmenistan, Uzbekistan reported no measles cases and Azerbaijan, Croatia, Russian Federation, Serbia, and Turkey, reported ,1 case of measles per 1,000,000 population.

Conclusion
Because of the measles immunity gap in older cohorts reflected by the ageing of the disease in
Europe, SIAs in the European Region usually targeted a wider age range than in developing countries, rarely including children <6 years of age and largely focusing on older children and

adults. Until the immunity gap was addressed by supplementary vaccination of older children and adults, measles incidence remained high in most of the 16 countries that have conducted SIAs, even with successful 2-dose routine childhood immunization programs. Therefore, SIAs along with maintaining strong routine immunization programs should remain an important strategy toward achieving the regional elimination goal. In most SIAs in the European Region, combined vaccines containing both measles and rubella components were used.

Sever et al 2011
Objective: To compare measles elimation startegies using one dose and two dose schedules in countries in the Americas
Methodology:
Data on socioeconomic factors, demographic characteristics, vaccination coverage, and the estimated proportion of children (<15 years of age) susceptible to measles were compiled. Countries were grouped using propensity score methods, and Kaplan-Meier curves were used to compare time to measles elimination between countries with a 1-dose schedule and those with a 2-dose schedule.

Countries included in the study
The region of the Americas includes 35 countries and 13 territories and is demographically and economically diverse; public health policy in the region is guided by PAHO. Countries and territories in the English-speaking Caribbean, French, and Dutch territories, and Bermuda (n 524) were excluded from the analysis because of small population size and geographic isolation. The United States (including Puerto Rico) and Canada were also excluded, because vaccination policy in these countries differed from that in the rest of the countries in the region. This analysis focused on the remaining 21 countries in Latin America and the Caribbean. These countries were categorized into whether they added a second routine dose of measles vaccine (‘‘2-dose country’’) or not (‘‘1-dose country’’) according to the routine.

Definitions used
Three definitions for measles elimination year (MEY) were used: (1) a case-based MEY was defined as the year after which the last endemic (nonimported) measles case was reported, (2) a population-based MEY was defined as the year measles incidence of <1 laboratory-confirmed case per 1 million population was achieved and sustained, and (3) a combination MEY was defined as the year in which both the case-based and population-based definitions were met. The case-based definition was used because this encompasses the traditional definition for measles elimination, in which no further endemic cases exist; in addition, the population-based definition was included because this is one of the current factors being assessed globally and used by the World Health Organization as a requirement for measles elimination.
Time to elimination was calculated as the difference between 1992 (the year in which the first countries introduced MCV2 and in which the first vaccination campaigns occurred) and the year of measles elimination. For each country, time to measles elimination was evaluated for each of the 3 definitions for measles elimination given above.

Results:
One-dose (n = 14) and 2-dose (n = 7) countries did not differ with respect to median routine firstdose measles vaccine coverage >90%, median coverage for 3 measles campaigns >85%, or estimated percentage of susceptible children after routine first vaccination dose and campaigns: The estimated proportion of persons 15 years of age who were susceptible to measles for both 1-dose (mean susceptibility, 7.4% [95% confidence interval {CI}, 5.5%–9.2%; median susceptibility, 7.1%) and 2-dose (mean susceptibility, 5.9%; 95% CI, 3.9%–7.9%; median susceptibility, 5.5%) countries were similar after the first routine vaccination dose and vaccination campaign doses. The estimated
Percentage of susceptible persons aged <15 years was lower in 2-dose countries than in 1-dose countries, assuming MCV2. Compared with 1-dose countries, 2-dose countries had higher median gross national income per capita (P 5.002), percentage of population living in urban areas (P 5.04), and female literacy (P 5.01), as well as lower infant mortality (P 5 .007); however, no differences in time to elimination were found.

Conclusion:
Findings from this analysis suggest that, in the Region of the Americas, countries that added a second routine measles dose to the ‘‘catch-up, keep-up, follow-up’’ strategy did not hasten measles elimination, compared with countries that did not have a second routine vaccination dose, despite apparent socioeconomic advantages in countries with a second routine dose.
Possible explanations for the lack of impact of a second routine measles vaccine dose in the Region of the Americas are the high overall population immunity achieved with high quality implementation of the PAHO measles elimination strategy [34] and the age of MCV2 administration (4–6 years of age). The PAHO measles elimination strategy included vaccination campaigns that were often synchronized in multiple countries and which led to a rapid increase in overall population immunity. In addition, high first-dose measles vaccine coverage through routine vaccination resulted in a low number of accumulated susceptible persons throughout the region. With the population immunity achieved through this strategy at or near the herd immunity threshold, it is likely that the addition of a second routine dose had little overall effect on measles elimination. Furthermore, the second routine dose in country childhood vaccination schedules was administered at 4–6 years of age, after children had received a first routine dose and a vaccination campaign dose.

Limitation:
Although no impact of a second routine dose was found in the Region of the Americas, these findings might not be applicable to other countries and regions. In particular, a second routine dose might have greater impact when administered at 2 years of age and in countries and regions with lower measles vaccine coverage than was achieved in the Region of the Americas from routine vaccination and from vaccination campaigns.

South Korea 2007

Objective: to document South Korea’s measles eliminatin strategy

Methodology: Literature review
The South Korean measles elimination strategy included:

1. Maintaining 2-dose measles coverage >95% by requiring completion of MCV 2 for school entry by children aged 7 years
2. Conducting catch up campaign for children aged 8-16 years
3. Strengthening case based surveillance with laboratory confirmation of reported cases.

Results:

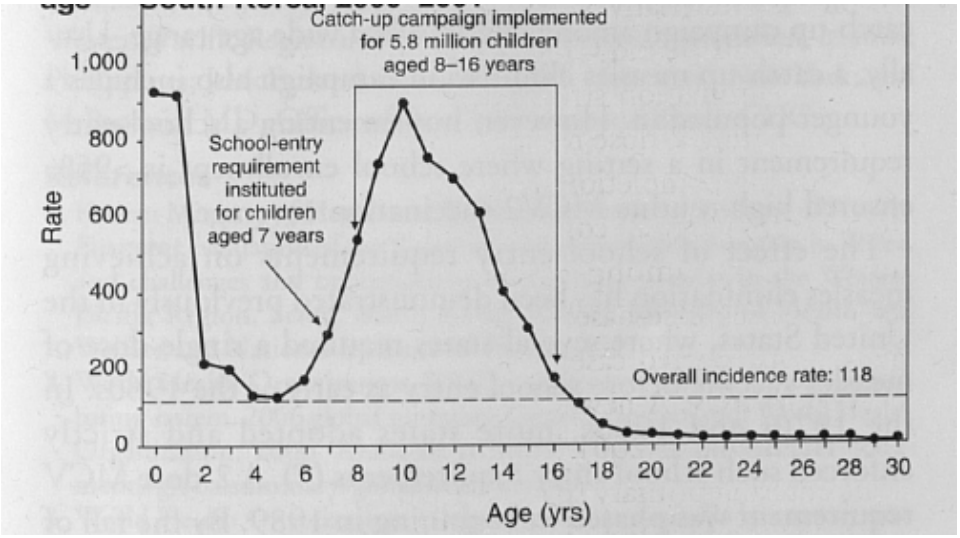


Figure 3: Incidence rate of reported measles cases, by patient age- South Korea 2000-2001

Table 4. Number of reported and confirmed measles cases, by year – South Korea, 1990-2006

Year	Total no. of reported cases	No. of confirmed cases
2006	126	25
2005	63	6
2004	71	6
2003	58	13
2002	143	11
2001	23,060	—*
2000	32,647	—
1999	88	—
1998	4	—
1997	2	—
1996	65	—
1995	71	—
1994	7,883	—
1993	1,503	—
1992	38	—
1991	258	—
1990	3,415	—

* A full year confirmed case count was not available before 2002. Beginning in July 2001, specimens from all persons with reported measles were routinely sent for laboratory confirmation; cases were confirmed serologically or virologically.

During 2002-2006, South Korea satisfied nearly all interim criteria for measles elimination as established by WHO/WPRO. During 2002-2006 after implementation of the national plan, the number of confirmed measles cases ramnged from six to 25, with corresponding annual incidence ranging from 0.13 to 0.52 cases per million. One confirmed case in 2002 was impore, as were two cases in 2003, one in 2005 and five in 2006.

Conclusion: the experience of South Korea demonstrated that introduction of a 2nd dose measles vaccination schedule in 1997 without school entry requirements was insufficient to prevent the 2000-2001 epidemic because of low MVC 2 coverage. TO eliminate indigenous measles virus circulation in the presence of repeated importations, high population immunity was ensured through 1) simultaneous implementation of a catch up campagn targeting a wide age range, and requirements thet students have documentation of MCV2 before scholl entry and 2) enhanced case based measles surveillance. Maintaining elimination will require sustaining 2 dose measles vaccination coverage >95% and maintaining sensitive case based surveillance to identify whether and when preventive SIAs or other interventions might be required.

Mupere et al. 2006

Objective: to study Measles vaccination effectiveness among children under 5 years of age in Kampala, Uganda.

Method: prospective study among household contacts aged 9–59 months to assess measles vaccination effectiveness. Index cases were measles patients seen in Kampala hospitals in 1999. Household contacts were defined as children aged 9 months to 5 years living in households of the index cases, exposed to the index case for at least one day in the 4 days before the index case
Developed rash, and who had a vaccination card documenting measles vaccination status 14 days prior to the onset of measles in the index case. Children were only classified as vaccinated if measles vaccine had been given at a minimum of 9 months of age and at least 14 days prior to the onset of measles in the index case. IgM measurement in serum were done at the Uganda Virus Research Institute (UVRI) Entebbe in March 2000, while IgG testing in filter paper blood samples was done at the Erasmus MC in Rotterdam, the Netherlands, in November 2001. At UVRI, MV-specific serum IgM antibodies were detected using a commercial measles IgM ELISA. At Erasmus MC, baseline MV- specific IgG levels were determined using an in-house indirect ELISA assay based on coating with propiolactone-inactivatedMVantigen [13]. Total IgG1 levels were determined in reconstituted filter paper samples as a control on the effectiveness of reconstitution [13]. Results were expressed in international units per milliliter (IU/mL), based on standard dilutions of the international standard serum for measles run in parallel with each assay.

Results:

Table 5: Measles age-specific attack rate among household contacts

Age (months)	Attack rate in vaccinated children		Attack rate in unvaccinated children		Vaccine effectiveness
	Contacts[a]	Measles cases (attack rate)[b]	Contacts	Measles cases (attack rate)	VE (95% CI)
9–11	1	0(0)	6	5(83)	100(100, 100)
12–23	19	4(21)	14	12(86)	75(40, 90)
24–35	34	9(26)	12	9(75)	65(33, 82)
36–47	47	9(19)	6	6(100)	81(66, 89)
48–59	44	11(25)	5	5(100)	75(58, 85)
Total	145	33(23)	43(23)	37(86)	74(64, 81)

[a] Number of household contacts in age subgroup.
[b] Number of measles cases in baseline antibody subgroup (attack rate: measles cases as percentage of total number of household contacts in subgroup); χ^2 for linear trend vaccine effectiveness = 5.296, $p < 0.05$.

Measles was diagnosed in 37/43 (86%) of unvaccinated and in 33/145 (23%) of vaccinated exposed contacts, respectively. Vaccination effectiveness was 74% (95% CI; 64–81)

Conclusion:
Our findings suggest that, vaccination failure may be an important cause of the severe recurrent measles outbreaks and epidemics that have been occurring in Uganda. A reduced VE appears to have persisted for several years.

Limitations:
This study had a number of limitations. Some children in the households could not be included because of missing vaccination cards. In addition, MV-specific IgM was only tested in household contacts who met the WHO clinical case definition for measles. Unapparent infections may have been missed, so that the measles ARs obtained could be an underestimate. No testing for serum antibodies to human immunodeficiency (HIV) was performed, so a potential role of HIV in influencing protection levels against measles could not be assessed.

Wood et al. 2009

Objective: modelled the effect on measles elimination status and population susceptibility of shifting delivery of MMR2 from 4 years to 18 months using relevant Australian data.
Also examined the potential effects of waning of vaccine-derived immunity, and changes in the following on the performance of the two schedules:
• Proportional uptake of MMR2 amongst recipients and nonrecipients of MMR1;
• Degree of contact between infants; and
• Coverage and timing of vaccination.

Methodology: mathematical modelling
Projections based on simple mathematical models of measles transmission use serological and vaccine coverage data to predict susceptibility to measles and then combine this with information about contact patterns to predict the reproduction number (R). R is the average number of secondary cases in a population where not all individuals are susceptible to infection. When R is above 1, the potential for large outbreaks and endemic transmission is high, whereas whenR is maintained below 1, outbreaks will tend to be self-limiting and endemic transmission should cease.

Population susceptibility was estimated using a national serosurvey and vaccination coverage data obtained from the Australian Childhood Immunisation Register (ACIR), a national register that captures data on over 99% of Australian children aged up to 7 years. The value of R in the Australian community was then estimated for the current and alternate schedules using these data, previously described methods, and assumptions outlined below and each scenario.

Assumptions:
We assumed that MMR vaccine provides immunity to 90% and 99% of one and two dose recipients respectively. For the current schedule, we assumed that future coverage would be the same as
the average coverage between January 2004 and December 2006 of one-dose of MMR by 2 and 6 years of age and MMR2 coverage by 6 years of age (94%, 95%, and 86% respectively). These time points are routinely used to assess 12 month and 4 year coverage levels in Australia.
Estimates of measles susceptibility for persons aged >6 years and at 1 year of age were derived from the 2002 serosurvey It was assumed that infants are protected by maternal antibodies until 6 months of age.

Scenarios:

In the base-case scenario, we assumed that all vaccinees who seroconverted remained immune throughout their lives and that MMR2 uptake only occurred in children who had already received
MMR1.

Wanning of vaccine derived immunity: In order to explore the sensitivity of our conclusions to waning of vaccine-derived immunity we allowed immunity to wane in 6% of vaccinees who seroconverted after each dose.Waning of immunity was applied only to cohorts born during or after 1996 as they have high levels of 2 dose coverage with MMR vaccine and little exposure to naturally circulating measles virus. We assumed that on average the duration of immunity in the group of vaccinees subject to waning was 10 years. A greater proportion of recipients of just one-dose was to wane (25%) in a sensitivity analysis.

Proportional vaccine uptake: We tested the effect of varying vaccine distribution by setting the chance of receiving MMR2 after not having received MMR1 as either 0.2 or the same as for children who had received MMR1.

Increases in child care usage: Increased contact is likely to increase the potential for measles transmission. We tested the sensitivity of this assumption by doubling the rate of contact between children under the age of 5 over the whole period of analysis.

Results

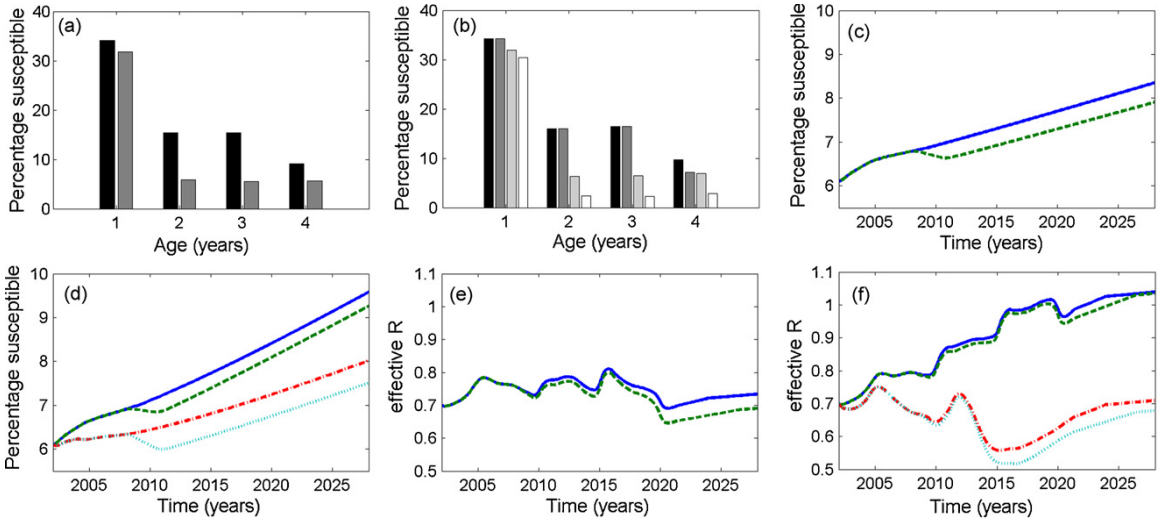


Figure 4**.** (a) Expected percentage of susceptible 1–4 year olds when MMR2 is given at 4 years (black) and 18 months (dark grey); (b) same but with 6% of vaccinees losing immunity (black: MMR2 at 4 years, dark grey: MMR2 at 18 months from 2008) or in addition to this waning, MMR2 is distributed with equal likelihood to vaccinees andnon-vaccinees (light grey: MMR at 4 years, white: MMR at 18 months from 2008). (c) Overall population susceptibility from 2002 until 2028 with MMR2 given at 4 years (solid) and 18 months from January 2008 (dashed). (d) Same but with 6% of vaccinees losing immunity (solid: MMR2 at 4 years, dashed: MMR2 at 18 months from 2008) or in addition to this waning, MMR2 is distributed with equal likelihood to vaccinees and non-vaccinees (dash-dot: MMR at 4 years, dotted: MMR at 18 months from 2008); (e) value of *R* for measles from 2002 to 2028 with MMR2 given at 4 years (solid) or 18 months from 2008 (dashed); (f) same but with 6% of vaccinees losing immunity (solid: MMR2 at 4 years, dashed: MMR2 at 18 months from 2008) or in addition to thiswaning, MMR2 is distributed with equal likelihood to vaccinees and non-vaccinees (dash-dot:
MMR at 4 years, dotted: MMR at 18 months from 2008).

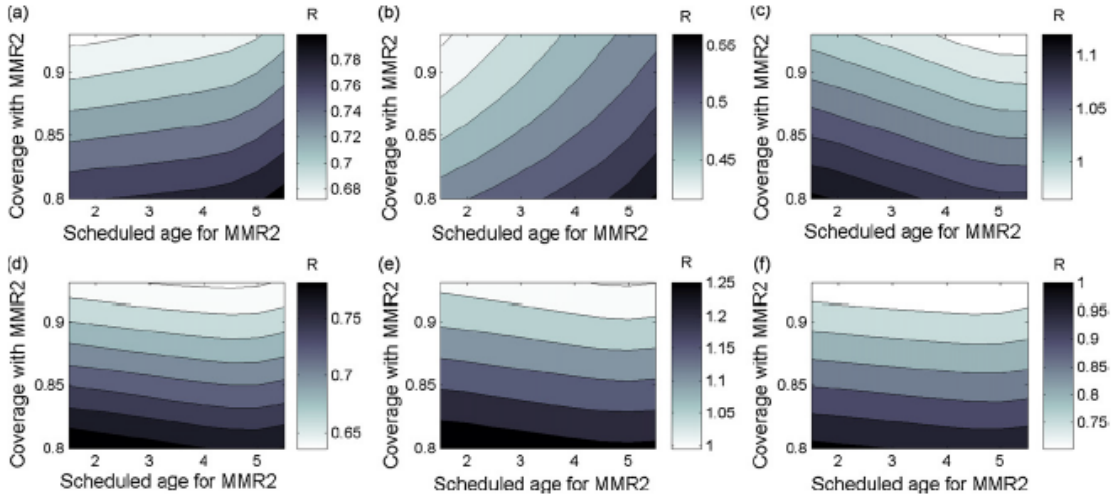


Figure 5. Effect ofwaning immunity in combination with scheduling of and coverage with MMR2 on effective *R* in 2018: (a) nowaning; (b) same but equal likelihood of vaccines and non-vaccinees receiving MMR2; (c) 6% of vaccinees who seroconverted wane; (d) same but equal likelihood of vaccinees and non-vaccinees receiving MMR2; (e) 25% of one-dose vaccinees who seroconverted wane, while 6% of 2-dose vaccinees who seroconverted wane; (f) same but equal likelihood of vaccinees and non-vaccinees receiving MMR2.

In summary, we found that providing MMR2 at 18 months of age should considerably reduce susceptibility in the pre-school cohort with a modest reduction in population susceptibility from inception in 2008 until at least 2028. However, the impact of a schedule change will be influenced by whether and to what extent waning of vaccine-derived immunity occurs. If waning occurs following a two dose schedule, a later date for MMR2 is favoured. While greater coverage with two doses of MMR would be welcome, increasing the population coverage with at least one dose of MMR is more important for maintaining elimination. In addition to continued surveillance of immunity in vaccinated cohorts, strategies that would encourage the maximum uptake of one dose of MMR, such as school entry as a key time for identifying and rectifying incomplete vaccination, should be considered.

d) Is there any interference with the immunity of MR vaccine or monovalent Measles vaccine when co-administered with other vaccines in children at 9 months or in the 2nd year of life?

Immunogenicity and reactogenicity of the individual components are similar when MCVs are administered as combined products or simultaneously at different anatomical sites with other vaccines, such as diphtheria toxoid, tetanus toxoid, pertussis vaccine, Haemophilus influenzae type b vaccine, poliovirus vaccines (oral poliovirus vaccine [OPV] or inactivated poliovirus vaccine), varicella vaccine, hepatitis B vaccine, or heptavalent pneumococcal vaccine. Similarly, available date suggest that vaccines against measles and yellow fever or Japanese encephalitis may be

administered at the same time at different sites. As a general rule, live vaccines should be given either simultaneously or at intervals of 4 weeks. An exception to this rule is OPV. (WHO, 2009).

The vaccine can be safely and effectively given simultaneously with DTP, DT, TT, Td, BCG, Polio vaccine (OPV and IPV), Haemophilus influenzae type b, Hepatitis B, Yellow fever vaccine and vitamin Asupplementation.(SERUM INSTITUTE OF INDIA LTD Manufacturers' insert)

iii. Vaccine indirect effect

a) What is the coverage threshold of RCV in children under 2 years of age that confers herd immunity against Rubella??

b) Coverage threshold required in routine immunization to avoid the paradoxical effect (i.e. change in age of infection) of MR vaccine?

WHO 2011

- ✓ When vaccine coverage is low – for example, in a suboptimal childhood-only immunization programme the circulation of the virus may be decreased enough so that those who would normally be infected as children will remain susceptible until they reach adolescence and adulthood including increase in susceptibility among women of childbearing age that may increase the risk of CRS above levels prior to the vaccine being introduced (known as a paradoxical effect.). If vaccination coverage is sufficiently high, rubella transmission will be markedly reduced or interrupted, thereby removing the risk of rubella exposure for pregnant women. To avoid the potential of an increased risk of CRS, countries should achieve and maintain immunization coverage of 80% or greater with at least 1 dose of an RCV delivered through routine services or regular SIAs, or both. (WHO 200).

- ✓ When vaccine coverage is low – for example, in a suboptimal childhood-only immunization programme the circulation of the virus may be decreased enough so that those who would normally be infected as children will remain susceptible until they reach adolescence and adulthood including increase in susceptibility among women of childbearing age that may increase the risk of CRS above levels prior to the vaccine being introduced (known as a paradoxical effect.). If vaccination coverage is sufficiently high, rubella transmission will be markedly reduced or interrupted, thereby removing the risk of rubella exposure for pregnant women. To avoid the potential of an

increased risk of CRS, countries should achieve and maintain immunization coverage of 80% or greater with at least 1 dose of an RCV delivered through routine services or regular SIAs, or both.

Lessler and Metcalf 2013

✓ Presents an age specific model of rubella transmission to predict the level of R0 that would result in an increase in CRS burden for specific birth rates and coverage levels. The vaccination coverage necessary to reduce CRS depends on the birthrate in a country and the reproductive number, R0, a measure of how efficiently a disease transmits. R0 varies between settings and can be difficult to measure. The model aim to provide guidance on the safe introduction of rubella vaccine into countries in the face of substantial uncertainty in R0.

Methods: 1) Determining R0 Thresholds for Rubella Introduction For a given R0, birthrate, and vaccine coverage they simulated 30 years of rubella incidence using an age structured TSIR model , and determined whether the number of CRS cases increased or decreased when compared to having the same R0 and birthrate but no vaccination. The model assumes mild seasonal forcing of transmission and that vaccine efficacy reaches a maximum of 97%; various structures of contact between age classes were deployed, including constant, and the empirically derived POLYMOD structure; 2) Estimation the Distribution R0s: R0 was estimated based on the age distribution of infection using laboratory-confirmed rubella case data collected as part of WHO measles surveillance in 40 different countries in Africa from 2002–2009. None of the countries considered had introduced rubella vaccine during the period considered, hence the age distribution of cases can be used to provide an estimate of R0; 3) Figure Design: The data on the distribution of R0s and the threshold value of R0 are combined to make a figure summarizing the confidence that rubella vaccination would result in a reduction of CRS cases. The figure is a grid, where each cell represents a particular combination of birthrate (indicated by the column) and vaccine coverage (indicated by the row). In each cell is indicated the R0 threshold value calculated as described above. 4) Scenarios: the authors considered scenarios where there was only routine rubella vaccination among children and infants, administered as part of a country measles vaccination program, and where rubella vaccine was administered in combination with supplemental immunization activities (SIAs). All statistical analyses were done using R 2.15 (www.r-project.org)

Results: In the country included in the analysis, the median of the estimated R0 distribution for rubella is 5.2. Individual country estimates ranged from 3.3 (95% CrI: 3.0, 3.7) for Burkina Faso to 7.9 (95% CrI: 7.7, 8.1) for South Africa.

For Uganda the R0 is 4.7. Considering different vaccination strategies, different mixing populations scenarios, the country birth rate (4.5) and WHO UNICEF 2011 MCV1 coverage (71%) the results of the model for Uganda are as below:

- Routine vaccination only, assuming even mixing across all population age groups.: the R0 threshold value is 6.3; the model predicts with 90-95% confidence that introduction of the vaccine with this strategy will decrease CRS
- Routine only, assortative mixing of population: R0 threshold value is 6.5, the model predicts with 90-95% confidence that introduction of the vaccine with this strategy will decrease CRS
- Routine vaccination supplemented with SIAs of 1–4 year olds with 60% coverage every 4 years (assortative mixing): threshold value is 9.3, the model predicts with > 95% confidence a decrease of CRS if the vaccine is introduced
- (D) Routine vaccinations and SIAs supplemented with a catch-up campaign covering 1–14 year olds with 60% coverage conducted when rubella vaccine is introduced: R0 threshold value is 9.5, threshold value is 9.3, the model predicts with >95% confidence a decrease of CRS if the vaccine is introduced

The results support the WHO recommendation that countries introduce rubella vaccine into their regular vaccination program if they can maintain coverage above 80% through a combination of routine vaccination and SIAs

Limitations of the study: Data on rubella incidence is based on the analysis of suspected measles cases, and relies on surveillance systems that differ markedly by country and may be biased towards detecting rubella in particular age groups; most countries considered in the analysis have a pyramidal age structure, but some some do not, which may lead to a slight overestimation in the overall distribution of R0 across countries; assumptions about age specific mixing are based upon studies conducted in Europe, where MMR vaccine is already used widely, and may not apply to African and Asian countries considering MR vaccine introduction. The projections also ignore the effect of local disease dynamics on CRS burden: local extinction of rubella may lead to an increase in the CRS burden by allowing individuals to enter into childbearing years without exposure to the infection, up until the point where rubella is re-introduced

Ang et al 2010.

Authors reviewed the epidemiological features of rubella in Singapore and the impact of the national immunisation programme in raising the population herd immunity against rubella, with special reference to females in the reproductive age group, and in the elimination of congenital rubella syndrome (CRS). The country adopted in January 1990, extension of rubella vaccination to include all children of 1 year of age and monovalent measles vaccine was replaced by trivalent measles, mumps and rubella (MMR) vaccine. The second dose of MMR vaccine was introduced in 1998.

Materials and Methods:

Case Surveillance: The epidemiological data of all cases of rubella notified to the Ministry of Health (MOH) under the Infectious Disease Act from 1991 to 2007 were collected and analyzed. Cases of CRS among infants born in Singapore and therapeutic abortions performed for rubella infections were identified from the Central Claims Processing System, a national inpatient discharge database which covered all hospitals in Singapore.

Immunisation Coverage: The annual MMR immunisation coverage of each cohort of Singapore citizens and permanent residents aged 2 years old from 1995 to 2007 was obtained from the National Immunisation Registry (NIR). In the case of primary school leavers, data on the proportion of children aged 11 to 12 years immunised against rubella were obtained from the School Health Service of Youth Health Division, Health Promotion Board.

Serological Surveys: To assess the herd immunity of the population against rubella, 4 seroepidemiological surveys were conducted; the first from 1989 to 1990 just prior to the introduction of the trivalent MMR vaccine into the national childhood immunisation programme,11 the second in 1993,12 the third in 1998 and the last in 2004.In the first 3 surveys, blood samples were collected from healthy children and adults aged between 6 months and over 45 years old at designated government polyclinics. The last survey was based on stored blood samples of the National Health Survey (NHS 2004) collected between September and December 2004. NHS survey which was representative of the general population aged 18 to 74 years old. The titre of rubella IgG antibody was determined using a microparticle enzyme immunosay. A titre of10 IU/mL or greater was considered positive.

Statistical Analysis: For the calculation of annual age-specific incidence rates, the denominators used were the corresponding estimated mid-year populations compiled by the Department of Statistics, Singapore. The annual incidence rates of infants with CRS were calculated based on the number of live-births of the corresponding years obtained from the Registry of Births and Deaths. Differences in rubella seropositivity rates by age, gender and ethnicity were computed and tested for statistical significance.

Results

Epidemiology : A 3-year cyclical pattern in rubella incidence was observed during the period from 1991 to 1999, with high incidence in 1993 (12.8 per 100,000 population), 1996 (13.3 per 100,000 population) and 1999 (10.9 per 100,000 population). This was followed by a significant decline to an incidence of 2.1 per 100,000 population in 2003 (P <0.05,☒ test for trend), and 1.8 per 100,000 population in 2007. The incidence of rubella among women in the reproductive age group of 15 to 44 years old had decreased from 13.5 per 100,000 population in 1996 to 2.1 per 100,000 population in 2007. The proportion of therapeutic abortions performed on account of rubella infections had decreased from 0.10% in 1996 to 0.01% in 2007. The incidence of CRS declined from 0.08 per 1000 live births in 1992/1993 to 0.03 per 1000 live-births in 2004. No cases of CRS were reported in 1997, 1998,2000, 2003, 2004, 2006 and 2007.

Immunisation Coverage: The annual MMR immunisation coverage among Singapore citizens and permanent residents at 2 years of age had been maintained at a high level (93% to 98%). In the case of primary school leavers, the annual coverage rate had been above 93% (93% to 96%). Based on mathematical modelling, rubella virus transmission in children may be eliminated with a vaccination coverage rate of about 90%

Seroepidemiology: Compared to the serological survey conducted prior to the introduction of the trivalent MMR vaccine in 1990, there had been a significant increase in the overall prevalence of antibody to rubella among healthy children and adults aged between 6 months and over 45 years old from 47.6% in 1989 and 1990 to 71.7% in 1993, and 80.2% in 1998 . In NHS 2004, of 4152 adult resident population aged 18 to 74 years old tested for rubella IgG antibody, 84.0% were seropositive. While the proportion of women aged 15 to 44 years old susceptible to rubella infection decreased from more than 20% in the period of 1989 to 1990 to 17% in 1993, and 13.6% in 1998, a significant proportion of women in the reproductive age group remained susceptible to rubella infection (15.8% seronegative) in 2004.One possible explanation for this observation is the rise in immigrants and non-residents from rubella endemic countries in Singapore. The study did not report on the breakdown of the residents in terms of Singapore citizens born in Singapore and Singapore permanent residents who originated from other countries where the rubella immunisation programme might not be as comprehensive as in Singapore therefore was not able to fully examine the impact of high levels of immigration on the overall level of herd immunity in Singapore.

Kinoshita and Nishiura 2016

This study is a retrospective seroepidemiological analysis aimed to epidemiologically assess rubella herd immunity as a function of time, age and gender in Japan. Although Japan is

considered to be on its way to establishing sufficient herd immunity through vaccination, the country has recently experienced two major rubella epidemics, in 2004 and 2012–2014, involving 4248 and 12 614 reported rubella cases, respectively, and yielding 45 CRS cases in the most recent epidemic. Rubella vaccination was introduced in 1976 (focusing on women aged from 12 to 15 years. In 1995, the vaccination policy shifted, targeting both genders aged from 12 to 90 months to elevate and maintain herd immunity.

Methods

Epidemiological data: Three pieces of information were analyzed: (1) reported cases of rubella and CRS, (2) seroepidemiological data and (3) vaccination coverage. The sero epidemiological data and vaccination coverage were investigated to assess herd immunity.

The rubella and CRS data: reporting of cases to the National Epidemiological Surveillance for Infectious Diseases (NESID) including notifications from rubella sentinel surveillance paediatric site

The seroepidemiological data (cross sectional serological survey, quantifying haemagglutination

inhibition (HI) titres) were derived from the National Epidemiological Surveillance of Vaccine-Preventable Diseases (NESVPD).The present study takes into consideration the survey data from every 5 years since 1983 to investigate the longitudinal trend of age at rubella infection, standardised seronegative proportion, and the number of live births that were born to seronegative mothers and considered to be at risk of CRS.

The vaccination coverage data were retrieved from the immunisation records of the Ministry of Health Vaccination coverage was calculated as the ratio of the annual number of vaccinations to the population size of an age-group that newly entered the participant age-group of vaccination, and this was overlaid.

Statistical analysis

Time-dependent and age-dependent epidemiological dynamics of confirmed rubella cases from 1982 to 2014 were examined using the reported case data along with the changes in the vaccination coverage over this time period. Additionally, the reported rubella and CRS cases from 2012 to 2014 (age and gender specificity) were examined. Seroconversion was defined as an HI titre $\geq$32.24. The basic reproduction number, R0, acknowledged as the average number of secondary cases generated by a single primary case, was estimated at 6.1 for rubella using an age-structured realistic model. The herd immunity threshold against rubella was calculated and came to 83.6%.

Evaluation metrics:

To assess herd immunity at the population level, two evaluation metrics were employed. These metrics focused on the seroprevalence data (and did not use vaccination coverage) because a substantial fraction of immune individuals, especially adults, acquired their immunity through a natural infection rather than through vaccination.

Results

Coverage under the routine immunisation programme that began in 1995 to raise herd immunity has been maintained well above 90%.

Overall, the seropositive proportion among adults increased over time from 2003 to 2013, except for those aged 20–24 and 45–49 years among males, and 20–29, 35–39 and 50–54 years among females

In 2013, the seropositive proportion among males was mostly below the prespecified herd immunity threshold, with the lowest values of 68% and 70% among those aged 35–39 and 20–24 years, respectively. Among females the seroprevalence in the majority of the age groups was greater than the herd immunity threshold in 2013, but in those aged 20– 24 years, the seropositive proportion was only 78.3%. To allow an explicit comparison between the herd immunity threshold and the observed representative value of the seropositive fraction, the age-standardised seronegative proportion, m1, was calculated as a function of time from 1983 to 2013. The results show that the estimate of seronegative fraction m1 in 1983 were 45.7% (95% CI 32.5% to 58.9%) and 35.6% (95% CI 31.2% to 40.0%) among males and females, respectively; the proportions decreased in 2013 to 18.3% (95% CI 16.8% to 19.8%) and 15.6% (95% CI 10.0% to 21.2%), respectively.

The seroprevalence by birth years found cohorts born from 1974 to 1978 and 1989 to 1993 at low seroprevalence levels. The comprehensively demonstrated an elevated age at infection with rubella and the presence of susceptible pockets. These two factors characterised the rubella epidemic in Japan from 2012 to 2014 (figure 2C).

Edmunds et al 2000

A mathematical model of the transmission dynamics of rubella virus to investigate the likely impact of different vaccination policies in Europe and explore if any of the current immunization programmes are likely to lead to perverse health outcomes As part of the European Sero-Epidemiological Network (ESEN) project 6 of the 8 participating countries (England and Wales, The Netherlands, Finland, Germany, Denmark and Italy) each tested at least 3400 serological samples for rubella antibodies

METHODS

The structure of the model: The model is a deterministic age-structured SEIR model (susceptible, exposed, infectious and recovered). It assumes that all hosts are in one of the following mutually exclusive epidemiological classes : infants protected by maternal antibody; susceptibles who have neither been infected nor vaccinated; vaccine failures, i.e. vaccinated but remaining susceptible ; latently infected individuals, who have been infected but are not yet infectious ; infectious individuals; and immune persons. Immunity can be gained via vaccination or via natural infection and is assumed to be permanent.

Parameter estimates and assumptions: The biological parameters, such as the average infectious period were estimated from the literature; the epidemiological parameters concerning were estimated from case notification or serological data; where these were available, or from vaccine coverage data were taken from official data.

The natural history of rubella and host demography: All individuals are assumed to be protected for exactly 180 days after birth (a step function is assumed). The average latent period and infectious period are assumed to be 10 and 11 days respectively

Transmission parameters: The pre-vaccination equilibrium force of infection was estimated from pre-vaccination case notification, or age-serological data from the individual countries and regions where this was available using standard techniques

Seroconversion rates and coverage data: In all cases it was assumed that 95% of vaccines seroconvert, developing life-long immunity

RESULTS

Comparison of model results to data: model output was compared to observed patterns of infection in an attempt to validate it.

Observed and predicted patterns of infection in different countries:

- in the countries which have maintained high rates of coverage, there is very little endemic circulation of virus. As the level of infant vaccination increases (in the absence of selective vaccination) there is an initial rise in the proportion of women expected to be infected during their at-risk years. If infant vaccination coverage is high enough then the decrease in incidence of infection is sufficiently large to result in fewer infections in adult women than occurred before immunization.
- Vaccination of schoolgirls has very little effect on the transmission dynamics as immunization occurs after a significant proportion of the population are already immune. Thus such programmes result in a roughly proportionate reduction in the risk of infection in adult women.
- The risk of women being infected is predicted to be higher in low transmission areas (such as Finland) than in higher transmission areas (such as the United Kingdom and

East Germany). This is because in low transmission areas a significant proportion of women are still susceptible on entering the childbearing age classes

- The higher the force of infection the greater the relative increase in CRS cases for low-intermediate levels of infant immunization, and the wider the range of coverage likely to lead to adverse public health effects. In high transmission areas (such as East Germany) vaccination of infants alone is expected to lead to an increase in cases of CRS for all levels of coverage up to 70±80%
- In these high transmission areas the level of infant immunization required to avoid causing more harm than good is close to the elimination (70%-87%)
- in high transmission areas, endemic circulation of rubella virus can be maintained even at levels of infant coverage above the elimination criterion (roughly 87%under East German parameter): importance of early vaccination if an infant programme is to be relied on to control rubella infection.

Limitations of the use of a deterministic age structured model to evaluate different vaccination: As stochastic (chance) effects are ignored the model is suited for use only in large populations where each of the subgroups (in practice the infectious and latent groups) are large.

Metcalf et al 2012

The article reports on a modelling study of 30-year CRS burdens across epidemiological and demographic settings, including the effect of local interruption of transmission via stochastic fadeout. The researchers focused their analyses on low-income countries, where rubella vaccination is rare. The research questions to explore CRS dynamics after introduction of vaccination across globally representative scenarios are: (i) when is 80%vaccine coverage of infants and young children sufficient to prevent increases in CRS incidence, and how sensitive is this to R0, seasonality, and birth rate? (ii) how is this 80%requirement altered by the addition of typical measles control immunization strategies [regular SIA ('follow-up') campaigns or a starting ('catch-up') campaign], or vaccination of women of childbearing age? and (iii) how will stochastic dynamics affect these conclusions, and what spatial scenarios are of particular concern?

Materials and Methods

The age-structured model was developed to quantify the effects of rubella vaccination in settings with different birth rates, basic reproduction numbers, and magnitudes of seasonal variation in transmission. The key element of the model is a matrix that at every time-step defines transition from every possible epidemiological stage (e.g. infected, susceptible, and recovered) and age combination to every other epidemiological stage and age combination. The population was stratified into 80 age groups (monthly strata up to age 4 years; yearly thereafter)

Exploring different vaccination strategies: outcomes considered for different immunization strategies included: (i) universal vaccination of infants and young children only (rarelyused alone, but serves as a baseline to be combined with other strategies) ; (ii) universal vaccination of infants and young children and regular SIAs ('follow up campaigns') targeting all children aged between 1 and 4 at 4-year intervals, starting in the fourth year after initiation of vaccination; (iii) universal vaccination of infants and young children, regular SIAs of 1- to 4-year-olds, and a starting ('catch-up') campaign in the first year of vaccination targeting 1- to 4-year-olds; (iv) the same, but with the starting campaign targeting 1- to 14-year-olds; and (v) the same, but with additionally a campaign targeting women of childbearing age (include both sexes to allow for vaccination of women only)

The range of demographic and epidemiological contexts: outcomes were explored for birth rates ranging from 12/1000 per year (e.g. European countries, China) to 50/1000 per year (Niger, at the upper end of the scale ; many African countries have lower birth rates) ; and for R0=6 (the average reported for rubella in Europe), R0=8 (at the high end of the scale reported for Europe) and R0=12 (reflecting the high end of the scale for estimates in Africa and Mexico; for seasonality, from 0 (no seasonality) to 0.6 (high, as estimated in Niger for measles [23

Results

CRS burden in a deterministic setting: The minimum level of coverage increases with birth rate and R0 and is reduced by implementation of SIAs or vaccination of women of childbearing age. Seasonality had little effect.

Requirements for implementing infant and young children immunization only: If R0=6, the yearly risk ratio remains <1 even for low vaccination coverage and thus coverage levels required to retain total CRS cases below pre-vaccination levels are low. If R0=12, after an initial 'honeymoon' period during which the risk ratio drops for insufficient coverage, the risk ratio may increase, i.e. more CRS cases are obtained under the vaccination programme than in the absence of vaccination; consequently, for birth rates >20/1000, coverage levels of >80% (and nearing 100% for birth rates of 30/1000 or higher) are required.

Requirements for implementing measles-like SIAs: Regular SIAs reduce routine coverage needed to see reductions in CRS relative to the pre-vaccination burden, since children missed by routine services may be vaccinated in the SIA. However, for high birth (>35/1000 per year) and reproductive (R0=12) rates, even with regular SIAs with coverage of 90%, at least 80% routine vaccination coverage is required (and more if SIA coverage is lower). Augmenting routine SIAs with a starting campaign extends the length of the honeymoon period, i.e. the time after the start of routine infant and young children vaccination before the susceptible population reaches the critical size for an epidemic. A greater age range in the starting campaign extends the reach of this effect e.g. vaccinating children up to age 14 years vs. up to age 4 years means that it takes 16 years rather than only 8 years before a

new birth cohort can build-up sufficiently to cause an outbreak in older children. Over time, the benefits of the starting vaccination campaign disappear as new susceptibles born after the starting vaccination campaign enter the at-risk age groups. Vaccinating women of childbearing age reduces the relative burden of CRS and the minimum level of coverage required in routine programmes.

Spatial dynamics in a stochastic environment e-g The CRS burden per 1000 live births predicted by a stochastic model that allows for local extinction/re-introduction: This outcome is variable: in some simulations, rubella becomes locally extinct, and by chance, the population never experiences the arrival of an infected immigrant, so that the total CRS burden can be lower than that obtained in the absence of vaccination of the neighboring location (city or country)

Overall results show that necessary minimum vaccination coverage increases markedly with birth and transmission rates, independent of amplitude of seasonal fluctuations in transmission. Susceptible build-up in older age groups following local stochastic extinction of rubella increased CRS burden, indicating that spatial context is important (heterogeneity in vaccination coverage). In low birth-rate settings, 80% routine coverage is a conservative guideline, particularly if supplemented with campaigns and vaccination of women of childbearing age. Where birth and transmission rates are high, immunization coverage must be well above 80% and campaigns may be needed.

Ang et al 2013.

In January 1990, the trivalent measles, mumps and rubella (MMR) vaccine was introduced into the Singapore childhood immunization programme with one dose of the vaccine given to children at age 12 months. Following a small resurgence of measles in 1992/1993 and a larger one in 1997, a ‘catch-up’ measles immunization programme for secondary and pre-university students aged 12–18 years, using the MMR vaccine, was implemented between July and November 1997, and a two-dose schedule (with the first dose given at between 1 and 2 years and the second dose at 11–12 years) was introduced in 1998. This study reports a national paediatric seroprevalence survey of measles, mumps and rubella (MMR) in Singapore aimed at assessing the impact of the national childhood immunization programme against these three diseases about two decades after introduction of the trivalent MMR vaccine.

Materials and Methods

The national paediatric seroprevalence survey (NPSS) was conducted between August 2008 and July 2010. Residual sera of Singapore citizens and permanent residents of the three major ethnic groups (Chinese, Malay, Indian) aged between 1 and 17 years attending inpatient services or day surgery were collected prospectively. Sera of children known to be immunocompromised, on immunosupressive therapy, or who had been diagnosed with infectious diseases such as measles, mumps, rubella, chickenpox, diphtheria, pertussis,

poliomyelitis, hepatitis B, dengue or hand, foot and mouth disease were excluded to minimize selection bias. A total of 1200 serum samples were collected, comprising 400 in each of the three age groups (1–6, 7–12, 13–17 years). The age-ethnic distribution of the subjects by gender is comparable to that of the Singapore resident population aged 1–17 years in 2009.
The IgG antibody against measles and mumps was determined using enzyme immunoassay. A titre > or equal to 250 mIU/ml was considered positive for measles, while a titre > or equal to 20 RU/ ml was considered positive for mumps. The rubella IgG antibody was measured using chemiluminescent immunoassay. Statistical analyses were performed using SPSS software with P values <0.05 were considered statistically significant.

Results

Seroprevalence of measles, mumps and rubella

Measles: The overall prevalence of antibody against measles in subjects aged 1–17 years was 83.1% The seroprevalence in adolescents aged 13–17 years (75.8%) was significantly lower than in the two younger age groups (P=0.005), while the seroprevalence in those aged 1–6 years (84.3%) was also significantly lower than in the 7–12 years group (89.3%) (P<0.05). There was no significant difference in seroprevalence by gender.

Mumps: The overall prevalence of antibody to mumps was 71.8%. Seroprevalence increased significantly with age from 61.5%in the 1–6 years group to 73.3% in the 7–12 years group and 80.5%in adolescents aged 13–17 years. No significant difference detected as far as gender is concerned.

Rubella: The overall prevalence of antibody against rubella was 88.5% (95% CI 86.6–90.2) (Table 4).
Seroprevalence was not significantly different in the three age groups: 1–6 years (87.3%), 7–12 years
(90.0%) and 13–17 years (88.3%). Seroprevalence increased from 59.4% in 1-year-olds to about 92.6% in children aged 2–14 years, followed by a dip to about 81.0%in adolescents aged 15–17 years. No significant difference by gender was observed.

Seroprevalence in subjects vaccinated against MMR

Of the 1200 subjects, 92.2% had received at least one dose of vaccine against measles, 91.7% against mumps and 91.8% against rubella, prior to the collection of their residual samples. The prevalence of antibody against MMR were all significantly higher in subjects with a past history of vaccination compared to those with an unknown or no history of vaccination (P<0.005). For measles, it was 86.5% vs. 42 . 6%; for mumps it was 75.3% vs. 33 . 0%; and for rubella it was

92.9% vs. 39. 4%. The post-vaccination seroprevalence of rubella was highest compared to measles and mumps. It
was between 88.8% and 99.3% within 9 years post-vaccination but declined to 78.4% at o10 years post-vaccination.

In summary, the overall prevalence of antibodies against measles, mumps and rubella was 83.1% [95% confidence interval (CI) 80.9–85.1], 71.8% (95% CI 69.1–74.2) and 88.5% (95% CI 86.6–90.2), respectively. For all three diseases, the lowest prevalence was in children aged 1 year (47.8–62.3%). The seroprevalence of the vaccinated children declined over time. The national MMR immunization programme is effective in raising the herd immunity of the childhood population, although certain age groups are more susceptible to infection, in particular, those who are not eligible for vaccination at age <15 months
About 8% of the subjects had not received any MMR vaccine prior to the collection of their residual samples. Of these subjects with an unknown or no history of vaccination, seroprevalence was 42.6%for measles, 33.0%for mumps and 39.4% for rubella. It is likely that they acquired the antibody by natural infection through close contact with other infected persons.

The overall prevalence of rubella IgG antibody in children and adolescents aged 1–17 years (88.5%) was above the threshold of 83–85% for herd immunity against rubella.

Limitation
The national paediatric seroprevalence survey is not representative of the childhood population in Singapore. It is based on laboratory based design instead of population-based sampling so as to ensure an adequate sample size, since population-based sampling is known to suffer from lower response rates due to parental concern about collecting blood samples from their children. However, national serosurveys using sera from diagnostic laboratories have been performed in other developed countries.

Metcalf et. al. 2013

Rubella vaccination has not been introduced into the public sector in South Africa, but incidence data are available via measles surveillance activities. The Authors used a uniquely detailed spatio-temporal dataset from South Africa to explore both the basic epidemiology of the infection, and the repercussions likely to follow the introduction of a rubella-containing vaccine, using recent measles coverage as a template. In addition to estimating rubella transmission rates and contact patterns, a key question addressed here is whether spatial variation in vaccine coverage (as reported in South Africa for measles) is likely to lead to increases in the CRS burden at either global or local scales. Specifically, they explore what spatial patterns of vaccination might inadvertently favour metapopulation rescue effects (i.e. re-introduction of the infection into districts where it has gone locally extinct) developing

methods to test for the effect of the link between connectivity, coverage and population size. They then assess whether observed measles coverage levels are likely to result in global or local increases in the CRS burden.

Materials and Methods

The data on laboratory-confirmed cases of rubella were obtained from the South African National Institute for Communicable
Diseases. Specimens were submitted as part of national, active, case-based measles surveillance. All serum specimens from suspected-measles cases were tested for the presence of rubella-specific immunoglobin antibodies, using an enzyme-linked immunosorbent assay.

District-level population sizes were obtained from Statistics South Africa and birth rates through adjusting census microdata on numbers of infants with subnational data on infant mortality rates.

To quantify spatial dynamics, they define a spatial coupling parameter that measures how tightly each region is linked to the metapopulation.

Using the magnitude of seasonality, and connectivity between locations, we developed a simulation model of rubella in South Africa. The key element of the model is a matrix that, at every time-step, defines transition from every possible epidemiological stage (e.g. infected, susceptible and recovered) and age combination to every other epidemiological stage and age combination, following methods developed in [26]. This was extended to also capture spatial dynamics where the number of immigrants was specified according to connectivity estimates described above.

To identify how spatial heterogeneity in vaccination might affect age-incidence for rubella, and consequently the CRS burden, authors generated vaccination profiles reflecting the same overall mean coverage.

To evaluate the prospects of introduction of rubella-containing vaccine in South Africa, they implemented vaccination scenarios reflecting actual reported coverage levels for measles across districts using the data described above. To be conservative, they considered only the first dose of measles containing vaccine, and did not model supplementary immunization campaigns.

Results

The data consist of weekly time-series of reported rubella incidence from 1998 to 2010, stratified by the 52 districts of South Africa. The dataset report on a total of 16 466 cases. The

country-wide median age of infection was 6 years (figure 1b), and within any single week the case numbers ranged from zero to 90 reported cases (figure 1a). Country-wide outbreaks follow a predominantly annual pattern, but local dynamics are more variable.

The estimated seasonal pattern of transmission reflects the timing of school holidays with low transmission during the school summer vacations in South Africa (usually around four weeks including the 25 December and 1 January). The model provides a good fit to the short-term dynamics of the infection.

The simulations of the observed coverage for South Africa indicate that if the current estimates reflect future coverage, the chances of an increase in the burden of CRS per 1000 live births across 30 years are relatively low. Even with coverage as low as 65% the CRS burden was reduced, via a range of sensitivity analyses. Repeating the analysis using a fitted WAIFW resulted in no increase in the CRS burden at the national scale, indicating robustness in the pattern of transmission over age.

Data available for South Africa shed light on basic aspects of rubella epidemiology but also highlight areas of consideration in a public health setting, including metapopulation-induced changes in age-incidence, which can lead to public health equity issues. Interestingly, the model predictions are broadly positive relative to the introduction of routine rubella vaccination in South Africa, despite the relatively low measles vaccine coverage levels explored, with possible relevance to a number of countries in the region. Model misspecification is always a risk, and key areas for future research include further detail on the age-transmission profile of rubella in developing and middle-income country settings.

Takeuchi et. al. 2014

The World Health Organization recommends 95% immunization to eliminate measles but only 80.7% of Japanese people of all ages had received immunization for measles in 2001. The government then launched a campaign with the theme “Give a measles vaccine as a first birthday gift!” in 2001. Nevertheless, Japan experienced measles outbreaks mainly among high school and college students in both 2006 and 2007. Therefore, a two-dose policy with a measles/rubella combined (MR) vaccine, requiring immunization at age 12–23 and at age 5–6 years was enforced in 2006. In addition, a catch-up campaign with MR vaccinations at age 12–13 years and at age 17–18 years has been carried out. This study sought to evaluate the efficacy of the catch-up campaign in detail.

Methods

This study was carried out as an analytical epidemiological study at a single institution. The 2008 and 2009 first-year students were invited to participate in the study. The questionnaire

included items on demographic characteristics and past medical history, including measles and rubella infection.

Titers of anti-measles and anti-rubella immunoglobulin (Ig) G antibodies were measured on enzyme immunoassay (EIA) and hemagglutination inhibition (HI) test. The cut-off levels of anti-measles and anti-rubella antibody titers were set at 6.0 IU/mL and 8 (dilution ratio of 1 : 8), respectively. An HI titer 8–10 corresponds to an EIA level of 15 IU/mL. During the research period, no incidence of measles or rubella was reported on campus.

Vaccine coverage, antibody titer levels and the prevalences of seropositivity for measles and rubella were compared between the two groups: the the target age group and the non-target age group All tests of significance were two-tailed, and $P < 0.05$ was considered statistically significant. Statistical analysis was done with STATA 10.0

Results
A history of two or more rubella vaccinations in the target age group was significantly more frequent than in the non-target age group (54.9% vs. 13.2%, $P < 0.001$).

The prevalence of seropositivity against measles was significantly higher among the target age group than the non-target age group (98.9% vs. 91.0%, $P = 0.001$)

The prevalence of seropositivity against rubella was significantly higher among the students in the target age group than in the non-target age group (97.8% vs. 87.5%, $P < 0.001$).

Bechini et al 2012

In order to evaluate the impact of the immunization campaigns performed in Tuscany during 2004 and 2005 in school-aged children (7–14 years), and to establish the susceptibility of the Tuscan population, a seroepidemiological survey was planned for both measles and rubella infections. A previous survey, carried out in Tuscany in 2003 (before the implementation of the NPMCRE) was compared with the 2006 survey.

Methods
Serum samples belonged to a population aged 1–49 years and were stratified into the following age groups: 1, 2–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–39 and 40–49 years. Results of the 2006 survey on measles antibodies, were compared with those of a previous survey conducted in Tuscany in 2003 (before the implementation of the NPMCRE), on a total of 552 serum samples (279 males, 273 females, age range 1–49 years, corresponding to 0.3% of the resident Tuscan population at 1 January 2004) collected from the same two hospitals, using the same sample selection criteria and the same detection kits. Results were also

compared with available national data. For rubella antibodies, the 2006 Tuscan serosurvey was compared only with the available national data.

Results

The results of the seroepidemiological survey for rubella antibodies detection showed a total seropositivity of 90.6%; considering only the female sample, this percentage increased to 92.8%. In all age groups, the seroprevalence of rubella antibodies was >80%, except for the sera of 1-year-old subjects. The WHO-Euro threshold for the elimination of congenital rubella (5%) was exceeded in all women aged 15–29 years. On the other hand, in the age group 30–39 years, the desired threshold was almost achieved (6.4%); only in the last age group (40–49 years), the percentage of susceptible women resulted under the WHO-Euro threshold (4.5%).

The results of the 2006 seroepidemiological survey for measles antibodies detection showed a total seropositivity of 84.3%, and no statistically significant differences were observed between genders. A comparison between seronegative samples found in both Tuscan serosurveys of 2003 and 2005–06 is shown. No statistical significant differences were found between the two surveys comparing the age groups, except for the age group 2–4 years.
The survey shows that percentages of susceptible fertile women are still too high to reach CRS elimination. As a matter of fact, the WHO-Euro threshold of susceptibility (5%) was exceeded in all females up to 29 years (range: 10–13% seronegative).

iv. Vaccine characteristics

a) Available presentations and formulations of monovalent Measles vaccine and MR vaccine?

Table 6: Available Formulations of monovalent Measles vaccine and MR vaccine

	Presentation	Formulation	Storage
Measles Vaccine.. [WHO 2009		Monovalent or combination (MCV) with rubella, mumps or varicella vaccines, or some combination of these Each dose of 0.5 ml (monovalent or MCV) contains ≥1000 viral infective units of the vaccine strain; may also contain sorbitol, hydrolysed gelatin as stabilizers, small amount of neomycin, but it does not contain thiomersal	After reconstitution, the vaccine must be stored in the dark at 2–8 °C and used within 6 hours. Reconstituted measles vaccine loses about 50% of its potency after 1 hour at 20 °C; it loses almost all potency after 1 hour at 37 °C The vaccine is also sensitive to sunlight,

	Presentation	Formulation	Storage
Manufacturers SERUM INSTITUTE OF INDIA LTD.	1 Dose vial plus diluent (0.5 ml) 2 Dose vial plus diluent (1 ml) 5 Dose vial plus diluent (2.5 ml) 10 Dose vial plus diluent (5 ml)	The vaccine is lyophilized and is provided with diluent. The product has the appearance of a yellowish-white dry cake. Each sidose when reconstituted in a volume of 0.5 ml contains not less than 1000 CCID50 of measles virus and 1000 CCID of rubella virus.	It is important to protect both the freeze-dried and reconstituted vaccine from the light. The vaccine should be stored in the dark at a temperature between 2-8ºC. If the vaccine is not used immediately then it should be stored in the dark at 2-8ºC for no longer than 6 hours
Rubella vaccine [WHO 2011		monovalent formulations or in combinations with other vaccine viruses, as RCVs, against measles (MR), measles and mumps (MMR), or measles, mumps and varicella (MMRV) Each dose of an RCV contains a defined number of infectious units (≥1000 PFU or CCID)	For monovalent rubella, MR and MMR formulations, the vaccine should be stored at +2°C to +8°C, and be protected from light

b) Recommended form of administration and dosage for monovalent Measles vaccine and MR vaccine?

Measles vaccine is generally injected subcutaneously, but it is also effective when administered intramuscularly. (WHO 2009)

An RCV is normally administered as a subcutaneous injection (but may also be given intramuscularly). (WHO 2011)

Ensure that the vaccine is administered by subcutaneous route only. A single dose of 0.5 ml should be administered by deep subcutaneous injection into the anterolateral aspect of upper thigh in toddlers and upper arm in older children (SERUM INSTITUTE OF INDIA LTD Manufacturers insert).

c) Recommended schedule for monovalent Measles vaccine and MR Vaccine in the second year of life?

Measles vaccine: Since primary vaccination failure occurs in up to 10–15% of infants vaccinated at age 9 months, the strategy is to offer 2 doses of measles Vaccine (routine 2-dose schedule when routine programmes are strong or supplementary immunization activities (SIAs) where health systems are weak). Countries with ongoing measles transmission and MCV1 delivered at age 9

months should administer the routine dose of MCV2 at age 15–18 months. The minimum interval between MCV1 and MCV2 is 1 month. In countries with low measles transmission and where MCV1 is administered at age 12 months, the optimal age for delivering routine MCV2 is based on programmatic considerations that achieve the highest coverage of MCV2(WHO 2009)

Rubella vaccine: usually at age 12–15 months, but it can also be administered to children aged 9–11 months. If given as MR the age of administration first dose is usually given 9 months or 12–15 months and a second dose at 15–18 months or 4–6 years (WHO 2011)

d) Logistical and cold chain requirements:
   - Logistical and cold chain requirements for the EPI when introducing a second dose of monovalent Measles vaccine in the second year of life?
   - Logistical and cold chain requirements for the EPI when introducing MR vaccine at 9 months and in the 2nd year of life?

UNICEF website :https://www.unicef.org/supply/files/Measles-Containing_Vaccines_(MCV)_Supply_Update.pdf

Table 6: Manufacturers with WHO Prequalified MCV

Vaccine	Manufacturer	WHO Prequal.	Formul.	Sched.	Vial	Shelf Life	Cold Chain Capacity / ds
MV	Bio Farma (Indonesia)	1997	Lyophilised	2 ds	10 ds	24 months	1.3 cm³
		2006	Lyophilised	2 ds	20 ds	24 months	0.75 cm³
	GPO-MBP (Thailand)	2010	Lyophilised	2 ds	10 ds	36 months	2.13 cm³
	Sanofi Pasteur (France)	2002	Lyophilised	2 ds	10 ds	36 months	2.46 cm³
	Serum Institute of India Ltd	1993	Lyophilised	2 ds	1 ds	24 months	26.11 cm³
		1993	Lyophilised	2 ds	2 ds	24 months	13.1 cm³
		1993	Lyophilised	2 ds	5 ds	24 months	5.22 cm³
		1993	Lyophilised	2 ds	10 ds	24 months	2.611 cm³
MR	Serum Institute of India Ltd	2000	Lyophilised	1 ds	1 ds	24 months	26.11 cm³
		2000	Lyophilised	1 ds	2 ds	24 months	13.1 cm³
		2000	Lyophilised	1 ds	5 ds	24 months	5.22 cm³
		2000	Lyophilised	1 ds	10 ds	24 months	2.611 cm³
MMR	GlaxoSmithKline (Belgium)	2001	Lyophilised	1 ds	1 ds	24 months	9.6 cm³
		2011	Lyophilised	1 ds	2 ds	24 months	4.8 cm³
	Merck (USA)	2009	Lyophilised	1 ds	1 ds	24 months	15 cm³
	Sanofi Pasteur (France)	2002	Lyophilised	1 ds	1 ds	24 months	12.66 cm³
		2002	Lyophilised	1 ds	10 ds	24 months	2.46 cm³
	Serum Institute of India Ltd	2003	Lyophilised	1 ds	1 ds	24 months	26.11 cm³
		2003	Lyophilised	1 ds	2 ds	24 months	13.1 cm³
		2003	Lyophilised	1 ds	5 ds	24 months	5.22 cm³
		2003	Lyophilised	1 ds	10 ds	24 months	2.611 cm³

Source: WHO.

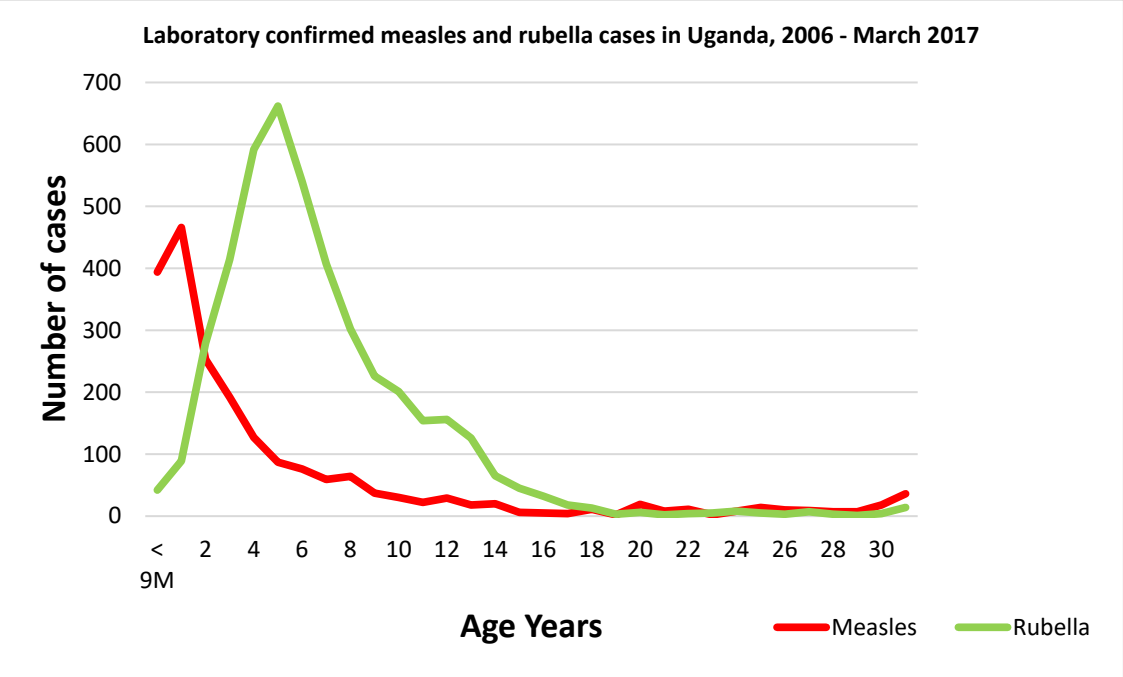
https://extranet.who.int/gavi/PQ_Web/

2. The disease

i. Burden of disease

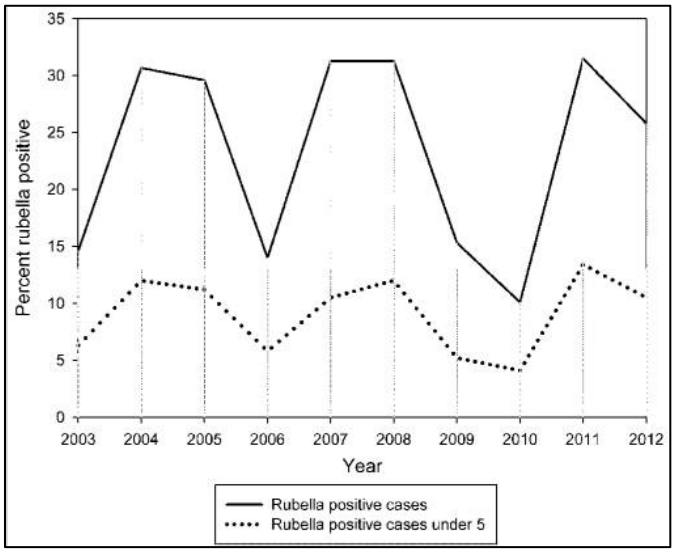
a) Current age specific incidence of Measles infection in Uganda (with 1st dose of Measles vaccine part of routine)?

b) Current age specific incidence of Rubella infection in Uganda?



Source: Autthor Generated using figures from Uganda Virus Research Institute database

Figure 6: Laboratory confirmed measles and rubella cases in Uganda by age, 2006-March 2017



Source: Namuwulya et al 2014

Figure 7: Precentage of Rubella positive cases in under 5s in Uganda 2003-2012

Fig 7: Percentage of serum samples collected for measles surveillance purposes in Uganda that tested positive for Rubella IgM by year of collection.

c) Current incidence of CRS in Uganda

A report from the WHO Measles Ruella Technical Adviosry Group meeting held in Nairobi in June 2015 had the following report on the incidence of CRS in the AFRO region

Tablex 6: Results from CRS sentinel surveillance sites.

Country	Total cases in data-base	Median age in months, range (% 1 year +)	Sex n	IgM result available n
Senegal	11	0, 0-15 (10%)	M 4 (36%) F 7 (64%)	11 (100%)
Tanzania	55	5, 0-10 (0%)	M 25 (46%) F 30 (54%)	53 (98%)
Togo	42	3.5, 0-20 (14%)	M 17 (40%) F 25 (60%)	42 (100%)
Uganda	6	8, 1-21 (33%)	M 3 (50%) F 3 (50%)	6 (100%)
Zambia	30	9, 0-80 (40%)	M 7 (23%) F 23 (77%)	10 (33%), pending
Zimbabwe	109	0, 0-23 (4%)	M 65 (60%) F 43 (40%)	107 (98%)
Total	**242**	**2, 0-80 (10%)**	**M 117 (49%) F 124 (51%)**	**225 (93%)**

Of the 6 Uganda cases 4 were less than 1 year old, 3 of whom had clinically confirmed CRS, and 1 laboratory confirmed. Of the total cases, 73% had congenital heart disease, 61% had cataracts, 12% had glaucoma, , 7% had hearing loss and 20% had pigmentary retinopathy.

Measles Rubella Initiaitive website.
http://webcache.googleusercontent.com/search?q=cache:_aDr4fqInvoJ:www.measlesrubellainitiative.org/wp-content/uploads/2015/07/01.-CRS-surveillance-in-AFR-lessons-learned-Nairobi-TAG-June-2-3-2015_June-2.pptx+&cd=6&hl=en&ct=clnk&client=firefox-b

Bukenya 2014

Objective: This study was conducted to establish the rubella sero-prevalence among pregnant women attending antenatal clinic at Mulago national Referral Hospital.

Methods: Between June and July 2014, a cross-sectional study was conducted among 626 pregnant women selected randomly from those attending antenatal clinic at Mulago National Referral Hospital. Their socio-demographic, socio-economic and clinical data was collected on standard questionnaire and 5mls of blood drawn and tested for both

rubella IgM and IgG using SIEMENS ELISA Kit. Rubella IgG titers were calculated and titers ≥15IU/mL were considered protective. Knowledge of rubella infection among pregnant women and associated consequences were also determined. Binary logistic regression and multivariate analyses were performed to determine factors associated with rubella infection using STATA version 10. Factors associated with rubella infection were determined based on Odds ratios at 95% CI and statistical significance of a P-value ≤0.05.

Results: None of the pregnant women was found with acute rubella infection (ie IgM positive). A total of 598(95.5%) tested positive for rubella IgG (ie past exposure). Of these, 569(95.15%) had attained protective levels of IgG antibodies. Overall rubella susceptibility (exposed and non-exposed) was found among 57(9.1%) pregnant women. Decreasing age below 24 years was found to be associated with reduced susceptibility to rubella infection and this was statistically significant in a multivariate analysis (OR=2.35, 95% CI= 1.01 – 5.50, P=0.048). Rubella and its associated consequences among pregnant women were very low and only known to only 13(2.1%).

Conclusion: Rubella IgG sero-prevalence among pregnant women attending antenatal care at Mulago National Referral Hospital is high and this is all presumed to be from natural infection. However, the proportion of susceptible women remains significant and this poses a risk of giving birth to babies with CRS. It was also noted that awareness on rubella infection is very low

d) Frequency of Measles infection outbreaks in Uganda (with 1st dose in routine)?

Baliraine et al 2011.

Since the inception of Uganda's 2002–2006 accelerated measles control strategic plan, the number of measles cases in the country declined dramatically (Figure 1). After the 2003 campaign, virtually no cases of measles occurred in Uganda for 3 years, until the outbreaks in 2006. Data show that 819 (78%) of 1,053 of the serologically confirmed measles cases for the 4-year surveillance period occurred during the 2006 outbreaks (Figure 1), confirming that the strategic interventions quickly subdued the 2006 transmission cycles. Moreover, the pattern of measles genotypes detected from 2000–2009 (2006–2009 reported in this study) suggests that transmission of the previously endemic genotype D10 in Uganda had been interrupted and replaced by genotype B3.1.

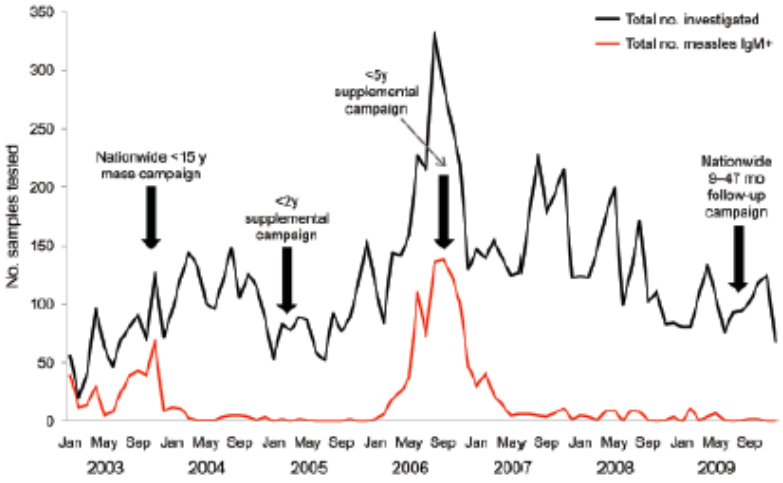
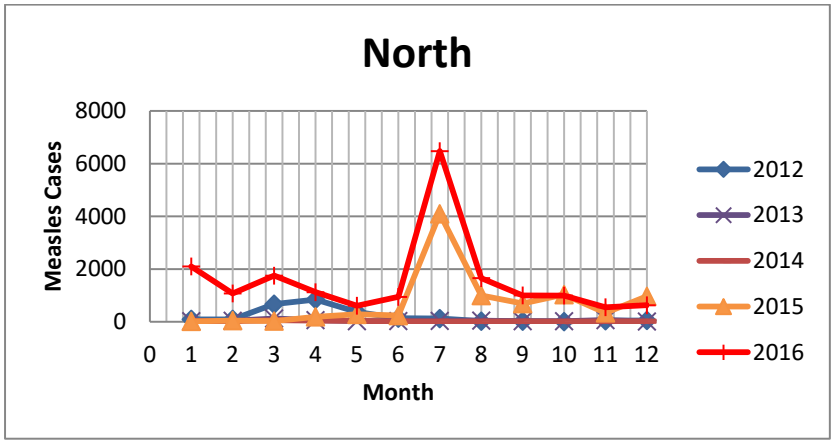
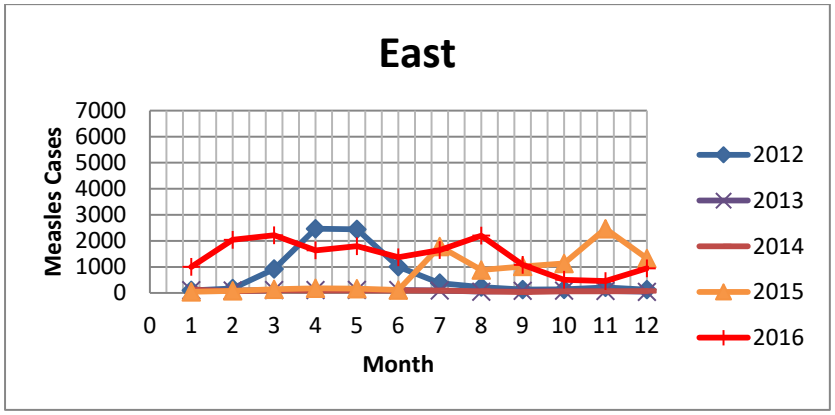


Fig 8: Laboratory confirmed measles cases in Uganda 2006- 2009. Data from the accelerated measles control period 2003-2005 are included for comparison. The surge in measles cases during 2006 was caused by a resumption of measles outbreaks after a 3 year lag period, due to accumulated number of susceptible persons.

Source: Baliraine et al 2011.

Measles cases by region as reported in eHMIS 2012-2016





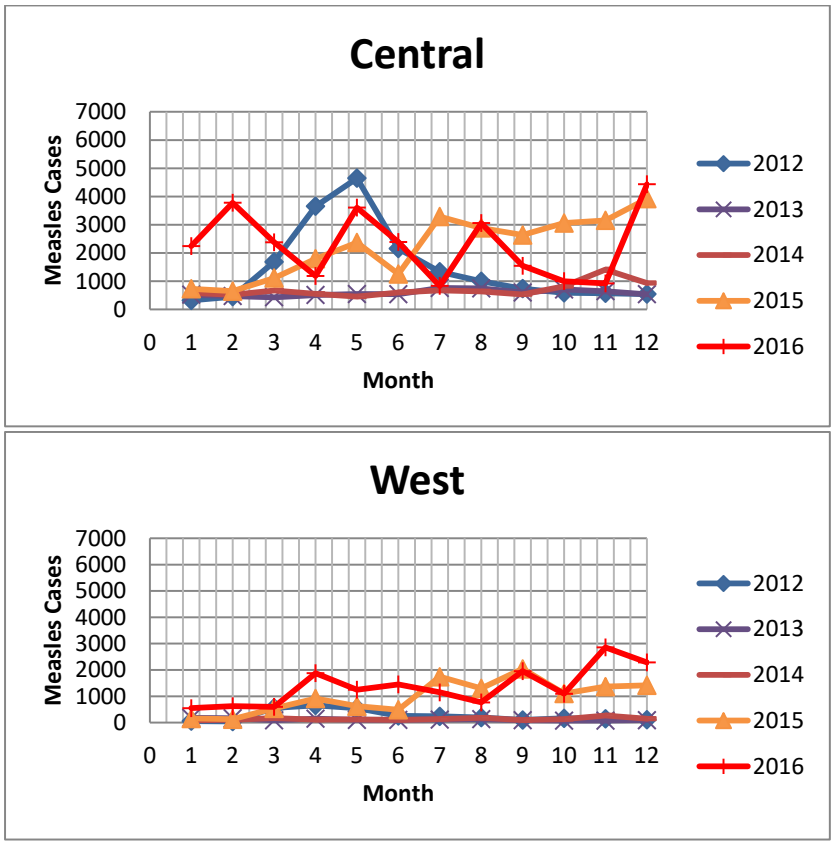


Figure 9: Measles cases by region as reported in eHMIS 2012-2016
Source: Author genrated using data from Minsitry of Health, eHMIS database

e) Frequency of Rubella infection outbreaks in Uganda?
No data found

ii. Clinical characteristics of the disease

a) Signs and symptoms of Rubella infection and CRS?

✓ Rubella Apart from the congenital infection, rubella is a mild self-limited illness that usually occurs during childhood. Its public health importance is due mainly to the teratogenic potential of the virus. Rubella infection occurring just before conception and during early pregnancy may result in miscarriage, fetal death, or congenital defects known as congenital rubella syndrome (CRS). (WHO 2011)

b) Severe forms of Rubella infection and CRS?

✓ Serological studies have shown that 20–50% of all rubella infections occur without a rash, or are subclinical. Severe manifestations (Haemorrhagi manifestations and Guillain–Barré syndrome) are rare. The defects associated with CRS are: ophthalmic, auditory, cardiac and craniofacial. The complications of thrombocytopenia can be fatal. (WHO 2011)

c) Long term complications of Rubella infection and CRS?

- ✓ Those that survive the neonatal period may face serious developmental disabilities and have an increased risk for developmental delay, including autism, type I diabetes mellitus and thyroiditis. [WHO Position Paper29, 2011, 86, 301–316/ Medical literature]

-At 50 years, 5 of 40 patients (12.5 percent) were diabetic; at 60 years, the prevalence of type 2 diabetes (22 percent), thyroid disorders (19 percent), early menopause (73 percent), and osteoporosis (12.5 percent) was increased compared with the Australian population.

d) Medical management of Rubella infection and CRS?
There is no specific treatment for rubella but the disease is preventable by vaccination.
[WHO Position Paper29, 2011, 86, 301–316

iii. Use and cost of health care

a) With 1st dose of Measles vaccine already part of routine immunization are there any physical and economic implications to the current primary/secondary/tertiary health care systems of a Measles infection in Uganda?

In 2001, the World Health Organization (WHO) estimated that about 30 million cases and over 700 000 deaths from measles occur annually in developing countries. Most deaths follow complications such as pneumonia, croup and diarrhoea, and are also frequently associated with malnutrition. In addition, measles may result in long-term health problems including blindness, deafness, chronic lung disease, poor growth and recurrent infections.
There is no specific treatment for measle; Vitamin A combined with standard management to relieve symptoms is recommended, which may be outpatient for mild cases and hospitalization for severe cases.
http://www.who.int/immunization/programmes_systems/interventions/TreatingMeaslesENG300.pdf

b) Physical and economic implications to the primary/secondary/tertiary health care systems of Rubella infection and CRS in Uganda?

https://www.uptodate.com/contents/congenital-rubella-syndrome-management-outcome-and-prevention

A long tern study in Australia documented the following impacts of rubella infection:

Short-term — the risk of mortality is increased in neonates with severe defects (eg, extreme prematurity, extensive meningoencephalitis, gross cardiac lesions or myocarditis with early heart failure, fulminant interstitial pneumonitis, and rapidly progressive hepatitis). In the original case series, the mortality rate among symptomatic infants was approximately 20 percent.

Long-term — Long-term follow-up (at 25, 50, and 60 years) of a cohort of 50 patients born during the 1939-1943 rubella epidemic in Australia provides the following information about long-term outcome:

-At 25 years, 48 of 50 patients were deaf, 43 of the 48 had severe bilateral deafness, and hearing impairment was detected in all patients by seven years of age, in most patients by three years of age, but in only five patients by one year of age.

-At 25 years, 11 patients had congenital cardiovascular defects (patent ductus arteriosus, pulmonary stenosis, and elevated systemic blood pressure); only two of these were detected in the first year of life. At 60 years, 21 of 32 patients had mild aortic valve sclerosis on echocardiography, and 12 were being treated for hypertension.

-At 25 years, 26 of 50 patients had typical rubella cataracts or chorioretinopathy; at 60 years, virtually all 32 patients had ocular conditions: rubella retinopathy (12), glaucoma (8), cataracts with onset between the 50- and 60-year follow-up (3), blindness (1), and other ocular conditions (8).

-At 25 years, 50 percent of patients were below the 10th percentile for weight and/or height; at 50 years, 6 of 40 patients (15 percent) were below the 3rd percentile for height.

iv. Regional and international considerations

c) Current global recommendations on the elimination of Measles and Rubella infections?

- ✓ In 2010, WHO committed to the Gloabal Measles and Rubella Strategic Plan 2012 – 2010 with the targets to reduce global measles mortality by at least 95% compared with 2000 estimates by end 2015, and achieve measles and rubella elimination in at least five WHO regions by end 2020.
  Measles Rubella Initiaitve website. http://www.measlesrubellainitiative.org/wp-content/uploads/2013/06/Measles-Rubella-Strategic-Plan.pdf

- ✓ Population immunity needs to be >93–95% in all districts to prevent measles epidemics.

The coverage targets depend on national goals for disease control. In countries aiming at reducing mortality from measles, immunization coverage should be ≥90% at the national level and ≥80% in each district. Countries aiming at measles elimination should achieve ≥95% coverage with both doses in every district.

- ✓ Experience in the Region of the Americas has shown that measles elimination can be achieved through high coverage of MCV1 and the use of regular, high-quality SIAs. Hence, adding routine administration of MCV2 is not necessary to interrupt measles transmission. Nevertheless, a country may decide to add MCV2 to their routine schedule (while continuing SIAs) for one or more of the following reasons: (i) to slow the accumulation of susceptible children and thereby allow a lengthening of the interval between SIAs; (ii) to decrease the country's reliance on SIAs and eventually stop SIAs once high population immunity (>93%) can be maintained with a routine 2-dose schedule alone; and (iii) to establish a well-child visit during the second year of life to maximize linkages with other routine doses (for example, the diphtheria–tetanus–pertussis vaccine [DTP] booster) as well as with other health interventions such as deworming, delivering mosquito nets or administering vitamin A.
- ✓ Before introducing routine delivery of MCV2, countries should determine a suitable age for administering this dose, establish a system for recording doses both for the individual (for example, with an immunization card) and the health system (for example, with a vaccination register), and train health staff to ensure the timely scheduling of doses and tracking of those who are missed.

(WHO 2009)

3. Economic and operational considerations

i. Vaccine related cost and resource use

a) Cost per child of administering 2 doses of monovalent Measles vaccine at 9 months and in the 2nd year of life / Cost per child of administering a single dose of monovalent Measles vaccine at 9 months followed by a single dose of MR in the 2nd year of life / Cost per child of administering 2 doses of MR vaccine at 9 months and in the 2nd year of life?

It is estimated to cost $2 to fully immunise a child against measles and rubella. Measles Rubella Initiative website: http://measlesrubellainitiative.org/learn/the-solution/

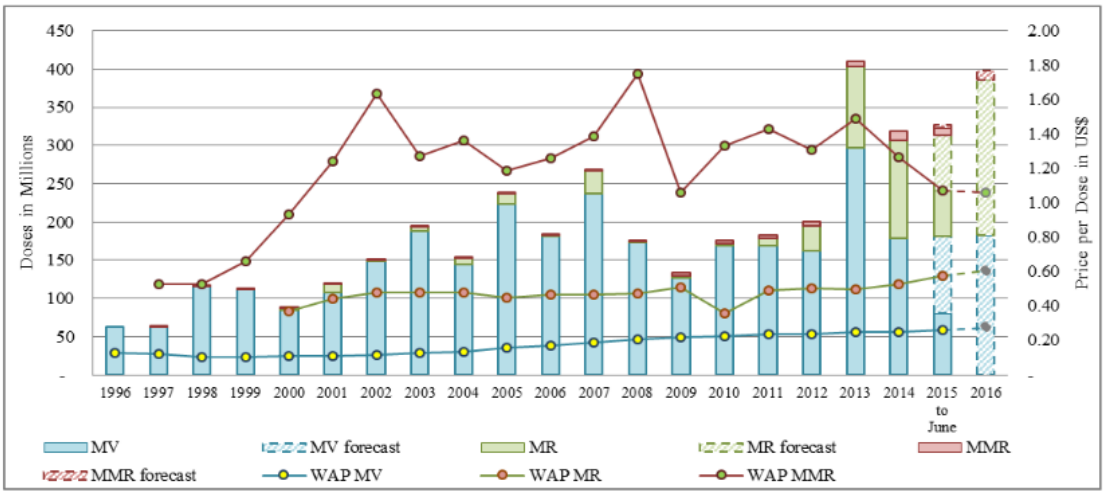
A rough estimate conducted by Healthnet Consult put the cost of introducing 2 doses of MR in Uganda's routine schedule between 2017-2021 at $3.8-4.6 million. (Healthnet Consult 2017).

b) Cost of educating the public and training health care workers when introducing monovalent Measles vaccine in the 2nd year of life / when introducing MR vaccine in children under 2 years of age?

Based on the recent immunisation costing study (WHO 2016), training costs vary by vaccine, with HPV introduction, training costs accounted for 19% of the total financial costs while with PCV introduction, training accounted for only 1.9% of the total financial costs.

ii. Vaccine availability

a) International production/stock of monovalent Measles vaccine with reliable long term supply / of MR vaccine for either single or two doses?
UNICEF website:
https://www.unicef.org/supply/files/Measles_Containing_Vaccines_Supply_Update_July_2015.pdf



Source: UNICEF Supply Division.

Figure 10: MCV Supply through UNICEF and demand forecast 1996-2016

b) Distributors currently supplying monovalent Measles vaccine to Uganda and price / Supplying MR vaccine and price?
UNICEF website :
https://www.unicef.org/supply/files/Measles_Containing_Vaccines_Supply_Update_July_2015.pdf
The latest market update on UNICEF website is dated July 2015, with forecasts to 2016.

For MV vaccine: 2015 year-to-date(June) estimated MV vaccine requirements could reach up to ~180million doses in response to routine country demand, outbreak

response, and supplementary immunization activities(SIAs). An additional 114.6 million doses were awarded in January 2015 to increase supply from an initial 65 million doses of MV vaccine to meet these requirements. In anticipation of 2016-forecast country demand, UNICEF made separate additional awards of 100 million doses of MV vaccine in March2015, increasing secured supply to 145million doses from an initial 45million doses for next year.MV vaccine production capacity is sufficient to meet forecasted demand, but is vulnerable with one manufacturer producing~90% of supply. This manufacturer also produces the only WHO prequalified MR vaccine.

For MR vaccine: UNICEF anticipates 2015year-to-date (June) MR vaccine country requirements to reach 131 milliondoses. Althoughannual supply awarded through UNICEF is sufficient to meet current forecasted demand, UNICEF will work with the manufacturer and countries to ensure that vaccine delivery schedules are accelerated to meet the programmatic requirements.

For MMR vaccine: UNICEF anticipates 2015 year-to-date (June) MMR vaccine country requirements to reach almost 15 million doses. UNICEF awarded an additional 7.2 million doses of MMR vaccine in January 2015 (across Leningrad-Zagreb and Jeryl-Lynn strains); doubling supply from an initial 7 million doses to 14.2million doses to meet country requirements. Whereas MMR vaccine supply containing a Leningrad-Zagreb mumps strains is available in sufficient quantities to meet current forecasted country demand, as of 2014, MMR vaccine containing an Urabe mumps strain is no longer being produced. There is imited availability of the MMR vaccine with a Jeryl-Lynn mumps strain, and is only offered to countries that previously procure this vaccine through UNICEF.

iii. Vaccine affordability

a) Annual fiscal implications to the government of introducing 2nd dose of monovalent Measles vaccine into routine immunization i.e. in the 2nd year of life?

Based on the costs of PCV introduction, vaccine purchase takes up approx. 90% of the total financial cost of new vaccine introduction (WHO 2016).

The WHO 2017 Immunisation financial sustainability study put the total cost of introducing Rota and MR into Uganda's routine Immunisation program at $ 802.6 Million.

b) Annual fiscal implications to the government of introducing 1 dose of MR vaccine into routine immunization in the 2nd year of life?

MR (10 dose vial) costs approx. three times ($0.61-0.64 cost per dose) the cost of Monovalent measles ($0.24-0.28per dose), and MMR about 5 times the cost ($1.13 per dose).(UNICEF website: https://www.unicef.org/supply/files/Measles_Containing_Vaccines_Supply_Update_July_2015.pdf)

c) Annual fiscal implications to the government of introducing 2 doses of MR vaccine into routine immunization i.e. at 9 months and in the 2nd year of life?

Gavi provides support for large-scale catch-up campaigns with the measles-rubella (MR) vaccine. This is done on the basis that countries then self-finance routine introductions of the vaccine.
(Gavi website : http://www.gavi.org/support/nvs/measles-rubella/)

Uganda is listed among the priority countries to recieve support from the Measles Rubella Initiative (a joint effort of he American Red Cross, United States Centers for Disease Control and Prevention, United Nations Children's Fund, United Nations Foundation and World Health Organization aimed at supporting the goal of reducing global measles mortality by 95 percent by 2015 and eliminating measles and rubella in at least five of the six World Health Organization Regions by 2020) which in addition to financial support, provides the following types of support

- ✓ Advocacy with countries and international partners to fully fund and implement the Measles Rubella Strategic Plan 2012-2020, in close collaboration with child survival initiatives.
- ✓ Technical support to governments and communities in priority countries:

- to improve markedly coverage with the first and second doses of measles- and rubella-containing vaccines, delivered through either routine immunization or SIAs;
-to document and share best practices in conducting measles SIAs and in using SIAs to strengthen routine vaccination;
- to improve the quality of data used for monitoring and evaluating vaccine coverage and disease incidence;
- to expand and enhance the quality of measles and rubella surveillance and the LabNet;
-to provide appropriate measles case treatment.

- ✓ Assistance to enable countries to respond rapidly to measles outbreaks, and advocacy for a special outbreak emergency fund.
- ✓ Support to operational research needed to address the challenges and achieve the goals of the Measles Rubella Strategic Plan.
- ✓ Monitoring and evaluation of progress in implementing the Strategic Plan annually, and communication of progress and challenges to all stakeholders.

✓ Close collaboration with eligible countries and partners, including the GAVI Alliance:

- to facilitate applications for measles second dose and rubella vaccine support;
- to provide technical support to countries to plan for and introduce MR in campaigns and routine immunization;
- to monitor and evaluate progress in the introduction of measles second dose through routine services and RCV in eligible countries;
-to identify areas requiring partner support.

(Measles Rubella Initiative website. http://measlesrubellainitiative.org/wp-content/uploads/2017/01/Measles-Rubella-Strategic-Plan.pdf)

d) Prevailing price of Measles vaccine being obtained through current supplier? Estimated price of Measles vaccine purchased through other suppliers?

While prices vary between MV, MR and MMR vaccines, all low-and middle-income countries procuring MCV through UNICEF access these vaccines at the same prices irrespective of their per capita income levels, and regardless of the Gavi -eligibility status.

Table 7: WAP Measles Vaccine prices: https://www.unicef.org/supply/files

	Manufacturer	**Price per dose USD**
Monovalent Measles		
10 dose vial	P.T Bio Farnma	0.2370
10 dose Vial	Serum Institute of India	0.2790
MMR		
1 dose vial	Norvatis Vaccines and Diagnosis	2.3700
2 dose vial	GSK	3.2500
5 dose vial	Serum Institute India	1.1460
10 dose vial	Serum Institute India	1.1300
MR		
10 dose vial	Serum Institute India	0.606-0.644 (based on delivery terms)

Source : UNICEF website : https://www.unicef.org/supply/files/Measles_Containing_Vaccines_Supply_Update_July_2015.pdf

iv. Socio economic and social impact

a) Indirect economic and qualitative costs to the family with a Rubella/CRS patient? Productivity losses to a patient with Rubella/CRS?

v. Economic impact on the immunization programme

a) Potential reductions in healthcare costs if Measles or Measles-Rubella is eliminated in Uganda?

b) Cost benefit of Measles only elimination versus Measles Rubella elimination to the EPI / Cost benefit of CRS elimination versus Rubella elimination to the EPI?

MEASLES

Tulchinsky et al, 1993

Objective: The aim of this report was to provide the experience of some developed and developing countries in using two doses of measles, and also includes cost-benefit studies.

Methodology:
Measles incidence data were examined as reported to the WHO European Regional Office, the Centers for Disease Control in Atlanta (USA), the Laboratory for Disease Control in Ottawa (Canada), the Govemment Health Services in Judea/Samaria (West Bank) and Gaza, and the Department of Epidemiology of the Ministry of Health of Israel. The authors also examined published data for the Ministries of Health of the Philippines, Nigeria, and Malawi, and data assembled by UNICEF on population, mortality and immunization coverage. No further information on the data-analysis was carried out.

Results:
Previous cost-benefit studies of measles vaccination were related to a single dose and found high benefit-to-cost ratios. The authors carried out a cost-benefit analysis by comparing the existing single-dose vaccination programme at 15 months to a two-dose programme, with the second dose at age 6 years, for Israel, the West Bank and Gaza. The benefit-to-cost ratios were 4.5/1 in Israel, 5.7/1 in the West Bank, and 9.6/1 in Gaza.
By adjusting the models' parameters to the new vaccine cost of $ 0.42 per dose in 10-ml vials, and adding $ 0.70 per inoculation for the labour costs of giving the vaccination in a school setting, they estimated the break-even incidence rate (where the benefits to society equal the costs to society) of measles to be 3.5 cases per 100 000 population. Considering direct benefits and costs to the health services alone, the break-even incidence rate is approximately 9 per 100 000.
Higher benefit-to-cost ratios than those found in Israel would be expected in those countries which have higher incidence rates, whether due to higher vaccine failure rates, or for other reasons. The cost benefit findings from the West Bank and Gaza are more like those relating to developing countries, with lower hospital-bed-to-population ratios, but where, as in the case of Malawi, Nigeria and the Philippines, measles is a predominant cause of hospitalization

of children. The benefits from reductions in outpatient services (including medication) may be far lower in developing countries, owing to poor access to such services. However, this reduced benefit may be compensated for by the vaccination having a greater impact in terms of greater reduction in mortality.

RUBELLA

Babigumira et al 2013

Objective: The authors present findings of an updated review of economic analyses of rubella and rubella vaccination. They examined the evidence on costs of rubella and CRS, the cost-effectiveness of adding RCV to national immunization programs, and the cost-effectiveness of different policy strategies that might be employed to add RCV to national childhood immunization schedules. Their aim was to examine the economic evidence base, assess differences in findings by country income levels, identify gaps in the evidence, and propose potential areas of future enquiry into the economics of rubella and rubella vaccination.

Methodology:
The authors reviewed studies published in English on the costs and resource use for rubella and CRS and the costs, cost-effectiveness or cost-benefit of rubella vaccination between 1970 and 2012. The review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The authors performed a systematic search of MEDLINE (PubMed) and the National Health Services Economic Evaluation Database. The studies identified were reviewed one-by-one by reading their abstracts and identifying the design of the study as reported. The review included health economic evaluations i.e. cost analyses, cost-effectiveness analyses, costutility analyses, cost-benefit analyses, cost-consequences analyses, and cost-minimization analyses. After reviewing the studies chosen, they categorized them by study design and income level of countries in which they were performed. They used the World Bank definition, which categorizes countries according to Gross National Income (GNI) per capita in 2011 as follows: low income, $1,025 or less; lower middle income, $1,026 -$4,035; upper middle income, $4,036 - $12,475; and high income, $12,476 or more. For the cost-effectiveness and cost-utility analyses, they used the 16-item Quality of Health Economics Studies (QHES) questionnaire to assess study quality. A higher score on the QHES indicates a study of better quality.

Results:
Cost-benefit analyses of rubella vaccination programs
Tables 4, 5, and 6 below present summaries of the cost-benefit studies of rubella vaccination. Of these, ten studies were performed in high-income countries1, while the other (Irons et al.) was performed in a number of upper-middle-income countries. The studies compared the

costs and benefits of 1) vaccinating with MMR vs. monovalent rubella vaccine, 2) vaccinating various age groups vs. no program, 3) introducing a second dose of MMR, and 4) rubella elimination.

Four studies compared MMR with monovalent rubella vaccine. All but the study performed in 1979 in Finland found that vaccination with MMR is preferable. White et al. performed a cost-benefit analysis of a routine childhood MMR vaccine program in the US compared to no vaccination, or vaccination with individual (measles, mumps or rubella) antigens and found that the MMR vaccine had a higher benefit to cost ratio than the monovalent ones and would be preferred. Hatzandrieu and Halpern replicated the methods of White et al. with similar findings, that introducing MMR vaccine was more cost-beneficial than monovalent rubella vaccine. Berger conducted an analysis in Israel of the costs and benefits of introducing a mumps-rubella vaccine to monovalent antigens and found that the combined vaccine was preferable. Elo on the other hand, found that vaccination with rubella vaccine in Finland was more costbeneficial.

Table 8 : Cost-benefit analyses of vaccination programs in the general population

First author [Reference]	Stray-Pedersen [25]	White [26]	Hatzandrieu [27]	Schoenbaum [24]
Country	Norway	USA	USA	USA
Year	1982	1985	1994	1976
WB income group	High	High	High	High
Comparators	1. Vaccinate infant girls	1. Rubella vaccination	1. Rubella vaccination	1. Vaccinate all 2-yr-olds
	2. Vaccinate pubertal girls	2. MMR vaccination	2. MMR vaccination	2. Vaccinate all 6-yr-olds
				3. Vaccinate all 12-yr -olds
				4. Vaccinate 2-yr-olds and 12-yr-olds
Perspective	Societal	Societal	Societal	Societal
Cost components measured	Vaccine; immunization; serology; CRS treatment (including special care; indirect costs (lost productivity and premature mortality)	Vaccine; immunization; physician visits; hospitalization; supportive care; special schooling; institutionalization; indirect costs (lost wages, lost lifetime earnings due to retardation or death)	Vaccine; immunization; physician visits; hospitalization; supportive care; special schooling; institutionalization; indirect costs (lost wages, lost lifetime earnings due to retardation or death)	Vaccine; immunization; OP care; hospitalization; CRS treatment and care; indirect costs (lost lifetime earnings)
Method of cost estimation	Micro-costing (for vaccination and treatment; expected lifetime earnings (for indirect costs)	Micro-costing (for direct costs; expected lifetime earnings (for indirect costs)	Micro-costing (for direct costs; expected lifetime earnings (for indirect costs)	Micro-costing (for direct costs; expected lifetime earnings (for indirect costs)
Method of benefits estimation	Averted costs	Averted costs	Averted costs	Averted costs
Time period for costs and benefits	Lifetime	Lifetime	Lifetime	Lifetime
Discounting (Rate)	Yes (7%)	Yes (10%)	Yes (10%)	Yes (6%)
Results—Benefit-cost ratio	1. 5	1. 7.7	1. 11.1	1. 8
	2. 11	2. 14.4	2. 21.3	2. 9
				3. 27
				4. 8
Stated conclusion	Vaccination of pubertal girls preferable	Routine MMR vaccine program was cost-effective	Routine MMR vaccine program was cost-effective	Vaccination at 12 years better than vaccination at other ages
Sponsor	NR	CDC*	CDC*	NR

*Not explicitly reported but inferred.
WB, World Bank; *NR*, Not Reported; *NA*, Not Applicable; *CDC*, US Centers for Disease Control and Prevention.

Six studies compared immunization delivery strategies targeting different age groups. Three studies, one in Denmark and two in Israel, found that it was more cost-beneficial to vaccinate infants and pubertal girls. One study in the US found that it was better to vaccinate 12 year old girls than two year old children. The other study in Finland found that it was better to vaccinate pubertal girls and postpartum women.

Table 9 : Cost benefit analyses od vaccination programs in the general population

First author [Reference]	Bjerregaard [28]	Pelletier [29]	Elo [31]	Berger [30]
Country	Denmark	Canada	Finland	Israel
Year	1991	1998	1979	1990
WB income group	High	High	High	High
Comparators	1. Vaccinate 15-month and 12-yr-olds	1. 1-dose child vaccination campaign	1. Vaccinate 13-yr-olds & post-partum women	1. Vaccinate children from 1 – 12 years
	2. Vaccinate only 15-month-olds	2. 2-dose child vaccination campaign	2. Vaccinate 13-yr -olds & 1-yr-olds	2. Vaccinate only 12-yr-olds (routine)
		3. 1-dose child vaccination	3. Vaccinate only 1-yr-olds over 20 years	
		4. 2-dose child vaccination		
Perspective	Societal*	Societal*	Societal*	NR
Cost components measured	OP visits; prescriptions; hospitalizations; vaccines	OP visits; hospitalizations; laboratory tests; nursing home care; special education; indirect costs (lost productivity for illness, disability and premature death)	Fetal loss; fetal damage; annual costs; long-term costs	Vaccine; vaccination side effects; serology; OP visits; hospitalizations; hearing aids; mothers' work loss;
Method of cost estimation	Micro-costing	Micro-costing; Lifetime earnings (for indirect costs)	Top-down costing based on Delphi panel	Micro-costing
Method of benefits estimation	Averted costs	Averted costs	Averted costs	Averted costs
Time period for costs and benefits	20 years	Lifetime	30 years	13 years
Discounting (Rate)	NR	Yes (5%)	Yes (6%)	Yes (5 and 10%)
Results—Benefit-cost ratio	1. 3	1. 2.6	1. 10	1. 1.1
	2. 2	2. 2.9	2. 3	2. 1.8
		3. 3.6	3. 6	
		4. 4.3		
Stated conclusion	Vaccinating both age groups is preferable	The benefits of a second dose outweigh the costs	Vaccinating 13-yr -old girls and postpartum women was preferable	Vaccinating infants and adolescent girls is preferable
Sponsor	NR	LCDC	NR	NR

*Not explicitly reported but inferred.
WB, World Bank; *NR*, Not Reported; *NA*, Not Applicable; *OP*, Out Patient; *CDC*, US Centers for Disease Control and Prevention; *LCDC*, Canada Laboratory Center for Disease Control.

Two studies evaluated the costs and benefits of rubella elimination. Kommu and Chase estimated a benefit to cost ratio of 4.7. Irons et al. (2000) performed a costbenefit analysis of rubella elimination in the English-speaking Caribbean. They estimated a disease burden of 1,500 cases in all the countries and an expenditure on CRS of (2012) US$ 126 million. A campaign to interrupt rubella transmission would cost (2012) US$9.1 million and result in a benefit to cost ratio of 13.3 for a rubella and CRS eradication campaign involving mass vaccination in 18 countries.

Table 10. Cost-benefit analyses of vaccination programs in the general population

First author [Reference]	Golden [32]	Kommu [33]	Irons [34]
Country	Israel	Barbados	Caribbean
Year	1984	1998	2000
WB income group	High	High	Upper-middle
Comparators	1. Vaccinate all 1 - 12-yr-olds	1. Rubella elimination initiative	1. Initiative to interrupt rubella transmission
	2. Vaccinate pubertal girls	2. None	2. None
	3. Vaccinate adult females		
Perspective	Societal*	Payer*	Payer*
Cost components measured	Laboratory tests; abortions; primary care; institutional care; lost work days;	NR	NR
Method of cost estimation	Micro-costing	NR	NR
Method of benefits estimation	Averted costs	NR	NR
Time period for costs and benefits	10 years	15 years	20 years
Discounting (Rate)	Yes (10%)	NR	NR
Results—Benefit-cost ratio	1. 1	1. 4.7	1. 13.3
	2. 2	2. –	2. –
	3. Negative		
Stated conclusion	Vaccination of children and pubertal girls is preferable	The rubella elimination program using MMR was cost-beneficial	The rubella elimination program using MMR was cost-beneficial
Sponsor	NR	NR	NR

*Not explicitly reported but inferred.
WB, World Bank; *NR*, Not Reported; *NA*, Not Applicable; *OP*, Out Patient; *CDC*, US Centers for Disease Control and Prevention; *LCDC*, Canada Laboratory Center for Disease Control.

c) Cost effectiveness of Measles only elimination versus Measles Rubella elimination in Uganda? Cost effectiveness of CRS elimination versus Rubella elimination in Uganda?

MEASLES

Dayan et al 2004

Objective: This study compares, from the Zambian health-care system perspective, the costs and benefits of providing a single dose of measles vaccine to the costs and benefits of providing two opportunities for measles immunization. Analyses of cost-effectiveness can help guide the selection of measles vaccination strategies.

Methodology:

A decision analysis model based on published and unpublished data was used to compare the economic impact of three vaccination strategies against measles in Zambia. The strategies considered were as follows:

- ✓ *Strategy 1*: 1 dose of measles vaccine delivered through routine health-care system at 9 months of age.
- ✓ *Strategy 2*: 1 dose of measles vaccine delivered through the routine health-care system at 9 months of age and a second opportunity for immunization through SIAs.
- ✓ *Strategy 3*: Two doses of measles vaccine delivered through the routine health-care system at 9 months and 18 months of age.

The probability of contracting measles was directly related to susceptibility and the disease attack rate in the population. Susceptibility to measles was determined by vaccination coverage and vaccine efficacy. Because vaccine efficacy is less than 100%, some vaccinated children remain susceptible to infection and have a risk of contracting measles. Measles cases may be hospitalized and/or die. Additionally, vaccination may be associated with adverse events that may require medical care.

Vaccination costs were estimated by assigning a value to each dose of measles vaccine given based on the allocations for SIAs in Zambia in 2000. The direct costs of outpatient medical care and hospitalization were based on the average costs to patients for medical services in Zambia. Information for calculation of these costs was based on personal communications from staff of the CBoH. The analysis was performed from the health-care system perspective. The primary outcome measure was the cost per averted case of measles; however, the costs per averted death were also calculated.

Results:
In strategy 1, each annual birth cohort of 400,000 children would experience 38,476 measles cases and 1924 deaths between the ages 2 and 15 (Shown in Table 11 below).

Table 11. Summary of program strategy outcomes and cost of strategies 1-3

	Strategy 1	Strategy 2	Strategy 3
Number of cases	38,476	9234	24,769
Number of deaths	1924	462	1238
Hospitalization days	92,342	22,162	59,446
Disease costs (costs in 2000) (US$)			
Direct costs			
Ambulatory visit costs	39,253	9421	25,269
Hospitalization costs	502,225	120,537	323,307
Total disease costs	541,478	129,958	348,576
Vaccination costs			
Vaccine cost	164,160	216,960	328,320
Injection equipment	40,640	81,280	81,280
Cold chain	9280	18,560	18,560
Transportation	7680	15,360	15,360
Personnel	24,960	49,920	49,920
Stationery	640	1280	1280
Social mobilization (SIAs)	0	23,360	0
Supervision (SIAs)	0	1600	0
Planning/training (SIAs)	0	7680	0
Administrative costs (SIAs)	0	1600	0
Additional transportation (SIAs)	0	1280	0
Additional personnel (SIAs)	0	4480	0
Adverse events	24,000	31,680	27,600
Total vaccination costs	271,360	455,040	522,320
Total	812,838	584,998	870,896

US$ 1 = 3200 Zambian Kwacha in 2000.

[a] Strategy 1: one dose at 9 months old. Strategy 2: two doses, second through SIAs. Strategy 3: two doses through routine system.

Measles disease would result in US$ 541,478 in medical costs. The cost of this vaccination program would be US$ 271,360. Compared with strategy 1, strategy 3 would prevent 13,707 measles cases and 686 deaths for each vaccinated birth cohort. However, vaccination using strategy 2 would prevent approximately 29,000 measles cases and 1460 deaths when compared with strategy 1. In the presence of a vaccination program using strategy 2, the numbers of both measles cases and deaths would be reduced by approximately 76 and 63% when compared to strategies 1 and 3, respectively (Table 11). Moreover, a total of approximately 70,000 hospitalization days would be saved when compared with strategy 1. A vaccination program following strategy 2 would be expected to cost US$ 455,040 including vaccine purchase, administration, treatment of adverse events and other SIAs costs. This would be US$ 67,280 less than strategy 3 (Table 11). Strategy 2 dominates the other strategies,

as it is both more effective and less costly. In addition, it is the only strategy which results in savings per case and death prevented, when compared to the one-dose strategy (As shown in Table 12 below).

Table 12 .Results of the cost-effective analysis comparing strategies 2 and 3 to strategy 1

	Costs in 2000 (US$)				Total measles cases	Additional cases prevented[b]	Total measles deaths	Additional deaths prevented[b]
	Disease costs	Vaccination costs	Total disease and vaccination costs	Additional cost of program (US$)[b]				
Strategy 1	541478	271360	812838	0	38476	0	1924	0
Strategy 2	129958	455040	584998	−227840	9234	29242	462	1462
Strategy 3	348576	522320	870896	58058	24769	13707	1238	686

US$ 1 = 3200 Zambian Kwacha in 2000.
[a] Strategy 1: one dose at 9 months old. Strategy 2: two doses, second through SIAs. Strategy 3: two doses through routine system.
[b] All strategies are compared to strategy 1. Negative values represent savings.

Even 100% vaccine coverage using strategy 1 would not reach the level of measles control achieved with strategy 2 at coverage of 80% for each of the two vaccine doses administered. Vaccination coverage for each dose using strategy 3 would have to increase from 80 to 99.5% to equal benefits in terms of disease prevented using strategy 2. As coverage for vaccine delivered through routine services increases, savings per averted case increases for strategy 3 but remains relatively unchanged for strategy 2. However, if 100% routine vaccination coverage were achieved, strategy 2 would still offer slight cost-savings while strategy 3 would approach being cost neutral. The impact of varying wastage factor in routine health services, vaccination costs and reporting efficiency of measles cases on savings per averted case, respectively. In each analysis, an increase in the variable resulted in a much greater and more rapid decrease in savings per averted case for strategy 3 than for strategy 2. The authors also performed sensitivity analysis on the percentage of children unvaccinated with the first dose reached with the second opportunity. As the percentage of children reached with the second opportunity increases, the savings per averted case uniformly increase for both strategies 2 and 3. The same is true when increasing ambulatory visit or hospitalization costs

Babigumira et al. 2011

Objective: The aim of this study is to assess the potential cost-effectiveness of measles elimination efforts in Uganda in the context of a global eradication target, assuming that all countries would be working concurrently toward elimination to achieve global eradication.

Methodology:
The analysis compared 4 alternative measles control goals with the present target already achieved of 90% MR. Hence, the scenarios considered were (1) baseline 90% MR by 2013 (although Uganda has already reached the target of 90%MR, the 2013 date was chosen, because the study was conducted in global context; globally, the 90% MR target was assumed

to be reached by 2013), (2) 95% MR by 2015, (3) 98% MR by 2020, (4) elimination in 2020, and (5) elimination in 2025.

> Scenario 1 (baseline 90% MR) was simulated by maintaining the current level of coverage of MCV1 (68%) and SIAs (90%). This scenario assumed that the status quo would be maintained with no additional investments in measles elimination and no decrease in current levels of funding.
>
> Scenario 2 (95% MR by 2015) represented the World Health Assembly target at that time for measles control and was simulated by gradually increasing MCV1 coverage to 83% starting in 2012, introducing MCV2 for 18-month-olds in 2013, and increasing SIA coverage to 95% for 9–59-month-olds.
>
> Scenario 3 (98% MR by 2020), which was included as an alternative to elimination—as an intermediate target in the event that elimination by 2020 is not cost-effective or is prohibitively costly—was simulated by gradually increasing MCV1 coverage to 83% starting in 2012, introducing MCV2 for 18-month-olds in 2013, and increasing SIA coverage to 95% for 9–59-month-olds.
>
> Scenario 4 (elimination in 2020) was simulated by gradually increasing MCV1 coverage starting in 2012, introducing MCV2 for 18-month-olds in 2013, and increasing SIA coverage to 95% for 9–59-month-olds.
>
> Scenario 5 (elimination in 2025) was simulated by gradually increasing MCV1 coverage starting in 2012, introducing MCV2 for 18-month-olds in 2013, and increasing SIA coverage to 95% for 9–59-month-olds.
>
> In both elimination scenarios (scenarios 4 and 5), it was assumed that the provision of MCV1 and MCV2 through routine immunization services would continue for the whole study period. Since this study was carried out in the context of a global eradication target, the authors assumed that SIAs would discontinue once elimination was certified (in Uganda and globally).

A dynamic age-structured compartmental model of measles transmission was developed to estimate health outcomes by age and year for the different scenarios over 2 time horizons: up to the year 2030 and up to year 2050. The model divided individuals into susceptible, exposed, infectious, and recovered/immune, as well as 5 age classes: 1 year, 1–2 years, 3–5 years, 6–15 years, and >16 years.

It was assumed that the different immunization scenarios would be implemented concurrently in countries neighboring Uganda and that there would be no measles cases imported from these countries. Parameters for the model were obtained from primary data collection in Uganda, the United Nations Population Projections, expert WHO opinion, and literature sources.

Costs were incorporated into the analysis by attaching a monetary value to resources used for each immunization and to savings from not treating measles cases. Estimates of model parameters and costs were obtained from primary data collection in Uganda and literature sources. The analysis was performed from a limited societal perspective with all prices and improved efficiencies assumed to increase at the same rate, and future costs and health outcomes were discounted at 3% per year. Costs were estimated in 2010 US dollars.

Scenarios were compared on the basis of projected measles incidence, costs, cases of measles averted, deaths averted, disability-adjusted life-years (DALYs) averted, and incremental cost-effectiveness ratios (ICERs) measured as costs per measles case averted, cost per death averted, and cost per DALY averted. Scenarios were judged to be very cost-effective if the ICER, measured as cost per DALY, was $474 per DALY (1 times per capita GDP) and cost-effective if the ICER was $1423 per DALY (3 times per capita GDP) through either year 2030 or 2050.

Results:

Measles Incidence

Measles incidence remained at a relatively constant low rate in each of the 3 scenarios, and the model predicts 230,428 measles cases under scenario 1, 156,828 cases under scenario 2, and 70,657 cases under scenario 3 by 2030. In the elimination scenarios (4 and 5) the incidence of measles gradually declines as the elimination target dates are approached, and the model predicts 26,595 measles cases under scenario 4 and 35,287 cases under scenario 5.

Measles Costs

The average cost of a single RI dose was $1.83 at the central level and $0.52 at the district level. The average cost of a single SIA dose was $1.24. The cost per additional percentage of coverage for RI was $0.04 between 60% and 80% coverage and $0.08 between 80% and 90% coverage. The cost per additional percentage point increase in coverage for SIA was $0.01. The household time and transport cost of obtaining measles immunization was $0.58. The estimated average cost of treating a measles case was $6.

Incremental Cost-Effectiveness Analysis

The cost and health outcomes of each of the 4 scenarios are compared with the baseline scenarios for 2030 (see Table 13 below) and 2050 (see Table 14 below).

Table 13 : Costs and Incremental Costs, Health Outcomes and Cost-effectiveness in Comparison with baseline scenarios in Uganda through the Year 2030.

Scenario	Cost, $	Cases	Deaths	DALYs	Incremental costs, $	Cases averted	Deaths averted	DALYs averted	ICER, $/case averted	ICER, $/death averted	ICER, $/DALY averted
Baseline	134,111,220	230,428	35,287	184,425	...	...	...	...	...	...	...
Elimination 2020	385,094,242	26,595	805	24,619	250,983,022	203,832	34,481	159,806	1231	7278	1570
Elimination 2025	400,993,954	35,287	1097	33,847	266,882,734	195,141	34,189	150,577	1367	7806	1772
98% MR 2020	454,257,788	70,657	2337	73,443	320,146,567	159,770	32,949	110,982	2003	9716	2884
95% MR 2015	325,958,785	156,828	4325	130,949	191,847,564	73,600	30,961	53,476	2606	6196	3587

NOTE. Costs are in US dollars, year 2010 values. Scenarios were arranged by increasing ICER. DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio; MR, mortality reduction; SIA, supplementary immunization activity.

Table 14 : Costs and incremental Costs, Health Outcomes and Cost Effectiveness in Comparison eith Baseline Measles Immunisation Scenarios in Uganda through the Year 2050.

Scenario	Cost, $	Cases	Deaths	DALYs	Incremental costs, $	Cases averted	Deaths averted	DALYs averted	ICER, $/case averted	ICER, $/death averted	ICER, $/DALY averted
Baseline	228,702,222	413,112	10,531	523,234	...	...	...	...	...	...	...
Elimination 2020	629,688,565	26,595	805	24,619	400,986,342	386,516.52	9,725.89	498,615	1037	41,228	804
Elimination 2025	650,433,859	27,733	1097	33,847	421,731,636	385,378.67	9,433.74	489,387	1094	44,704	861
95% MR 2015	577,918,530	244,168	6747	206,415	349,216,307	168,944.03	3,784.55	316,818	2067	92,274	1102
98% MR 2020	774,117,819	118,243	3922	124,775	545,415,596	294,868.29	6,609.48	398,458	1849	82,520	1368

NOTE. Costs are in US dollars, year 2010 values. Scenarios were arranged by increasing ICER. DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio; MR, mortality reduction; SIA, supplementary immunization activity.

Scenario 1 was the least costly but led to the least favourable outcomes in both time horizons. In comparison with baseline, each of the 4 alternative scenarios would appear to have an ‘‘acceptable’’ ICER, by conventional standards. Scenario 4 had the most favorable ICER in both the 2030 ($1570 per DALY averted) and the 2050 time horizon ($804 per DALY averted). Scenario 2 had the least favourable ICER in the 2030 time horizon ($3587 per DALY averted), and scenario 3 had the least favorable ICER in the 2050 time horizon ($1368 per DALY averted).

In the efficiency frontier analysis (Tables 15 and 16 below), in both the 2030 and 2050 time horizons, scenarios 3 and 5 were more costly and led to less favorable outcomes than $1 other scenario and were dominated. Using a GDP-based willingness-to-pay threshold, scenario 4

would be the optimal scenario for both the 2030 time horizon (ICER of $556 per DALY averted) and the 2050 time horizon (ICER of $284 per DALY averted).

Table 15 : Costs and Incremental Costs, Health Outcomes and Cost-Effectiveness of Measles Immunisation Scenarios in Uganda through the Year 2030 (Effecient Frontier Analysis)

Scenario	Cost, $	Cases	Deaths	DALYs	Incremental costs, $	Cases averted	Deaths averted	DALYs averted	ICER, $/case averted	ICER, $/death averted	ICER, $/DALY averted
Baseline	134,111,220	230,428	35,287	184,425	...	...	...	...	...	...	...
95% MR 2015	325,958,785	156,828	4325	130,949	191,847,564	73,600	30,961	53,476	2,606	6196	3587
Elimination 2020	385,094,242	26,595	805	24,619	59,135,457	130,232	3520	106,330	454	16,798	556
Elimination 2025	400,993,954	35,287	1,097	33,847	15,899,711	...	...	...	Dominated[a] by elimination 2020		
98% MR 2020	454,257,788	70,657	2,337	73,443	53,263,833	...	...	...	Dominated[a] by elimination 2020 and elimination 2025		

NOTE. Costs are in US dollars, year 2010 values. DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio; MR, mortality reduction; SIA, supplementary immunization activity.

[a] The dominated scenario is both more costly and less effective than the dominating scenario.

Table 16. Costs and Incremental Costs, Health Outcomes, and Cost-Effectiveness of Measles Immunisation Scenarios in Uganda Through the Year 2050 (Efficiency Frontier Analysis)

Scenario	Cost ($)	Cases	Deaths	DALYs	Inc. costs ($)	Cases averted	Deaths averted	DALYs averted	ICER, $/case averted	ICER, $/death averted	ICER, $/DALY averted
Baseline	228,702,222	413,112	10,531	523,234	...	...	...	...	...	...	...
95% MR 2015	577,918,530	244,168	6747	206,415	349,216,307	168,944	3784	316,818	2067	92,274	1,102
Elimination 2020	629,688,565	26,595	805	24,619	51,770,035	217,572	5941	181,796	237	8713	284
Elimination 2025	650,433,859	27,733	1097	33,847	20,745,293	...	...	...	Dominated[a] by elimination 2020		
98% MR 2020	774,117,819	118,243	3922	124,775	123,683,960	...	...	...	Dominated[a] by elimination 2020 and elimination 2025		

NOTE. Costs are in US dollars, year 2010 values. DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio; MR, mortality reduction; SIA, supplementary immunization activity.

[a] The dominated scenario is both more costly and less effective than the dominating scenario.

Bishai et al. 2011

Objective: Competition for the scarce resources of public sector finance, administrative costs, and the demands on health worker time make it important to justify the value of SIAs by estimating their contribution to human health. To estimate the benefit of SIAs, this study developed a dynamic stochastic model of measles transmission and integrated it with economic models of measles vaccination efforts. The results demonstrate the value of follow-up SIAs compares to that of other investments in human health.

Methodology:

The authors integrated a dynamic measles model with an economic model of disease control costs to examine the cost-effectiveness of conducting SIAs in Uganda.

For validation purposes, a natural history model was assessed in which measles cases and costs were estimated for the hypothetical situation in which Uganda never introduces measles vaccine. For policy purposes, they compared a ‘‘no SIAs scenario’’ in which Uganda continued its current level of performance in routine MCV1 delivery but conducted no SIAs from 2010 onward with a ‘‘with SIAs scenario’’ in which routine MCV1 coverage is identical but follow-up SIAs targeting children aged 9–59 months are carried out every 3 years during the period from 2010 through 2050. The SIAs are assumed to achieve a coverage rate of 95%.

The model is calibrated to have a 40-year horizon from 2010 through 2050 and a 2-week time step. The model is a dynamic, stochastic version of a susceptible, immune, recovered model with age structure and 2 compartments: a core (main) and a satellite (accessory) population to depict heterogeneity in vaccine coverage.

The cost model included the costs of routine MCV1, SIAs, measles treatment, parent productivity lost to measles, outbreak control, and surveillance and constitutes a societal perspective. The cost of immunizing 1 child through routine MCV1 was assumed to be $1 [6]. The cost of immunizing 1 child through an SIA in 2010 was estimated to be $0.58 per child immunized. Little was known about the medical costs of measles in Uganda. The baseline model assumes that for every 100 measles cases there would be 50 primary care visits, 200 lost parent productivity days, and 10 hospital bed days. The costs of inpatient stays subsumed the medical costs of all severe acute complications of measles, such as dehydration and pneumonia. The unit costs of medical utilization were derived from WHO–Choosing Interventions That Are Cost Effective. Productivity days were valued at gross domestic product (GDP) per capita. Measles-related encephalitis was conservatively assumed to have an incidence of 1.5 cases per 10,000 cases of measles and to result in 14 inpatient days per case and 10 lost years of GDP per capita per case [8].

Results:
Figure 11 below shows the 40-year discounted sum of total measles costs against the 40-year sum of discounted DALYs. One hundred iterations are shown for each policy scenario. Decision makers are assumed to prefer points that are lower on the vertical axis because these have lower cost and to prefer points that are farther to the left on the horizontal axis because these have fewer DALYs. One can see that the baseline scenario in which routine coverage is frozen at 68% while SIAs are continued every 3 years imposes similar costs but has 5 million fewer DALYs than maintaining the same routine coverage with no SIAs.

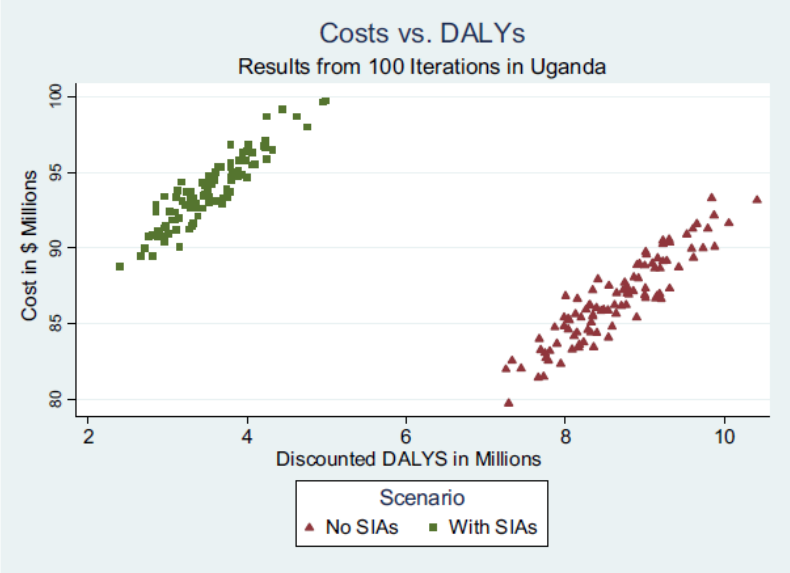


Figure 11. Costs vs measles disability adjusted life years (DALYs) in Ugandafor the scenarios with and without supplemental immunisation activity

In the ‘‘with SIAs’’ strategy, the model projects a total of 136,120 6 19,815 discounted measles deaths and 3.5 million 6 506,000 discounted measles DALYs from 2010 through 2050. This is 5 million fewer DALYs than a strategy without SIAs. The with SIAs scenario incurs a total discounted cost over 40 years of $94 6 2.3 million. SIAs account for 39% of this cost. The ‘‘no SIAs’’ scenario in Uganda would lower costs to $87 6 2.4 million during the same period. Roughly $4.2 million in SIA direct operational costs would be averted by discontinuing them but replaced by $3.5 million in health care costs for the additional measles cases. For a decision maker at the no SIAs position, adding SIAs will improve health but lead to somewhat higher costs. The slopes of the lines from the no SIA scenarios to the with SIAs scenarios in Figure 11 are called incremental cost effectiveness ratios (ICERs) and are shown in Table 17 below.

Table 17 : Costs, Deaths, Disability Adjusted Life Years (DALYs) and, Incemental Cost Effectivenss Ratios (ICERs) for Uganda with 3% Discounting and Horizon to the Year 2050

Scenario	Discounted deaths, mean ± SD	Δ Discounted deaths averted relative to no SIAs, mean ± SD	Δ Discounted DALYs averted relative to no SIAs level of 17,489,545, mean ± SD	Discounted costs, mean $ millions ± SD	Δ Discounted costs relative to no SIAs, mean $ ± SD	ICER $ per death averted, median $ (IQR)	ICER per DALY averted, median $ (IQR)
Natural	1,206,143 ± 33,778	…	…	196 ± 4.2	…	…	…
No SIAs	331,729 ± 25,165	…	…	87 ± 2.8	…	Reference	Reference
With SIAs	135,990 ± 19,026	194,539 ± 33,841	5,909,410 ± 900,440	94 ± 2.3	7 ± 3.9	39 (20–58)	1.5 (0.8–2.2)

NOTE. IQR, interquartile range; SD, standard deviation; SIA, supplemental immunization activity.

The median ICER is estimated at $1.5 (interquartile range, $0.8–$2.2). Figure 12 shows the components of costs in each scenario and includes a comparison with the costs of measles if Uganda had never adopted measles vaccine (top bar labeled ‘‘Natural’’). The analysis confirms that measles vaccination as currently practiced in the with SIAs scenario is indeed cost saving—the costs of the program are less than half what the medical and social costs of measles would be with no vaccination. The no SIAs scenario has slightly lower costs than the with SIAs scenario, but Figure 6 shows that the cost components differ. The no SIAs scenario generates a discounted value of costs of measles disease estimated at $60.8 million (interquartile range, $58.4– $62.5) between 2010 and 2050. By comparison, the with SIAs scenario has median costs of measles disease of $25.2 million (interquartile range, $24.3–$26.9) and a constant estimate of SIA operational costs at $42 million. Thus, stopping SIAs saves the costs of SIAs, but the newly incurred costs of the additional cases of measles undermine most of the savings.

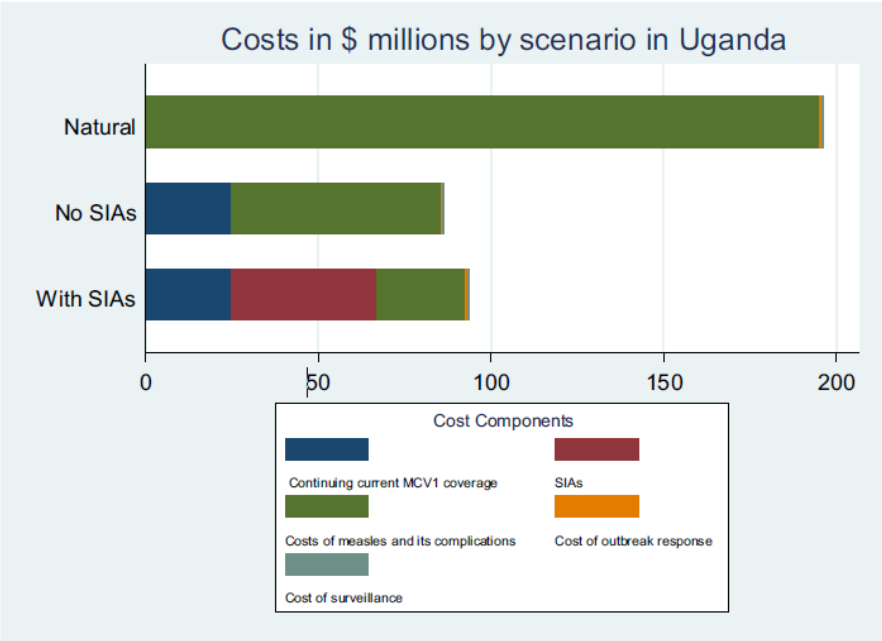


Figure 12. Cost structure between measles control scenarios in Uganda. Costs are cummulative discounted costs from 2010 to 2015, calculated as the average of 100 ierations of each scenario SIA Supplementary Immunisation Activity.

MR_SES_CostEff_2011.Levin

Objective: The objectives of the study were to (1) estimate the cost and cost-effectiveness of measles eradication and intermediate goals of 95% and 98% mortality reduction, compared with the baseline scenario (the 90% measles-associated mortality reduction global goal) in 6

countries, and (2) extrapolate this analysis to the global level to determine cost and cost-effectiveness of global measles eradication

Methodology:
Data collection and analyses of measles-associated mortality reduction were conducted in 6 countries. The countries chosen were to ensure diversity of costs with use of the following criteria: (1) measles first dose coverage and (2) gross national income per capita levels. Costs and health outcomes were evaluated using the following 4 scenarios in Bangladesh, Brazil, Colombia, Ethiopia, Tajikistan, and Uganda: (1) 90% mortality reduction by 2013 (baseline), (2) 95% mortality reduction by 2015 (95% RM), (3) 98% mortality reduction by 2020 (98% RM), and (4) eradication of measles by 2020 (E2020). The baseline scenario assumes 2013 as the target date for 90% mortality reduction, because at the time of publication, those countries that did not meet the original target date of 2010 were expected to do so by 2013.

The cost of measles eradication in a given country was defined as the aggregate incremental cost that would be needed to achieve eradication (ie, above the costs that would be incurred to achieve a lower level target; e.g. a 90% reduction in mortality by 2013, compared with the 2000 baseline). To estimate the costs of each specific strategy, the projected annual program costs were summed for the measles immunization activities for each scenario, country, and year until measles eradication was achieved. After eradication was achieved, the costs of maintaining it were estimated for each country until 2050. The mean cost per dose was estimated by dividing total annual costs by the number of doses administered.

The study team collected cost data from various sources: WHO headquarters and regional offices and visits to 6 countries. During the country visits, the study team (1) collected data on costs of conducting routine vaccination, SIAs, and surveillance from country immunization program offices and WHO offices; (2) conducted interviews with key stakeholders regarding the resources required to increase coverage of routine vaccination, SIAs, and surveillance to achieve measles eradication; and (3) traveled to a sample of districts and/or regions to collect information on local resources used for measles vaccination activities.

The costs estimated for each scenario were combined with outcome measures obtained from the dynamic transmission modeling. These measures include measles cases and/or deaths averted and disability-adjusted life-years (DALYs) averted for each strategy. Estimates of incremental costs and DALYs averted over the baseline for each of the scenarios were used to calculate incremental cost-effective ratios (ICERs) for the period 2010–2050.

Results:
The estimated mean cost per dose of routine vaccination is smaller in low-income countries, ranging from $1.35 in Ethiopia to $7.77 in Colombia. The cost of delivering a dose through SIAs was less expensive than through routine vaccination, ranging from $0.52 in Bangladesh to $2.87 in Colombia. The estimates of additional costs of increasing routine vaccination

coverage range from an additional $0.04 per percentage point increase in coverage level per dose in Uganda to $0.075 in Tajikistan.

Table 4 below shows the total costs, incremental costs, and ICERs of reaching the 95% mortality reduction, 98% mortality reduction, and eradication goals. Among countries that have not eliminated measles, the costs of measles vaccination during 2010–2050 are projected to increase as the program ramps up its activities to reach these goals. In comparison with 95% reduction in mortality, eradication would require additional resources in Ethiopia and Uganda to achieve a coverage level sufficient to stop transmission, whereas eradication would require fewer resources in Bangladesh and Tajikistan because of cost savings from reductions in outbreak response and SIAs, because these countries already have high coverage.

Table 18. Country ICERS FOR 95% and 98% Reduction in Mortality and E2020 Global Goals Relative to baseline of 90% Reductionin Mortality

	Strategy	Total cost (Millions, 2010 USD)	Incr. cost (Millions, 2010 USD)	Total DALYs	Incr. DALYS Averted	ICER,$ per DALY Averted (2010 USD)	GDP per Capita (2009)
Bangladesh	Baseline	$340	–	3,684,549	–	–	$551
	95%RM	$655	$315	2,466,202	1,218,000	$259	
	98%RM	$645	$305	2,394,268	1,290,281	$236	
	E2020	$388	$49	513,412	3,126,000	$16	
Ethiopia	Baseline	$254	–	2,396,529	–	–	$345
	95%RM	$405	$151	1,602,620	794,000	$190	
	98%RM	$645	$391	829,133	1,567,396	$250	
	E2020	$533	$280	312,528	2,084,000	$134	
Tajikistan	Baseline	$30	–	8,843	–	–	$716
	95%RM	$61	$31	4,662	4,181	$7,319	
	98%RM	$60	$30	4,276	4,567	$6,639	
	E2020	$41	$10	1,174	7,669	$1,355	
Uganda	Baseline	$229	–	523,235	–	–	$481
	95%RM	$578	$349	206,416	316,819	$1,102	
	98%RM	$774	$545	124,776	398,459	$1,369	
	E2020	$630	$401	24,619	498,616	$804	
Brazil	Baseline	$1,527	–	52	–	–	$8,070
	95%RM	$1,492	($35)	44	8	Cost/life saving	
	98%RM	$1,400	($127)	40	13	Cost/life saving	
	E2020	$1,107	($419)	15	37	Cost/life saving	
Colombia	Baseline	$925	–	49	–	–	$4,950
	95%RM	$918	($7)	36	13	Cost/life saving	
	98%RM	$920	($5)	38	10	Cost/life saving	
	E2020	$833	($92)	10	39	Cost/life saving	

In Ethiopia and Uganda, it would be more costly to achieve the 98% reduction in mortality goal in comparison with 95% reduction in mortality. On the other hand, the other countries would experience cost savings from fewer outbreak response activities as case importation

decreases. For all 6 countries, eradication is a less costly option than 98% reduction in mortality because of cost savings from discontinuing SIAs after 2023.

On the basis of the sensitivity analysis performed on the model, the key drivers of costs of reaching measles mortality reduction or eradication goals are the following: (1) initial cost per dose for routine vaccination, (2) cost per percentage point increase in routine and campaign coverage, and (3) cost of treating a measles case.

For the 2 countries that have eliminated measles (Brazil and Colombia), it is assumed that they would benefit from reduced case importation from other countries working toward measles elimination. Because less outbreak response would be required, vaccination costs in these countries would decrease to reach any of the 3 vaccination goals. All ICERs for 95% mortality reduction relative to baseline are cost-effective, being lower than the commonly cited threshold of 3 times the gross domestic product per capita, except for Tajikistan. (Of note, there were some data quality issues in Tajikistan that may account for the high cost per DALY averted in the country.)

For the 2 countries that have already eliminated measles, both costs and lives are saved and the ICERs are considered to be cost and life-saving. ICERs for the 2020 eradication scenario in the 4 countries that have not eliminated measles meet the criteria of being cost-effective; 2 are considered to be very cost-effective because the ICERs are less than the gross domestic product per capita. The ICERs are more cost-effective for this scenario than for reaching the 95% mortality reduction scenario because of cost savings from stopping outbreak response and SIAs.

Table 19 below shows the global ICERs by income group and elimination status. For countries that have not eliminated measles, ICERs in 3 of 4 of the income groups are projected to be very cost-effective for both of the global goals of 95% mortality reduction by 2015 and eradication by 2020. In the lower middle income group, both goals were projected to be cost and life-saving.

Table 19. Global ICERs for 95% and 98% Reduction in Mortality and E2020 Goals Relative to Baseline

	Strategy	Total cost (Millions, 2010 USD)	Incr. cost (Millions, 2010 USD)	Total DALYs (000s)	Incr. DALYS Averted (000s)	ICER,$ per DALY Averted (2010 USD)	GDP per Capita (2009)
Countries which have not eliminated measles by 2010							
Low (42)	Baseline	$903	–	37	–	–	$480
	95%RM	$1,088	$185	16	21	$9	
	98%RM	$1,213	$310	8	42	$11	
	E2020	$1,040	$137	137	32	$4	
Low-mid (41)	Baseline	$10,825	–	333	–	–	$2,078
	95%RM	$10,617	($208)	18	316	Cost/life saving	
	98%RM	$11,953	$1,128	75	258	$4	
	E2020	$10,529	($296)	41	292	Cost/life saving	
Upper-mid (24)	Baseline	$1,692	–	18	–	–	$7,604
	95%RM	$1,786	$94	8	10	$9	
	98%RM	$1,947	$255	4	14	$18	
	E2020	$1,759	$67	2,207	16	$4	
Upper (39)	Baseline	$45,607	–	1,778	–	–	$38,551
	95%RM	$56,635	$11,029	94	1,684	$6,548	
	98%RM	$63,156	$17,549	400	1,378	$12,737	
	E2020	$53,823	$8,216	229	1,558	$5,274	
Countries which have eliminated measles by 2010							
Low-mid (16)	Baseline	$1,091	–	2,325	–	–	$2,442
	95%RM	$1,082	($12)	996	1,329	Cost/life saving	
	98%RM	$1,530	($14)	524	1,802	Cost/life saving	
	E2020	$1,069	($140)	288	2,037	Cost/life saving	
Upper-mid (19)	Baseline	$2,172	–	2,888	–	–	$8,302
	95%RM	$2,148	($25)	1,235	1,648	Cost/life saving	
	98%RM	$2,146	($27)	649	2,234	Cost/life saving	
	E2020	$2,068	($104)	357	2,526	Cost/life saving	
Upper (12)	Baseline	$4,053	–	60	–	–	$43,659
	95%RM	$4,052	($1)	3	57	Cost/life saving	
	98%RM	$4,052	($1)	2	58	Cost/life saving	
	E2020	$4,006	($47)	2	58	Cost/life saving	

Driessen et al 2015

Objective: This paper evaluates three different measles vaccine delivery strategies in Ethiopia using extended cost-effectiveness analysis (ECEA) (Verguet et al., 2015; Verguet et al., 2013). The authors specifically, examined the health, financial, and social implications of routine immunization programs, SIAs, and routine immunization with financial incentives.

Methodology:
ECEA extends cost-effectiveness analysis (CEA) by considering additional, policy-relevant metrics that account for the economic and social effects of poor health (Verguet et al., 2015, Verguet et al., 2013). Thus, rather than simply conducting an economic evaluation of measles vaccination, this study looks at this intervention in the context of three different policy instruments. The broader household and economic effects of these policies are evaluated, including deaths averted, household expenditures averted and financial risk protection (FRP) provided, and government costs. There is an emphasis on the distribution of effects across income quintiles, which speaks to the equity impacts of the different approaches.

Using baseline information about measles prevalence and measles vaccination coverage by income quintile, for each vaccination they estimated the level and distribution (across income groups) of the measles deaths averted; the households' expenditures (direct medical costs and transport costs) related to measles treatment averted, the costs to sustain the program (vaccination costs borne by the government) and the measles treatment costs averted from the government's perspective; and the FRP afforded by the program measured by an imputed percent change in individual income after implementation of either vaccination program.

Before program introduction, individuals pay out of pocket for measles treatment and the cost of this service is assumed to be of about a third of the total healthcare treatment costs (Global Health Expenditure Database, 2012). Vaccine effectiveness is assumed to be 85% for MCV1 and 95% for SIAs, respectively (Sudfeld et al., 2010); the higher efficacy for SIAs reflects the fact that this platform tends to vaccinate older children (those older than twelve months of age). All costs are expressed in 2012 US$ using Ethiopia's consumer price index (World Development Indicators, 2013). Per child immunized, MCV1 vaccine price is about $0.58 and MCV1 cost of delivery is about $0.64 (Griffiths et al., 2009); SIA delivery cost is about $1.05 (Levin et al., 2010). For each incremental child immunized with MCV1, they assumed an additional cost of $0.09 if MCV1 coverage is below 80% and of $0.19 if MCV1 coverage is above 80% (Levin et al., 2010). These costs strictly reflect the direct costs associated with the program, and do not capture opportunity costs or other indirect costs. From the government's perspective, they estimated the total costs of each vaccination program, depending on the program implemented.

Results:
Table 2 below summarizes the health and financial implications of each vaccination strategy, including the overall impact and the impact by quintile. The largest number of deaths was averted under SIAs (39,700), while routine immunization with financial incentives averted more than twice as many deaths as the routine immunization without financial incentives (10,300 vs. 4900). This gap was due to sharp declines in the lower two income quintiles, the target group for the incentives; in these groups, deaths averted were almost three times higher under incentives as compared to routine immunization offered without incentives.

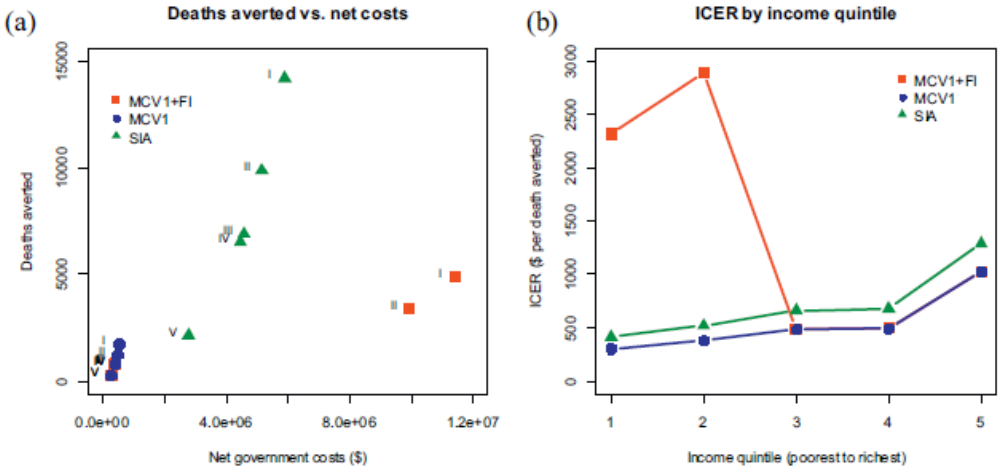
Table 20 : Extended cost-effectiveness analysis results for eachmeasles immunisation program, per income quartile, deaths avaerted, vaccination costs, household out f pocket expendiures averted, percent change in expected income, and increamental cost-effectivenss ratio.

Routine immunization						
Income group	I	II	III	IV	V	Total
Deaths averted	1749 (982–2727)	1216 (687–1892)	851 (482–1331)	805 (454–1256)	264 (150–413)	4885 (3751–6199)
Vaccination costs (thousands of $)	557 (458–666)	483 (396–578)	426 (351–510)	415 (341–496)	276 (231–326)	2158 (1779–2575)
Household expenditures averted (thousands of $)	59 (25–134)	41 (17–93)	29 (12–65)	27 (12–62)	9 (4–20)	165 (82–342)
Percent change in expected income	0.021 (0.009–0.046)	0.009 (0.004–0.021)	0.005 (0.002–0.012)	0.004 (0.002–0.009)	0.001 (0.0005–0.003)	0.006 (0.003–0.012)
Incremental cost-effectiveness ratio ($ per death averted)	303 (179–565)	382 (228–705)	486 (291–893)	500 (301–922)	1029 (629–1870)	427 (312–586)
Routine immunization supplemented by financial incentives						
Group	I	II	III	IV	V	Total
Deaths averted	4929 (2768–7687)	3426 (1935–5332)	851 (482–1331)	805 (454–1256)	264 (150–413)	10,276 (7483–13,611)
Vaccination costs (thousands of $)	11,499 (6772–17,553)	9974 (5874–15,225)	426 (351–510)	415 (341–496)	276 (231–326)	22,590 (13,754–33,910)
Household expenditures averted (thousands of $)	167 (70–377)	116 (49–262)	29 (12–65)	27 (12–62)	9 (4–20)	348 (168–731)
Percent change in expected income	10.534 (5.974–16.3)	5.969 (3.382–9.284)	0.005 (0.002–0.012)	0.004 (0.002–0.009)	0.001 (0.0005–0.003)	2.062 (1.170–3.205)
Incremental cost-effectiveness ratio ($ per death averted)	2318 (1154–4734)	2896 (1442–5874)	486 (291–893)	500 (301–922)	1029 (629–1870)	2183 (1227–3663)
Supplemental immunization activities						
Group	I	II	III	IV	V	Total
Deaths averted	14,216 (7984–22,169)	9882 (5582–15,381)	6918 (3918–10,817)	6544 (3690–10,211)	2149 (1217–3358)	39,708 (30,486–50,384)
Vaccination costs (thousands of $)	6117 (4957–7411)	5306 (4299–6427)	4681 (3793–5671)	4557 (3692–5520)	2809 (2276–3403)	23,470 (19,017–28,432)
Household expenditures averted (thousands of $)	481 (202–1086)	335 (140–756)	234 (99–528)	222 (93–501)	73 (31–165)	1345 (664–2784)
Percent change in expected income	0.040 (0.017–0.090)	0.018 (0.008–0.041)	0.010 (0.004–0.023)	0.008 (0.003–0.017)	0.002 (0.001–0.005)	0.012 (0.006–0.024)
Incremental cost-effectiveness ratio ($ per death averted)	415 (246–775)	522 (311–959)	662 (395–1213)	681 (409–1254)	1291 (780–2351)	576 (413–801)

Note: all costs are expressed in 2012 US$; 95% uncertainty ranges extracted from the multivariate sensitivity analysis are given in parentheses.

Costs, not surprisingly, increased with coverage and the intensity of effort. The incentive option ($22,590,000) was estimated to increase costs ten-fold over the standard routine immunization offering ($2,158,000). The most expensive undertaking was the SIAs, at over $23 million. Household expenditures averted were another outcome in which SIAs had a greater impact. Their four-fold advantage in averted household expenditures is a natural consequence of the higher number of individuals reached. This relationship also plays out when comparing routine immunization with and without financial incentives; expenditures averted are almost three times higher for the lower two quintiles under the incentive option due to a similar increase in coverage. The defining strength of routine immunization with financial incentives is the change in expected household income. The financial transfer augments income in the lower two income quintiles, leading to 10.5% and 6.0% increases in the first and second quintiles, respectively. The other two delivery mechanisms achieved expected changes in household income of less than 0.2%.

Finally, the incremental cost-effectiveness ratios (ICERs) balance the health and government financial implications of each option to present the cost per death averted. This is lowest for routine immunization without financial incentives and highest for the routine option with financial incentives. The findings of the economic evaluation (Table 2) suggest that the various delivery options are associated with strikingly different benefits and costs, and this contrast is emphasized in Fig. 1. Routine immunization with financial incentives and SIAs are most similar in terms of the magnitude of investment required, and their benefits are both dramatic and divergent. SIAs achieve a greater health impact across all quintiles, while the routine immunization with financial incentives results in more modest health gains overall but did create additional demand in households in the lower two quintiles, which ultimately generated dramatic welfare improvements through increased income due to the incentives.



MCV1 refers to routine immunization with and without financial incentives (FI), and SIA refers to supplemental immunization activities

Figure 12. Extended cost-effectiveness analysis results for each immunisation program per income quartile (a) deaths averted vs. Net programmatic costs ; (b) increamental coss-effectiveness rations (ICERs), I= poorest,II= Poorer, III= Middle, IV = Richer, V = Richest

MEASLES AND RUBELLA

Thompson and Odahowski 2016

Objective: Based on the approach used for global management of polioviruses, the authors sought to develop appropriate age-specific (and for rubella sex-specific) estimates of the inputs needed to value the benefits and characterize the costs associated with a range of different options for managing measles and rubella to support economic analyses of different prospective policies and to identify key uncertainties.

Methodology:
The Authors used the data collected as part of a comprehensive review and synthesis of the existing health economics literature,(11) data from the M&RI, and additional data extracted from the literature to characterize the inputs for previously developed cost and valuation equations,(10) including: probabilities and costs of health outcomes caused by measles or rubella disease or vaccination, costs of treatment, vaccination costs (including routine immunization (RI), supplemental immunization activities (SIAs), and outbreak response), surveillance, and global programmatic costs (e.g., vaccine stockpile, coordination, technical assistance). Although we focus on global policy, we seek to account for some of the significant variability in the world by stratifying the inputs into the four different World Bank income levels (WBIL): high-income (HIGH), uppermiddle-income (UMI), lower-middle-income (LMI), and low-income (LOW),(19) similar to the approach used for polioviruses.(18) Specifically, based on the approach we applied to characterize probabilities of sequelae and disability-adjusted life years (DALYs) for CRS,(20) we characterize DALYs for all measles and rubella infection and vaccine-related adverse health outcomes assuming optimal treatment in high-income countries, minimal treatment in low-income countries, and different ratios for optimal:minimal treatment in UMI and LMI, respectively.

Results:
Measles and rubella infections lead to a large range of complications that may cause permanent disability or death, while immunization for measles and/or rubella leads to relatively rare adverse events by comparison. At the individual level, the expected DALY loss associated with measles infection significantly exceeds (by over a factor of 100) the expected DALY loss associated with vaccination, with the loss of approximately 1 DALY on average expected per measles infection in young children in relatively lower income countries.

The expected costs of measles or rubella infection significantly exceed the expected costs of vaccine adverse events. The authors estimated costs per measles infection for high-income countries fall within the range reported by prior studies, although their results show higher costs for very young children and older individuals, similar to the other study that characterized costs by age. The cost estimates per rubella case generally fall below the costs per measles case, except for women _15 years old, for which the costs associated with arthropathy increase the costs. The very high costs per CRS case for high-income countries stem largely from the relatively high fraction (35%) of CRS cases assumed to require expensive institutional care for mental retardation. For low-income countries, the costs of surgery for CHD account for most of the cost of CRS for low-income countries.

The significant disability associated with the multiple congenital defects leads to high costs and DALYs per case.

The authors' analysis leads to estimates of approximately $2.3 billion per year (55%, 28%, 14%, and 3% for HIGH, UMI, LMI, and LOW, respectively) to immunize the approximately 134,000,000 surviving infants annually (11%, 28%, 42%, 19% in HIGH, UMI, LMI, and LOW,

respectively). The trends in coverage show the increasing shift toward the use of MRCV and increasing adoption of a second RI dose. This estimate includes costs paid by countries with or without the support of external donors, and emphasize that the global benefits and costs of measles and rubella control will differ from estimates that consider a smaller scale.

Given the significantly higher costs per measles or rubella case than per dose of vaccine, these results suggest significant cost savings associated with investments in measles and rubella control and elimination.

RUBELLA

Babigumira et al, 2013

Objective: The authors present findings of an updated review of economic analyses of rubella and rubella vaccination. They examined the evidence on costs of rubella and CRS, the cost-effectiveness of adding RCV to national immunization programs, and the cost-effectiveness of different policy strategies that might be employed to add RCV to national childhood immunization schedules. Their aim was to examine the economic evidence base, assess differences in findings by country income levels, identify gaps in the evidence, and propose potential areas of future enquiry into the economics of rubella and rubella vaccination.

Methodology:
The authors reviewed studies published in English on the costs and resource use for rubella and CRS and the costs, cost-effectiveness or cost-benefit of rubella vaccination between 1970 and 2012. The review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The authors performed a systematic search of MEDLINE (PubMed) and the National Health Services Economic Evaluation Database. The studies identified were reviewed one-by-one by reading their abstracts and identifying the design of the study as reported. The review included health economic evaluations i.e. cost analyses, cost-effectiveness analyses, costutility analyses, cost-benefit analyses, cost-consequences analyses, and cost-minimization analyses. After reviewing the studies chosen, they categorized them by study design and income level of countries in which they were performed. They used the World Bank definition, which categorizes countries according to Gross National Income (GNI) per capita in 2011 as follows: low income, $1,025 or less; lower middle income, $1,026 -$4,035; upper middle income, $4,036 - $12,475; and high income, $12,476 or more. For the cost-effectiveness and cost-utility analyses, they used the 16-item Quality of Health Economics Studies (QHES) questionnaire to assess study quality. A higher score on the QHES indicates a study of better quality.

Results:
Cost-effectiveness analyses of rubella vaccination programs
Table 7 below is a summary of the five cost-effectiveness studies that evaluated rubella vaccination. Of these, four were conducted in high-income countries (one each in France,

Slovakia, the USA and Netherlands and the other was conducted in a lower-middle-income country (Guyana). Three studies assessed the cost-effectiveness of national rubella or MMR vaccination, one study evaluated different approaches to screening women to identify candidates for immunization in the and the other evaluated rubella elimination in Guyana. The three studies of national-level vaccination found that it would be cost-effective. In Hudeckova's study in Slovakia, the introduction of MMR vaccination yielded cost savings of (2012) $16 million) and a cost per case prevented of (2012) $313. Zhou's study found that a two dose MMR program in the US would save (2012) $231 per rubella case prevented and (2012) $683,813 per CRS case prevented.

Lugner et al. [39], evaluated screening followed by vaccination of susceptible women. They compared the screening of non-vaccinated pregnant women in areas of low-vaccine coverage, the screening of all pregnant women in these areas, and the screening of all non-vaccinated pregnant women throughout the country. The study, which was performed from the perspective of the healthcare system, found that screening non-vaccinated women in areas with low vaccine coverage and vaccinating the susceptible was the most cost-effective with a cost/QALY of (2012) $2,300 compared to screening all women in areas of low vaccine coverage ((2012) $62,000/QALY) and screening all women in the country ((2012) $115,000/QALY).Kandola estimated that a rubella elimination campaign in Guyana would cost (2012) $950,000. The long-term financial savings would be US$ 36.9 million (undiscounted) for a cost-effectiveness ratio of (2012) $3,335 per CRS case prevented.

Table 21 : Cost effectiveness and cost-utility analysis of vaccination programs in the general population

First author [Reference]	Chapalain [35]	Kandola [36]	Hudeckova [37]	Zhou [38]	Lugner [39]
Country	France	Guyana	Slovakia	USA	Netherlands
Year	1978	1998	2001	2004	2010
WB income group	High	Upper-middle	High	High	High
Comparators	1. Vaccinate 13-yr-olds and women	1. Rubella eradication campaign	1. National vaccination campaign	1. Rubella vaccination program	1. Screen and vaccinate all unvaccinated in LVR
	2. No vaccination	2. No campaign	2. No campaign	2. No vaccination program	2. Screen and vaccinate all pregnant in LVR
					3. Screen and vaccinate all unvaccinated in NL
Perspective	Payer*	NR	Payer	Societal	Payer
Cost components measured	Vaccination; specialist training; research; antenatal supervision; improvement of obstetric care; intensive care	NR	NR**	Vaccination; OP care; hospitalization; institutional care; special care; Indirect (premature mortality, disability, missed work)	Vaccination; screening; healthcare costs
Method of cost estimation	Top-down costing	NR	NR**	Micro-costing; Human capital approach (indirect costs)	Micro-costing
Time period for costs and benefits	15 years	5 years	NR**	40 years	16 years
Discounting (Rate)	Yes (NR)	NR	NR**	Yes (3%)	Yes (4%)
Outcomes	Mortality; lives saved	CRS cases prevented	Rubella cases prevented	Cases prevented; lives saved	QALYs
Method of outcome measurement	Primary analysis of program data	NR	NR**	Decision model	Model-based
Results—ICER (2012 US $/Outcome)	$20,474/Life saved	$3,335/CRS case prevented	$313/Case prevented	Vaccination program was dominant	1 dominated 2; the ICER comparing 3 to 1 was $114,575/QALY gained
Stated conclusion	The immunization program was cost-effective	Rubella eradication is highly cost-effective	National MMR immunization program was cost-effective	Two-dose MMR vaccination program is cost-effective	Screening and vaccinating all unvaccinated women is the most cost-effective
QHES score	30	NS	NS	93	62
Sponsor	NR	NR	NR	CDC	NL CIDC

*Not explicitly reported but inferred **Article in Slovak.
WB, World Bank; *NR*, Not Reported; *NS*, Not Scored; *OP*, Out Patient; *LVR*, Low vaccination coverage regions; *NL*, Netherlands; *CDC*, US Centers for Disease Control and Prevention; *CIDC*, Center for Infectious Disease Control; *QALYs*, Quality-Adjusted Life-Years.

4. Health Policy and programmatic issues

i. Feasibility

a) Coverage of routine measles 1st dose vaccine in Uganda? What is the current uptake of preventive health services in Ugandan children in the second year of life?

Uganda Demographic Health Surevy 2016 put measles coverage in Uganda at 80%. (UBOS and IFC 2017)

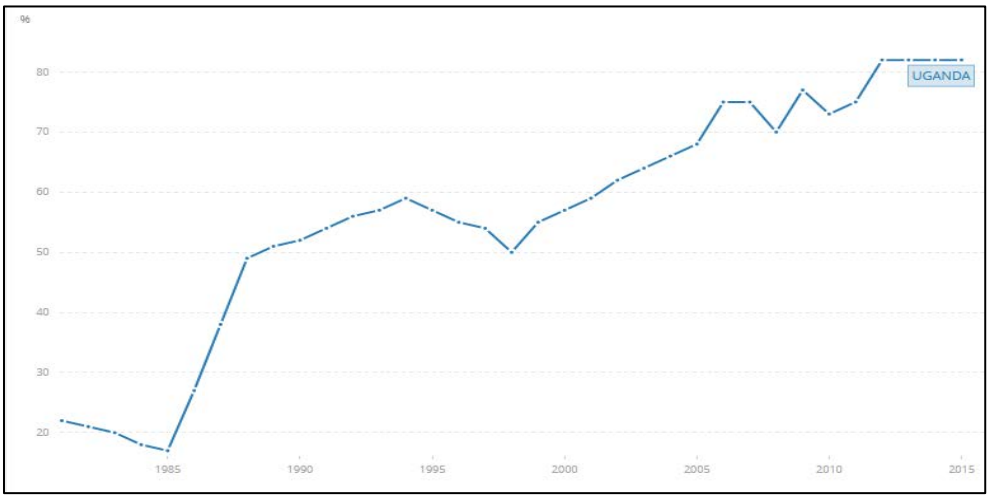


Figure 13. Trends of measles vaccine coverage for children aged 12-23 months in Uganda (1981 -2015).
Source : WHO website (who.int/immunization/monitoring_surveillance/en)

ii. Vaccine registration

b) MR vaccine registered for use in children under two years of age?

iii. Impact on resources

c) Human, technical and financial resources for distribution of monovalent Measles vaccine if introduced into routine immunization of children in the second year of life?
Same as Measles first dose.

d) Additional human, technical and financial resources required for distribution of MR if introduced as a single dose in routine immunization of children in the 2nd year of life? if introduced as two doses in routine immunization of children i.e. at 9 months and in the 2nd year of life?
Healthnet Consult, 2017
A rough estimate of costs put the cost of introducing 2 doses of MR vaccine into the routine schedule at $3.6 -$4.6 million per year between 2017 and 2021.
WHO 2015. Introducing rubella vaccine into national immunisation programs
The commonly used 10 dose MR vaccine presentation I similar in terms of packaged volume to 10-dose measles only vaccine. If the vial size does not change, the

introduction of rubella as a combination vaccine (MR) in routine immunisation program is a simple vial swap, replacing the exisiting measles vaccinein the cold chain and logistic system. As the introduction of a Measles Rubella containing vaccine must be accompanied by efforts to vaccinate women of reproductive age and health worksers, this may impacton cold chain capacity requirement.

e) Additional training needs of health workers if 2nd dose of monovalent Measles vaccine is introduced into routine immunization of children in the 2nd year of life? if a single dose of MR vaccine is introduced into routine immunization of children in the 2nd year of life? if two doses of MR vaccine are introduced into routine immunization of children i.e. at 9 months and in the 2nd year of life?

WHO 2013-A guide to introducing a second dose of measles Vaccin into routie immunisation schedules

Before implementinig MCV2, health staff wil need to receive training- even though they will be familiar with measles vaccine from administering MVC1 as part of the infant immunisation schedule. If well prepared and organized, it is feasible to cover all the necessary background information, operational issues and hands on practice in a one day training. Ideally, rather than organizing a special MCV 2 training, it is desirable to schedule the implementation so that the training can be included as part of any regular annual or refresher training. Once MCV2 is introduced in a country, implementation should be periodically reviewed through supportive supervision.

iv. Ability to evaluate

a) Is there a reliable and sustainable surveillance system for Measles infections in the country? for Rubella infections?

Mbabazi et al 2009

Measles surveillance in Uganda is implemented within the Integrated Disease Surveillance and Response (IDSR) framework. A suspected measles case is defined as any person with fever, a generalized skin rash lasting at least 3 days, and at least one of the following: cough, coryza or conjunctivitis. A confirmed measles case was defined as any suspected case (meeting the standard case definition) with a positive IgM or measles virus isolation and no history of vaccination in the 4 weeks prior to sample collection, or any suspected case that is epidemiologically linked in time, person and place to a laboratory-confirmed measles case or outbreak (WHO 1999). Any case that satisfies the suspected measles case-definition criteria is recorded in the health facility HMIS outpatients register. As with other epidemic-prone diseases, the investigating health unit maintains a line-list of suspected measles cases investigated. A weekly epidemiological surveillance report (including all suspected measles cases) is compiled from the health facility line-list of epidemic-prone diseases. At the end of each month, all suspected measles cases are aggregated in

the monthly HMIS reports sent by all health facilities of the country, through health sub-districts and district health teams, to the national health databank.
Following the initial pilot in four districts (2002) and the vaccination campaign (2003), case-based laboratory-backed measles surveillance was rolled out nationwide to improve measles surveillance. For case-based surveillance, all suspected measles cases meeting the standard case definition are investigated by filling an investigation form and obtaining a serum sample for laboratory confirmation. For each suspected measles case, detailed epidemiological information is obtained, including age, sex, vaccination status (vaccinated or not vaccinated against measles, and date of vaccination if child health card available), outcomes and serological markers (measles and rubella IgM). In outbreak settings, suspected measles cases have a throat swab and/or urine sample collected for measles virus isolation. At the health unit, case-based data is included in the monthly HMIS reports. The completed case-based measles investigation forms are transmitted to the Uganda National Expanded Programme on Immunization (UNEPI) along with serum samples (and throat swab or urine specimen) for testing at the Uganda Virus Research Institute (UVRI) Expanded Program on Immunization (EPI) laboratory

Uganda Virus Research Institute website:
http://www.uvri.go.ug/index.php/divisions/epi-labaratory?showall=1&limitstart=

The Unit lab under the Immunisable disease unit of the Uganda Virus Research Unit is mandated to conduct surveillance and research on vaccine preventable diseases in support of Uganda National Expanded Program for Immunization (UNEPI). It functions as a WHO measles regional reference laboratory.

Measles Rubella Initiative website:www.measlesrubellainitiative.org/wp-content/uploads/2015/07/01.-CRS-surveillance-in-AFR-lessons-learned-Nairobi-TAG-June-2-3-2015_June-2.pptx+&cd=6&hl=en&ct=clnk&client=firefox-b

Starting in 2007 all measles-surveillance sera were tested in parallel for measles and rubella at the Uganda Virus Resarch Insitute.(Namuwulya e al 2014). This is done in line with the Integrated Disease Surveillance and Response framework, and the Global Measles and Rubella Strategic Plan 2012-2020.

Uganda also had a CRS Sentinel surveillance site at Mulago Hospital, established in Octeber 2014.

b) Immunization program capacity to carry out AEFI monitoring of MR vaccine administered to children at either 9 months or in the 2nd year of life?

Below are findings from the latest EPI comprehensive review report (2014):

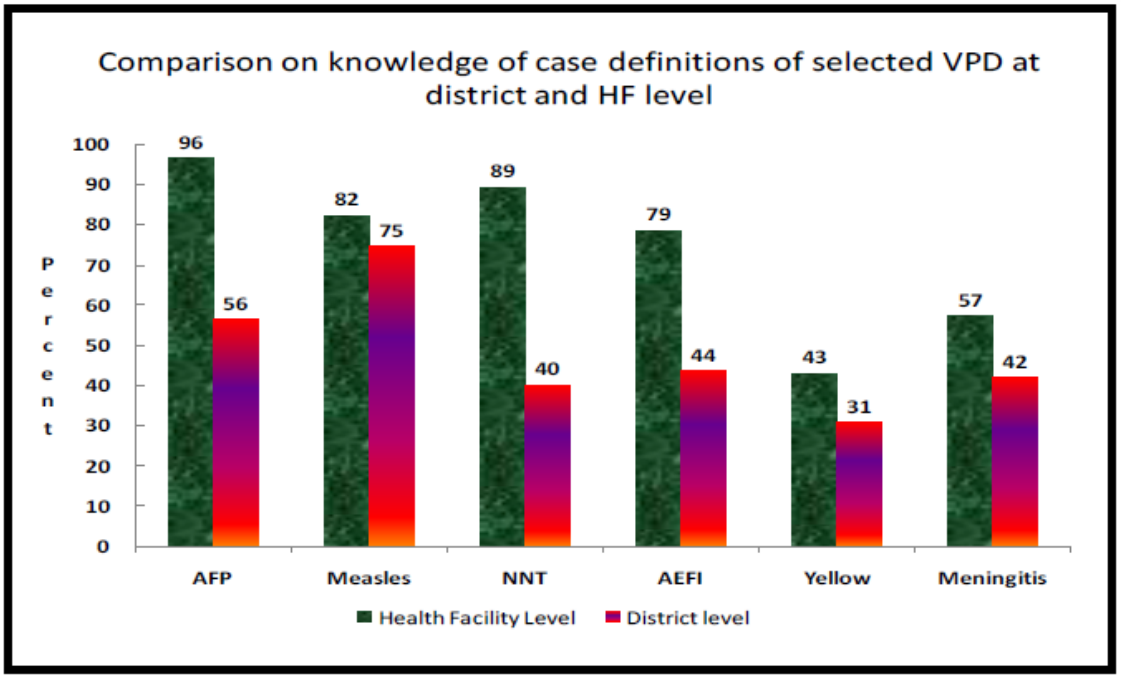


Figure 14: Health worker knowledge of selected VPD case definitions at District and Health Facility level.
Source: Ministry of Health 2014.

Surveillance guidelines were available in only 43% and AEFI guidelines in 34% of facilities visited (Ministry of Health 2014).

c) Immunization program ability to measure vaccine coverage and utilization for vaccines administered to children in the second year of life?
UNICEF website(b). https://data.unicef.org/wp-content/uploads/country_profiles/Uganda/Immunization_uga.pdf
WHO and UNICEF estimates of national immunization coverage report incorporates a grade of confidence ranking which reflects the degree of empirical support upon which the estimates are based. It is not a judgment of the quality of data reported by national authorities.
Below is the Uganda MCV 1 coverage grading :

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Estimate	66	68	75	75	70	77	73	75	82	82	82	82
Estimate GoC	•	•	••	••	••	••	•••	•••	•••	•	•	•
Official	91	86	89	86	77	81	73	75	82	97	96	94
Administrative	91	86	89	86	77	81	73	75	82	97	96	94
Survey	71	68	NA	NA	NA	NA	76	85	NA	NA	NA	NA

••• Estimate is supported by reported data [R+], coverage recalculated with an independent denominator from the World Population Prospects: 2015 revision from

the UN Population Division (D+), and at least one supporting survey within 2 years [S+]. While well supported, the estimate still carries a risk of being wrong.

•• Estimate is supported by at least one data source; [R+], [S+], or [D+]; and no data source, [R-], [D-], or [S-], challenges the estimate.

• There are no directly supporting data; or data from at least one source; [R-], [D-], [S-]; challenge the estimate

v. Acceptability

a) Perception of the public to monovalent measles vaccine administered to children in 2nd year of life?
b) Perception of the public to MR Vaccine administered to children in the 2nd year of life?

Negussie et al 2016

Context: In Ethiopia, the Expanded Program on Immunization (EPI) schedule is rarely completed as planned and the full immunization rate is only 24 % an d 15% of the infants have never received any vaccination. This study aims at identifying determinant factors of incomplete childhood immunization in Arbegona district, Sidama zone, southern Ethiopia.
Methods: A community based unmatched case-control study among randomly selected children aged 12-23 months. Cases included children that did not complete the recommended vaccination schedule. The total sample size was 548 (183 cases and 365 controls), A multi-stage sampling. Data was collected using a structured questionnaire translated into the local language. Respondents were primarily mothers. FGDs (semi-structured open-ended guide and in-depth interview guide) were performed to groups of health professionals, health workers and Head of Health Offices were used to qualitatively determined factors affecting immunization service delivery. Bivariate and multiple logistic regression analyses were done. Qualitative data were also generated and analyzed using thematic framework.
Results: Measles vaccine was the most defaulted vaccine, with a vaccination rate of only 10,9%. The BCG vaccination rate was 90 % among case and the pentavalent and BCG to measles dropout rates were 51.13 % and 87.7 %, respectively.
Quantitative Case-Control studies: From the different sociodemographic variables analyzed, maternal age, family size and birth order showed a significant positive correlation with the incomplete immunization status of children ($p<0,05$), whereas other variables such as mother's occupational or educational status, monthly income, or child sex had no significant effect. Mothers' knowledge about immunization and immunization benefits were also significantly associated with completion of child immunization schedule. In contrast different attitudes towards vaccination or perception of vaccine side effects do not have a statistically significant

impact on the completion of vaccination schedule, although the tendency is that mothers displaying negative attitudes and perceptions are more likely to have defaulter children than their counterparts. Different service delivery related factors, including missed opportunity, advice to vaccinate their child after delivery, difficulty for getting immunization shots were examined and postponing of the immunization schedule because vaccine unavailability or absence of vaccinators was the only significant variable.
Qualitative studies: FGD with health professionals or Heads of Health Centers indicated that mothers fear some common vaccine side effects. As a result, they may postpone, or not come back for, the next scheduled vaccination when they see common vaccine reactions. It was highlighted that a lack of information about common vaccine side effects Migration of mothers and unavailability of vaccines on the appointed immunization dates were found as major reasons for partial immunization of children by the qualitative method

Wolf and Madlon-Kay 2014

Context: The US were declared Measles free since 2001, however, outbreaks still occur mainly due to exported cases and low vaccine coverage. In 2011 an outbreak of measles in Minnesota was tracked back to an unvaccinated Somali child recently returned to USA from abroad. Somali constitutes a large population in Minnesota, and previous works have reported the concerns of Somali parent on vaccine safety regarding link between MMR vaccination and the risk of autism, which has caused a reduction in the numbers of Somali children vaccinated for MMR. The purpose of this study is to 1) ascertain whether Somali parents are more likely than non-Somali to refuse childhood vaccinations, and particularly MMR and 2) to determine what factor influence the decision not to vaccinate.
Methods: Parental perceptions and utilization of vaccines was explored thought the use of 35 items surveys covering the following topics: children vaccination status, reasons for vaccination compliance/noncompliance, sources of education/information on health topics, vaccination safety, MMR autism link, and demographics. Surveys were distributed to a sample of Somali and non-Somali parents of children under 5 years in a Child clinic of Minnesota. 99 surveys out of 200 were returned completed. Data were analyzed by applying descriptive statistics tests for groups comparison (2-tailed Fisher test, $P<0,05$)

Results: Results indicated that 22.2% of the Somali parents were more likely to refuse MMR vaccine specifically than non-Somali parents (5,8%) (OR=4,6 CI=1,2-1,8 $p<0,05$). For other vaccines, no significant differences were found. The solely reason that Somali parents reported for MMR vaccine refusal were linked to adverse events following vaccination. 38% of Somali parents believed that MMR could be responsible of autism vs only 8% of non-Somali ($P=0,02$). This belief is reinforced by

the discussion held within the community, and some parents claim to have found the scientific evidence supporting such connection. All Somali parents indicated to know at least one child who got autism following MMR vaccination. Other vaccines such as rotavirus, hepatitis B, varicella, DTaP were also mentioned as supposed to have a link with autism. Despite fear for MMR vaccine, 79% of parents have never refused any vaccination for their children, expressing their concerns on child becoming ill or spreading of the disease within the community if they don't get vaccinated. However, Somali parents believe that children received too many vaccines and they less comfortable than non-Somali parents with administering multiple vaccines at one visit.

Odebiyi and Ekong, 1982

Context: Measles is leading cause for children death and handicap in Nigeria. Burden of disease if often underestimated because of lack of reporting. In the ife-Ife town, one fourth of children in the handicapped classes were victims of measles complications. This study aims at understanding mother awareness regarding seriousness of the disease as well as their knowledge on its prevention.
Methods: In-depth interviews were realized to mothers addressing the following topics: 1) whether they are aware of measles vaccine and its usage, 2) measles vaccination status of their children, 3) general beliefs or feeling as regards the vaccine, 4) alternatives to prevent measles, and 5) mother's concept of the disease. The survey was realized in Ife-Ife town and sampling was done using an areal probability sampling technique (50 grid squares superposed into a city map, 10 squares randomly selected. 20 eligible households were chosen within each of the 10 selected squares. Interviews were done to the oldest mother in each household, meaning a total of 200 mothers. Data were analyzed by applying chi-squared tests.
Results: More than a half of the selected population was non-literate mothers. From the other half, most of the mothers had primary or intermediate education and only a small number had university education.
81 mothers did not believe in measles vaccine as a preventive measure, 9 claimed it to be harmful or have dangerous side effects in infants. They based their opinions on the fact the some children contracted measles even if vaccinated and some got sick after vaccination. 21 believed that measles vaccine should be combined with traditional medicine for being effective. 54 believed in the preventive capacity of the vaccine
When asked about other preventive measures, the most frequent mothers evoked traditional medicine, or traditional usages or costumes (wearing rings, disinfecting the houses, use of charms, prayers…).
The role of their socioeconomic status of the mothers on their positive or negative attitude toward measles vaccination was further analyzed. Results indicated that:

- the higher is the income level of a group, the more they will follow preventive recommendations.
- literacy level (literate vs illiterate) of interviewed mothers is correlated with beliefs in measles vaccine, although half of literate mothers did not believe in the vaccine
- similarly, mothers with higher occupational status tend to believe more in measles vaccination than unskilled, traders or unemployed mothers

The socioeconomic status of the mothers had also an impact on the beliefs regarding the origin of the disease. As thus, literate and higher occupational status tended to define measles within the natural realm, while socioeconomically disadvantaged conditions correlated with the belief of a supernatural origin of the disease. These evidences indicated that as long as people define disease within a supernatural context will be reluctant to use scientific preventive measures.
Children from socioeconomically disadvantaged sets were then less susceptible of receiving vaccination because of negative attitudes and beliefs of their mothers towards measles vaccination

Bahta and Askir, 2015

Context: Parents in Minnesota's Somali com¬munity have voiced concern that their children are disproportionately affected by autism spectrum disorder (ASD) compared with children of other ethnicities. Misinformation about a discredited study has led to the belief of an existing link between MMR vaccine and autism within the Somali community in US. As a result, MMR vaccination rates among U.S.-born children of Somali descent are declining (vaccination rate: 46%). This study proposes an approach to deal with vaccine hesitancy and increase vaccination rates within this population
Results: mains reason to refuse MMR vaccination within this community if fear to autism, and this is shared even by highly educated individuals. They based their hesitancy in the experiences with Somali Minnesotans children developing autism. The belief in an association between MMR vaccine and autism prevails over the information delivered by the Health Department. Yet, Somali community holds health care professionals in high esteem and shows an overall excellent confidence on them. Some parents are not aware of which disease MMR vaccine is preventing and they just avoid "triple-letter vaccine". Besides MMR vaccination, some parents also implicated receipt of multiple vaccines as the cause of autism. Some parents
Strategies for addressing low MMR vaccination in Somali Minnesotan children: Minnesota Depart¬ment of Health staff has been seeking ways to address the low MMR vaccination rate among children in Minnesota's So¬mali community. Staff members have had conversations with parents, interpreters, educators and community leaders about the issue, giving rise to the following strategies:

- informational session about child growth, development, autism and VPD for parents and spiritual leaders
- increase awareness of Somali children's growing vulnerability to preventable diseases
- building trust between Somali parents and clinicians which includes availability of professional interpreters that facilitate the relationship between clinician and patient, friendly and personalized treatment, straight forward information and advice
- educate parents about the safety and efficacy of vaccinating their children and provide sufficient vaccination related information before visiting the doctor, e.g. start MMR conversations at the 6 and 9 months visits.

Asfaw et al 2016

Context: Ethiopia has been implementing different strategies to reach a high complete vaccination rate among infants, however default to fully completion of child immunization is high and determinants of default to completions are not explored well. The aim of the study was to identify determinants of default to fully completion of immunization among children between ages 12 to 23 months in Sodo Zurea District, Southern Ethiopia.

Methods: Community based unmatched case-control study. Stratified sampling was used to select participants. Cases were infants aged of 12 to 23 months that missed at least one dose from a total of 8 vaccines. Controls were children in the same age interval that completed vaccination schedule. A total of 344 samples (172 cases and 172 controls) were selected. Data were collected via interview by using a pretested questionnaire. Data collectors were skilled health professionals. Data on immunization was collected from immunization cards or verbal reports. Bivariable and multivariable binary logistic regression was used to identify the determinant factors. Odds ratio, 95%CI and p - value less than 0.05 was used to measure the presence and strength of the association.

Results: Education status of care givers, maternal knowledge towards immunization and perception towards health services are statistically significant with default to complete immunization (p - value ≤ 0.05). Infants born from mothers who unable to read and write or had primary education were 9 times and 4 times more likely to default to complete immunization when compared to infants born from mothers who had secondary and above, respectively. Infants who were born from mothers that had PNC follow up were 60% less likely to default to complete immunization compared to infants who were born from mothers who didn't have PNC follow up. Infants born from mothers who had good knowledge towards immunization were 50% less likely to default to complete immunization as compared to infants born from mothers who had poor knowledge towards immunization. Regarding

perception towards uses of health institution for maternal and child health service, respondents who have good perception towards uses of health institution were 80% less likely to default complete immunization as compared to mothers who had not good perception

Brown et al, 1982

Context: One of the main problems encountered by EPI teams in low vaccine coverage in growing urban areas. This article presents a checklist to identify the reasons for such a low coverage in Yaoundé – Cameroon

Methods: a checklist with yes/no questions grouping "all imaginable questions" covering the following topics:

- Socio economic characteristics of the target population
- Poor immunization System
- Parents lack of information
- Unfavorable attitudes toward immunization

Checklist was applied to households, but it was also completed with information already available from other sources but unanalyzed (national census, national nutrition survey, EPI coverage survey etc)

Data was analyzed using chi-squared test

Results: analysis of the results indicated that children from low socioeconomic level families were largely unimmunized. Coverage for DTP and measles varied between 13 and 60% in different city neighborhoods and amongst different ethnic groups. Regarding immunization system, it was found that neither the immunization sites, immunization costs nor immunization schedule were barriers for immunization. Yet, difficulties in communication with care givers because of language may be consider a barrier since mothers may have difficulties in understanding French. Finally it was found a default in the follow up of vaccination status from EPI that do not have performing monitoring tools.

Although it was found that some parents had bad experiences on immunizations regarding vaccine low effectiveness, they show an overall favorable attitude towards immunization. Yet lack of information on children's diseases, vaccines and immunizations programme were identified as barriers for children immunizations.

Schoeps et al. 2013.

Context: Inadequate vaccination coverage is a major health problem in developing countries. Despite increase of vaccination coverage in Sub-Saharan Africa, compliance with vaccination schedules remains a challenge. Early or delayed vaccination may have potential negative consequences. This work aims at identify the determinants of timely vaccination among young children in North West Burkina Faso

Methods: Population: 1665 children between 12 and 23 months of age. The effect of socio-demographic variables on timely adherence to the complete vaccination schedule was studied in multivariable ordinal logistic regression with 3 distinct endpoints: (i) complete timely adherence (ii) failure, and (iii) missing vaccination. Three secondary endpoints were timely vaccination with BCG, Penta3, and measles, which were studied with standard multivariable logistic regression. Data collection: questionnaires (household, during routine visits and census).
Results: The study shows that only a minority of children receives timely vaccination according to schedule in Burkina Faso. Although vaccination coverage for BCG, Penta3 and Measles were relatively high (97%, 93% and 78% respectively), timely adherence for vaccination schedule was 70% for BCG, but only 48% for Penta3 and 46% for measles.
Area of residence, season of birth, mother's education, and socio-economic status were significant predictors for incomplete adherence to the whole vaccination schedule. Living in an urban area was strongly associated with failing to adhere to the vaccination schedule. Rural children living within 5 km to the closest health facility were least likely to fail timely completion of the vaccination schedule. Season of birth was significantly related to complete timely vaccination with children born in the dry season being at higher risk for failure than children born in the rainy season. Number of household members or number of siblings was not associated with timely vaccination coverage of the complete schedule. Children of older mothers appeared to be less likely to fail the vaccination schedule but this difference was not statistically significant. The effect of education on timely vaccination was strongest for Penta3 and still significant for measles vaccination. Children of mothers with some education were less likely to fail timely vaccination as compared to mothers without any reading ability. For BCG, there was no effect of mothers' education. The number of siblings or household members and the age of the mother at birth of the child were in general unrelated to vaccination failure, except that children with one or more sisters or brothers were more likely to fail timely vaccination of Penta3.

Onsomu et al 2015

Context: The purpose of this study is to examine the association between maternal education and child immunization in order to get insight on reasons for under vaccination in Kenya, since previous studies have shown the strong impact of maternal education on infant and child health.

Methods: retrospective cross-sectional data from the 2008–2009 Kenya Demographic and Health Survey for women aged 15–49, who had children aged 12–23 months (n=1717), and who answered questions about vaccination in the survey.

Data analyses for descriptive, bivariate, univariate and multivariate logistic regression analyses were conducted

Results: There was a significant difference between mothers with primary education or above, and those with less than primary or no education. Compared with those with no education, more women with primary education immunized their children (in the case of measles 75 vs. 64 %). For measles, women with primary and secondary Education were 2.50 (p\0.01) and 2.49 (p\0.01) (after adjusting for other covariates) times more likely, respectively, to immunize their children than those with less than primary or no education.

Wealth, age, desire for more children, and health insurance were associated with increased likelihood of immunization against measles. Women who were wealthier were 2.01 (p\0.01) times more likely to have their children immunized than those in the poorest category. All other age groups were more likely to immunize their children than those aged 15–19, with the highest odds observed among those aged 45–49 (OR 5.83, p\0.01). Women who desired to have more children after 2 years and those who had no desire, were sterilized, or infertile were 65 % (p\0.01) and 63 % (p\0.05) less likely to immunize their children than those who desired to have children within 2 years. Those who had health insurance were 2.03 (p\0.05) times more likely to immunize their children than those without (Similar results were obtained with other vaccines analyzed: polio, tuberculosis, DTP and BCG)

vi. Equity

a) Vulnerable, hard-to-reach and immigrant populations able to access vaccines administered to children in the second year of life?

UNICEF 2016. Uganda Immunization Equity Assessment Report,

- 'immunisation equity assessment' was commissioned to support national stakeholders and district stakeholders to get a list of districts with inequities and high risk communities, identify barriers to access and use of immunisation in those communities, then come up with recommendations and actions
- This exercise was done in Uganda in September 2016 through a process of collecting views of EPI stakeholders and DHOs by key informant interviews, desk review of documents like UDHS report 2011and EPI Review 2015, analysis of UDHIS2 data, surveillance data and Secondary analysis of GAVI FCE house hold data from 19 districts. This was followed by a consensus building workshop in Iganga
- The 36 districts with immunization inequities contribute 53% of the under immunised children for DPT3 for the period 2013 to 2015. On the other hand, the identified 241 sub counties out of 1386 (17.4%) contribute 49% of the under immunised children for the period 2014 – 2015.

- The high risk communities / underserved communities identified were: urban poor settlements, migrants, ethnic minorities, some religious sects (especially Muslims, Bisaka sect and triple 6), upcoming town settlements, fishing communities, Refugee communities, remote rural, Island and mountainous communities
- The districts with immunization inequities were: Adjuman, Amudat, Amuria, Arua, Buikwe, Butalejja, Butambala, Buyende, Hoima, Ibanda, Isingiro, Jinja, Kaabong, Kaliro, Kalungu, Kamwenge, Kapchorwa, Kibaale, Kibuku, Kisoro, Kween, Kyankwanzi, Kyenjonjo, Manafa, Masindi, Mayuge, Mbarara, Moyo, Mubende, Nebbi, Pallisa, Rakai, Sembabule, Sheema, Wakiso and Yumbe. However, Kampala district was considered to be the 37th district with immunization inequities because it had the largest number of under immunized children for DPT3 for the period 2013 to 2015
- The social economic factors that cause immunization inequities in Uganda were: religion, tribe, maternal education, wealth quintile, place of child delivery, travel time and transportation costs to service delivery points.
- The system factors that were prevalent in districts and sub counties with immunization inequities were: Human resource challenges like DHT teams with weak leadership, absenteeism, non-transparency with funds and poor supervision,; Logistics issues like non-distribution of vaccines from district vaccine stores to lower health facilities and gas shortages.

Table 22.Matrix for high risk communities and barriers

High risk communities	Barrier: HF (supply side)	Barrier: Community (demand side)
Urban Poor Settlements	There are few government facilities	Leaders do not attend immunization planning meetings eas and services are costly in private clinics
Migrants	Fixed Service delivery service points do not match mobility pattern of those communities -Lack of trained Village health teams	Rural Location ; Maternal Education (Primary education) - Inadequate mobilization due to limited facilitation to VHTs.
Ethnic Minorities	- Health workers in such areas are largely non-qualified staff or nursing assistants	Where such communities live, there are impassable roads during the rainy seasons and too dusty during the dry spells
Religious groups	Poor Communication & Mobilisation strategies	Religious beliefs and Misconceptions on

High risk communities	Barrier: HF (supply side)	Barrier: Community (demand side)
	-Inadequate sensitization of the religious leaders	immunisation on contents of the vaccine
Upcoming town settlements	Attitude as perceived by the parents towards health workers that they are rude, long waiting time for parents at facilities while the parents have little time	Low maternal education affects in such areas
Fishing Communities	Service delivery time not favouring their working patterns - Difficult to plan, locate and reach the fishing populations - Limited immunization Services/posts	Majority of the people sell their fish in the morning when immunisation services are being offered - They are mobile populations
Refugee communities	Failure to communicate due to language barrier	Lack of organised leadership structures in such communities - Lack of awareness on availability of service points
Remote rural, Islanders & mountain living communities	-Irregular and unreliable outreach sessions -Inadequate knowledge of the health workers; inadequate staffing in such areas -Rift valley escapements make transport difficult -Inadequate logistics for immunization -Poor road & building Infrastructure	high cost of travel from community to health centre, -Low education levels of care takers - District councils and sub county Local councils not prioritizing immunization service delivery -Low community awareness of benefits for immunisation

IV. Discussion

Disease Burden

a. Uganda continues to face sporadic measles outbreaks with the last large outbreaks in 2016. Several measles infections can lead to blindness, encephalitis, severe diarrhea, and death. The increased presence of measles could be attributed to the refugees entering from South Sudan and the Democratic Republic of the Congo. Uganda is currently not at the 92-95% immunity required to stop measles transmission.

b. Rubella is a mild, self-limiting disorder. However, when rubella infections occur shortly before conception or during early pregnancy, they can lead to babies getting Congenital Rubella Syndrome, which may lead to miscarriage, fetal death, or congenital defects. Many people are infected with rubella throughout their lifetimes. 95.5% of women in Mulago National Referral hospital in 2014 tested positive for rubella IgG (past exposure), indicating presence of circulating virus within the population, although none of the women in that study covering over 600 cases tested positive for Rubella IgM (active infection).
c. Incidence of CRS recorded between October 2014 and June 2015 at the Mulago surveillance site was 6 patients, 3 males 3 females, with a median age of 8 months. CRS cases were observed to suffer from congenital heart defects, hearing and vision impairments, mental retardation, and other serious and life debilitating conditions.
d. Information from surveillance sites showed that measles infections are highest between 9 months and 15 year olds, peaking at 1 year, and rubella infections are highest between 9 months and 16year olds peaking at 6 years. Confirmed Rubella infection cases were higher than measles cases, and considering that Rubella infections

Vaccine characteristics, safety, efficacy and effectiveness

a. Second doses of measles vaccine are effective in improving children's immunity. Sero-positivity values were higher in children that had received 2 doses of MCV nine months apart than those that received only 1 MCV dose; the improvements were even more marked in immunocompromised/HIV infected children. The introduction of MCV2 to routine schedule can (1) slow the accumulation of susceptible children and allow a lengthening of the interval between SIAs (2) decrease the country's reliance on SIAs and eventually stop SIAS once high population immunity can maintained with routine two dose schedule alone.
b. Sero-conversion was better in children that received their first measles vaccine at 9 months that those that received it at 6 months.
c. One dose of either type of rubella vaccine (monovalent formulations or in combination with other vaccine) is recommended for persons ≥ 12 months old to prevent rubella. MMR and MR vaccines are at least 95% effective in preventing clinical measles. The most effective MR containing vaccine out of the Urabe, Jeryl Lynn, and Leningrad strains is the Jeryl Lynn one Follow-up studies indicate that one dose of rubella vaccine can provide life-long immunity.

d. Evidence shows no serious adverse events because of the monovalent measles vaccination at all ages. Adverse reactions following measles vaccination are generally mild and transient. Slight pain and tenderness at the site of injection may occur within 24 hours; this is sometimes followed by a mild fever and local adenopathy. About 7–12 days after vaccination, up to 5% may experience fever of at least 39.4 °C for 1–2 days. The fever occasionally induces febrile seizures (in about 1/3000 people). Adverse events, with the exception of anaphylactic reactions, are less likely to occur after receipt of MCV2.

e. There was an associated risk for meningitis with MMR vaccinations with Urabe strain as found in Esteghamati's study (note: production with this strain has since been stopped). In addition, febrile seizures have been found to be associated with MMR vaccine, as found when administrated in preschool Danish children.

f. Based on the identified studies, no significant association could be assessed between MMR immunisation and the following conditions: autism, asthma, leukemia, hay fever, type 1 diabetes, gait disturbance, Crohn's disease, demyelinating diseases, bacterial or viral infections.

Economic Consideration

a. There is high benefit to cost ratio for measles 2 dose vaccination, with noted 4.5/1 ratios in Israel. Higher benefit to cost ratios should be expected for countries with higher incidence rates like Uganda.

b. A recent costing study by WHO (Uganda) indicated that vaccine purchase accounts for 90% of new vaccine introduction costs. MV, MR, and MMR vaccinations are all cost effective, in terms of cases averted, deaths averted, costs to health care averted, and DALYs averted. However, the relatively high prices of MR and MMR vaccinations must be greatly considered as health receives a small allocation (currently about 8%) of the country's budget. MR vaccines are 3x the price of MV vaccines, and MMR vaccine costs are 5x the cost of MV vaccines. Thimerosal, a vaccine preservative, increases the costs of the MMR vaccine packaged in 10 dose vials.

c. Gavi provides support for large-scale catch-up campaigns with the measles rubella (MR) vaccine. This is done on the basis that countries then self-finance routine introductions of the vaccine. The Measles-Rubella initiative also provides some funding to countries introducing MR vaccine as well as technical support.
It was not very clear if and how Gavi provides funding support to countries introducing a 2nd dose of monovalent measles vaccine.

Feasibility, ability to evaluate and equity issues

a. The percentage of children aged 9-23 months that have received measles vaccine by 12 months has improved from 58% in 2011 to 80% in 2016 (UBOS 2016). A vaccine effectiveness study in Kampala 2006 put the measles vaccine efficacy at 74% (Mupere et al. 2006). Current problems with measles immunization stem from low quality Supplementary Immunization Activities and lower sero-conversion at 9

months compared to 12 months and older. According to WHO, measles elimination is achieved when MCV 1 and MCV2 coverage is consistently above 95%. Studies show that countries should consider introduction MR vaccines if they are able to achieve and maintain 80% or higher coverage with their regular childhood measles vaccination campaigns. Including an RCV in regular childhood measles vaccination campaigns that cover less than 80% of the child population could result in decreased rubella virus circulation, which could increase the average age of rubella infection for females from childhood to the childbearing years, increasing risk of CRS.

b. There is limited availability of the MR vaccine as there is only one WHO prequalified manufacturer. The vaccine mostly available is the MMR Leningrad-Zagreb mumps strain. MMR vaccine with Jeryl-Lynn mumps strain is only offered to countries that previously procure this vaccine through UNICEF. Vaccine supply predictions should not be a hindrance to UNITAG recommendations as supply information changes

c. As found in studies conducted in Australia, there is the social impact of developing cardiac disease, diabetes that accompanies CRS and both the children with CRS and their families are negatively impacted throughout their lifetimes.

d. For elimination campaigns in immunization to be effective, they should be done as a regional block as evidenced by PAHO in the Americas. Within the East African region, Rwanda introduced MR vaccine in 2013 as a 2 dose schedule, as did Tanzania in 2014. Kenya conducted a mass MR campaign in 2016, with plans to introduce MR in routine in 2017, and Burundi conducted mass MR immunisation in May 2017.

V. Proposed recommendation (s) /options

1. Uganda should switch from monovalent measles to MR vaccine at as MCV 1 given at 9 months. However, it is important that Government and partners work to increase and sustain MCV1 coverage in rutine to >95% as recommneded by WHO. In addition, prioir to inroduction, a lage scale campaign with MR covering childen aged 9 months to 15 yearsis recommneded starting earliest 2019.

2. Introduce 2nd dose of MR at 15-18 months into routine schedule as a cost effective measure to improve overall measles vaccine coverage to >95%, reduce the burden of measles and rubella in the country, and reduce the need and frequency of Supplemental Immunisation Activities.

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VII. Annexes

1. Advise Request Letter from Ministry of Health

Telephone: General Lines: 340874/ 231563/9
Permanent Secretary's Office: 256 - 41 - 340872
Fax: 256 - 41 - 231584

THE REPUBLIC OF UGANDA

Ministry of Health
P.O. Box 7272
Kampala
Uganda

IN ANY CORRESPONDENCE ON
THIS SUBJECT PLEASE QUOTE NO: **ADM:215/306/01**

22nd June 2016

Dr. Nelson Sewankambo,
Chairperson for NITAG Uganda,

RE: REQUEST TO NITAG TO ADVICE THE IMMUNIZATION PROGRAM TO PRIORITIZE WHICH NEW VACCINES SHOULD BE INTRODUCED

The goal of immunization program is to ensure that every child and high-risk group is fully vaccinated with high quality and effective vaccines against the target diseases according to recommended strategies through five operational components: vaccine supply and quality, logistics, service delivery, surveillance, advocacy and communication.

SAGE has made several recommendations to countries to introduce new vaccines into their routine immunization program following evidence presented to them to show that they are effective and efficacious. Over the last three years, Uganda has introduced three new vaccines into the routine immunization program and plans to introduce yellow fever vaccine, Measles and Rubella Vaccine including second dose, Men A and Tetanus Diptheria(Td) Vaccine.
However along the way the program has observed some challenges and anticipates more to come as more new vaccines are introduced into the routine immunization program. Among these challenges, includes fulfilling co financing requirements for the recently introduced vaccine affecting the performance of new vaccine introduction

In line with the WHO recommendation, Uganda established the NITAG to provide evidence based advice to the Ministry of Health on immunization.

The purpose of this letter is therefore to request the NITAG to provide guidance on which new vaccine Uganda's immunization program should prioritize in order of importance in the next five years. Your response will highly be appreciated preferably by end of 2016.

Prof. Anthony K. Mbonye
FOR DIRECTOR GENERAL HEALTH SERVICES

Cc: The Permanent Secretary, Ministry of Uganda
Cc: The Director Health Services, Clinical and Community
Cc: Commissioner Health Services, National Disease Control
Cc: The Program Manager, UNEPI

2. List of Working Group Members

i. Prof. Nelson Sewankambo – Core member, Medicine(Chair)
ii. Prof. Sabrina Kitaka– Core member, Pediatrics amd Adolescent Health
iii. Dr. Eva Kabwongera– Liaison member, UNICEF
iv. Dr. Patrick Kadama – Liaison member, ACHEST

3. Evidence search process and results

Attached as separate excel document

Uganda Immunization Technical Advisory Group

Recommendation on Yellow fever vaccination in routine immunization

Uganda Immunization Technical Advisory Group

Recommendation on Yellow fever vaccination in routine immunization:

SHOULD YELLOW FEVER VACCINATION BE EXPANDED INTO THE ROUTINE IMMUNIZATION SCHEDULE OF ALL CHILDREN IN UGANDA?

SEPTEMBER 2017

Contents

Executive summary

The Ministry of Health asked the Uganda National Technical Advisory Group (UNITAG) to make recommendations on the prioritization of various new vaccines to introduce to the routine immunisation schedule. Current challenges to the immunization program's vaccine introduction efforts such as low coverage and limited financing prompted this request. The five new vaccines proposed for introductions are: Hepatitis B birth dose, Yellow Fever, Meningococcal A, 2nd dose of measles containing vaccine and a switch from Tetanus Toxoid to Tetanus diphtheria.

The vaccine considered in this dossier is Yellow Fever (YF). YF is a mosquito-borne viral disease of humans and other primates, and is currently endemic in 44 countries in the tropical regions of Africa and South America. Infection with yellow fever can either be asymptomatic or cause a wide spectrum of disease, from mild symptoms to severe illness with bleeding, jaundice, renal-hepato disease and, ultimately, death. In incidences of severe disease, sometimes intensive hospital care is needed. There is no evidence to date of antiviral or other pharmacological therapies that are effective against the YF virus. Severe cases have no clear treatment protocol and cases of renal-hepato disease have high fatality rates of 20-50%. WHO recommends that in YF endemic countries, YF vaccines be administered by a single dose (0.5 ml) that would offer protection for over 30 years and possibly life. Uganda falls within the YF endemic zone in Africa, but yellow fever vaccination is not part of the routine immunization schedule. While sero-prevalence of the disease was found to be low, the risk for a yellow fever outbreak remains.

A systematic review of literature found that Uganda has had 2 yellow fever outbreaks in the recent past: in 2010 and 2016. A WHO Yellow Fever Risk Assessment in 2012 reported that Uganda is vulnerable to Yellow fever sporadic outbreaks given its location in the Yellow Fever belt, the YF naïve population with low natural immunity, and the presence of potential vector carriers. Importations of yellow fever could lead to rapid spread.

YFV is a live attenuated vaccine packaged as a lyphosized vaccine that is reconstituted using a sterile diluent 0.5ml before being administered through sub-cutaneous injection. When well implemented by strong health systems, YF routine immunization for babies between 9 and 24 months in the EPI can provide sufficient population immunity in the long term. Sero conversion rates of 90-99% have been demonstrated. There are no serious adverse events related to yellow fever vaccination in people over 8 months of age. WHO recommends the vaccine not be given to children 6-8 months due to risks associated neurotropic disease. The vaccine is also not recommended for thymectomized individuals (treatment of thymoma), Thymus disease, severe malnutrition, and severely immunocompromised. Some studies showed interference from other vaccines applied simultaneously, particularly those from live attenuated viruses. A single dose of YF vaccine offers life-long protection.

Evidence from West African countries showed that routine schedule approach was more cost effective in the long run, compared to reactive vaccinations. Studies also found that adding preventive campaigns to complement routine YF immunization programmes is cost-effective, especially if the countries at highest risk are the focus of such prevention campaigns. It was calculated that it would cost about 1.6 million to introduce a yellow fever vaccine, but the yellow fever is not listed on the Gavi supported new vaccine introduction list for Uganda, therefore all its costs would be on the government.

Recommendation on Yellow Fever Vaccination in routine immunization

The supply of YF vaccine has been shown to outstrip demand in some countries following introduction, resulting on stock outs.

Based on this evidence, the working group made the following recommendations;

a. The introduction of a Yellow Fever Vaccine to Uganda's routine immunization schedule at 12 months of age, which is recommended if government has enough fiscal space to ensure sustainable financial support.
b. Uganda should quantify vaccine needs and submit timely request through UNICEF to ensure secure sustainable supply when ready for routine introduction.
c. Before routine introduction, there shouldl be concerted efforts needed in advocacy and communication to ensure high coverage with the immunization platform's extension to 12 months.

I. Introduction

a. Context of the question

The Ministry of Health (MoH) in Uganda through its Comprehensive Multiyear Plan 2016-2020, proposed to introduce five new vaccines into the routine immunisation program, one of which is Yellow Fever (YF) in 2017. MoH requested Uganda National Immunisation Technical Advisory Group (UNITAG) for advice on which new vaccines Uganda should prioritise in the next five years, in view of challenges facing the immunisation program, including under-performance and limited financing. (Request letter attached as Annex 1)

b. General information on the issue

YF is a mosquito-borne viral disease of humans and other primates, and is currently endemic in 44 countries in the tropical regions of Africa and South America. YF Disease is caused by a virus whose prototype of the genus Flavivirus, which is comprised of around 70 different arthropod-borne viruses. YF is transmitted in three ways:

i. Sylvatic (or jungle) YF is usually a disease of non-human primates and transmission is via several species of Haemagogus and Aedes mosquitoes found in the forest canopy. Transmission to humans is incidental, via bites from mosquitoes that have fed on viraemic non-human primates. This is most commonly seen in men in Central and South America that work in the forests.
ii. Intermediate YF transmission is seen in humid regions in Africa where Aedes species are able to breed both in the wild and around households, and to infect both non-human primates and humans. Intermediate transmission usually results in sporadic cases occurring simultaneously in different villages in the same area but large outbreaks of the disease have also been associated with this transmission cycle.
iii. Urban YF transmission results in large epidemics which occur when infected people move to densely populated areas where the local population has little or no immunity to YF and where *Aedes aegypti (A. Aegypti*) is active. Infected mosquitoes transmit the virus from person to person.

Infection with the YF virus can be asymptomatic or cause a wide spectrum of disease, from mild symptoms to severe illness with bleeding, jaundice and, ultimately, death. Physical symptoms usually appear 3–6 days after a bite from an infected mosquito. Typically, the disease onset is abrupt, with fever, muscle pain, particularly backache, headache, shivering, loss of appetite, and nausea or vomiting. Congestion of the conjunctivae and face are common, as well as relative bradycardia in the presence of fever. The patient is usually viraemic during this period, which lasts for approximately 3–6 days. In approximately 15% of infected persons, the illness recurs in more severe form after a brief remission of 2–24 hours. Symptoms include fever, nausea, vomiting, epigastric pain, jaundice, renal insufficiency, and cardiovascular instability. A bleeding diathesis can occur causing gastrointestinal bleeding, haematuria, skin petechiae, ecchymoses, epistaxis, and bleeding from the gums and needle-puncture sites. Physical findings include: scleral and dermal jaundice, haemorrhages at different sites and epigastric tenderness without hepatic enlargement. About 20%–50% of patients with hepato-renal failure die, usually 7–10 days after the onset of disease. Patients surviving YF may experience prolonged weakness and fatigue, but healing of the liver and kidney injuries is usually complete.

Clinical diagnosis of YF is difficult and is often confused with severe malaria, leptospirosis, viral hepatitis (especially fulminant hepatitis), other haemorrhagic fevers, infection with other flaviviruses (e.g. dengue haemorrhagic fever), and poisoning. Laboratory diagnosis of YF is generally accomplished by testing serum to detect virus-specific IgM and neutralizing antibodies. YF infection does not always induce a detectable specific IgM response, particularly in people who have previously been infected with other flaviviruses. A confirmatory test for Neutralizing anti-body levels is measured using the Plaque Reduction Neutralising Test (PRNT).

There is no evidence to date of antiviral or other pharmacological therapies that are effective against the YF virus. Treatment is based on supportive clinical management. In mild disease, paracetamol is used to treat the symptoms of fever, myalgia and back pain. In severe disease, management of specific manifestations requires intensive hospital care.

The WHO position paper on Yellow Fever (WHO 2013) recommends that in YF endemic countries, YF vaccines be given as a single dose (0.5 ml), which offers protection for over 30 years and possibly life. Uganda falls within the YF endemic zone in Africa. However, YF vaccination is not part of the routine national immunization programme in Uganda. The only category of the population that is routinely immunized against YF is international travellers.

In 2012, a yellow fever risk assessment was carried following a YF outbreak in 2010 in northern Uganda (who 2012). The assessment found low (6%) sero-prevalence for YF IgG in humans, no virus was isolated in the vectors sampled, and observed a non anthropophilic biting behaviour of several of the vectors available. However, the study noted that the risk for outbreaks still remains should the virus be introduced through infected travellers, because of the largely YF virus naive Ugandan population and that competent vectors are prevalent in the country.

II. Methodology

a. Establishment of a working group

In line with its internal procedures manual, the UNITAG Chair in consultation with the Secretariat commissioned a working group to develop a Recommendation Framework on Hepatitis B birth dose introduction in Uganda's routine immunisation program, and conduct a systematic review of relevant evidence based on which, recommendations would be proposed. The Working Group was chaired by the Vaccinology Core-member representative and comprised of the following UNITAG members: Paediatrician, Epidemiologist, Public Health expert and a Health Economist (List attached as Annex 2).

b. Recommendation framework.

The working group reviewed evidence on Burden of Yellow Fever Disease in Uganda and the region, Efficacy and safety of available yellow fever vaccines, Programmatic and Economic Considerations, Policy issues and Acceptability. A detailed Recommendation Framework is attached as Annex 3.

c. Evidence search and assessment.

The Working group followed the steps outlined below in its evidence search and assessment:

•Step 1: Framing questions for the review

The queries in the Recommendation Framework were reviewed to ensure that they were specified in the form of clear, unambiguous and structured questions before beginning the review work. Queries were categorised as those that required a systematic review, and those that could be answered using background information. Once the review questions had been set, modifications to the protocol was allowed only if alternative ways of defining the populations, interventions, outcomes or study designs became apparent. Queries requiring systematic reviews proceeded to step 2, while grey literature (Ministry of Health Reports, Immunisation partner surveys, websites and unpublished local reports) were searched for information to answer background data queries.

•Step 2: Identifying relevant peer reviewed articles

Search strategies were developed to ensure that search terms covered all known terms relevant to the question. Multiple journal resources (Pubmed, Scopus and Embase) were searched with English language restriction to generate relevant title-abstracts. Selection criteria were set for each query to flow directly from the review question and was specified a priori. Reasons for inclusion and exclusion were recorded.

•Step 3: Assessing the quality of articles

Selected title abstracts were extracted in full text and subjected to a more refined quality assessment by use a design-based quality checklists; CASP[1]. These detailed quality assessments were used for exploring for bias by evaluating its methodological quality, certainty of results, and relevance to the question, hence informing decisions regarding suitability of meta-analysis (Step 4).

•Step 4: Summarizing the evidence

[1] http://www.casp-uk.net/casp-tools-checklists

Selected full text articles were read and relevant findings under each query were summarised in a standard UNITAG working group outline report. These were then presented to the Working Group members for review, and discussion.

•Step 5: Interpreting the findings

The working group provided technical backstopping by checking that the issues highlighted in each of the four steps above were met. The risk of publication bias and related biases was explored to help determine whether the summary reports can be trusted, and, if the summaries were generated from high-quality studies that could be used for generating recommendations.

The working group members deliberated the evidence presented and developed recommendations which were graded by reference to the strengths and weaknesses of the evidence.

III. Presentation of the evidence

a. Vaccine and immunization characteristics

i. Safety

- Safety profile of Yellow Fever vaccination in children aged 6 - 24 months old

Belmusto-Worn, 2005.

- Type of study
    - Randomized, double-blind, phase III vaccine trial in Sullana in northern Peru in a pediatric population

- Objectives
    - To determine the safety, tolerability, and efficacy, by measurement of neutralizing antibody responses, of two YF vaccines (Arilvax and YF-Vax) and to assess the consistency in production of three different lots of Arilvax
    - Demonstrate non-inferiority in immunogenicity of Arilvax compared with TF-Vax

- Design
    - Healthy children 9 months- 10 years of age
    - Safety and efficacy by measurement of geometric mean neutralizing antibody triter response
    - Two yellow fever vaccines (17D vaccines Arilvax and YF-Vax)
    - Sullana lies outside the YF enzootic area and YF vaccination shortages have continued to exist; study population can be exposed to urban outbreaks
    - 2:1 ratio of Arilvax to YF-Vax was followed
    - Vaccinations were conducted between May and November 2002
    - Safety was assessed by recording all adverse events that occurred after vaccination
    - All subjects received a 31 day follow up

  - Immunity was determined by neutralizing antibodies (principal mediator of immunity)
    - Correlate of protection from disease in non-human primates
  - Sera collected on days 1 and 31—tested for neutralizing antibodies
  - Day 1 sera was also tested for pre-existing immunity to dengue virus serotypes 1, 2, 3, and 4 by ELISA and plaque-reduction neutralization test
  - Seroconversion to YF virus was defined as a log10 neutralizing index $\geq$ 0.7 (LNI)
    - Virus titer of a mixture of serum and virus between baseline and post-immunization samples
    - Represents the antibody titer required to protect against lethal challenge
  - Primary efficacy analysis consisted of comparing the proportion of subjects who seroconverted to YF virus 30 days post-vaccination in the two vaccine groups
  - Age groups: 9-18 months, > 18-36 months, >36-60 months, an d60 months plus one day to 10 years
  - Secondary analysis entailed the comparison of geometric mean titers of the two vaccines
  - Safety and tolerability were assessed by comparing incidence, expressed in percent, of adverse events across the vaccine arms by chi-square test
    - Looked at whether antibodies to YF or dengue at baseline differed with respect to the incidence of adverse events in the two vaccine groups
- Specific Results in relation with the query (include limitation of the study)
  - Safety results
    - No serious adverse events reported by Arilvax recipients
    - Two children had three unrelated serious adverse events in the YF-Vax group (bronchial pneumonia; urinary tract infection; E. Coli infection)
    - No subjects had febrile syndrome clinically suspicious of YF vaccine-associated viscerotropic disease
    - Majority of related adverse events were mild and resolved within 24-48 hours post-vaccination
    - >5% subjects reported adverse events, similar in both vaccine groups
    - Injection site pain 3.8% reported in Arilvax and 1.4% reported following YF-Vax
    - Incidence of encephalitis following YF vaccination in children $\geq$ 9 months of age is not known with precision, but believed to be very low
  - Seroconversion in Peru was lower than in the US (99% reported)
  - Factors that can potentially affect immune response to YF 17D vaccine
    - Pre-existing immunity to antigenically related cross-protective flaviviruses (dengue)
    - Immunosuppression due to underlying disease or drug treatment
    - Severe malnutrition
    - Pregnancy
  - Two vaccines are highly immunogenic and well tolerated
  - Limitations:
    - Younger age groups could have led to the under-reporting of mild adverse event symptoms

  - Small sample size to determine the seroconversion effects due to cross-reactivity in dengue immune individuals
  - Small sample size also poses limitations in identifying rare serious adverse reactions such as systemic allergic reactions

Nordin et. al 2013

- Type of study
  - Retrospective study using two large closed cohorts

- Objectives
  - To use automated claims data from the Vaccine Safety Datalink (VSD) and US Department of Defense (DoD) to estimate risks for medical visits following allergic or local reactions and mild systemic reactions and to evaluate the rate of hospitalizations due to medical conditions that have been associated with YF-vaccine (associated viscerotropic disease and associated neurologic disease)

- Design
  - Vaccine Safety Datalink (VSD) and US Department of Defense (DoD) data used to identify adverse reactions following YF vaccination
  - ICD9 codes were used to analyze allergic reactions, local reactions, mild systemic reactions, and possible visceral and neurologic adverse events
  - Cohort included pediatric (0-17 years) and adults (≥ 18 years)
  - VSD: January 1, 1991 to December 31, 2006
  - DoD: January 1, 1999 to December 31, 2007
  - Only first YF vaccine doses were studied
  - *VSD data—only one with pediatric cases, DoD were only military personnel adults only 18 years or older)*
  - Risk window for viscera was 0-16 days and for neurologic 0-36 days post-vaccination or matched index date
  - VSD for outpatient mild systemic reactions was set to 1-10 days post-vaccination or index date

- Specific Results in relation with the query (include limitation of the study)
  - VSD cohort, allergic, local, and mild systemic reactions were not statistically different between YF-vaccine-exposed and unexposed subjects
  - DoD cohort there was an increased risk for outpatient allergic events in the period following vaccination with YF and other vaccines, no increased risk for inpatient allergic reactions
  - Estimated death rate in DoD cohort was 0.89 for 1,000,000 YF vaccine doses and no YF vaccine-associated deaths in the VSD cohort
    - Consistent with previous reports
  - No increased risk for visceral or neurologic events following vaccination were detected

- YF-vaccine-associated neurologic diseases manifests as several distinct clinical syndromes, including meningoencephalitis, Guillain –Barre syndrome, or acute disseminated encephalomyelitis
- 70% of YF-vaccine-exposed were pediatric subjects
- Pediatric subjects had no inpatient allergic or local reactions, no subjects had presumed anaphylaxis
- Pediatric subjects had no significant increase in medically attended mild systemic reactions within 10 days of vaccination
- Visceral events
  - Only one inpatient visceral event in pediatric cohort
  - Occurred 16 days post vaccination (10/100,000 doses)
- Neurologic events
  - No inpatient events following YF vaccination occurred in the pediatric cohort
- Death
  - No deaths in the pediatric cohort
- Limitations
  - Neurologic events and visceral events were cases defined by the Brighton definition; no laboratory nor radiological data were available
    - These two case events were limited to inpatient hospitalizations (for allergic and local reactions included both inpatient and outpatient visits)
    - Relied on medically attended events and case definitions not diagnosis for the YF vaccine related neurological or visceral events
  - Chart reviews only available for the VSD subjects not for DoD
  - Underpowered to assess the risk of death following YF vaccine
  - Analysis of data from passive reports to the reporting system have suggested that advanced age was a risk factor for severe disease and death in these cases
  - Most subjects received multiple vaccines making it harder to assess whether any of the outcomes were due to YF vaccine or other vaccines
  - Study results may not be generalizable to YF vaccine in other setting, specific data to US and military

Seligman J. Stephen 2014.

- Type of study
  - Review

- Objectives
  - Purpose of the review was to identify and analyze risk groups based on gender, age, outcome, and predisposing illness

- Design
  - Using data in a CDC listing of YEL-AVD cases to evaluate the significance of YEL-AVD risk groups

- Listing of 65 YEL-AVD cases accepted by CDC as of January 2011 were used for the core of this review

- Specific Results in relation with the query (include limitation of the study)
  - Yellow fever live virus vaccine can cause severe, often fatal, multi-systemic illness, yellow fever vaccine-associated viscerotropic disease (YEL-AVD)
  - Predominantly neurological disease termed yellow fever vaccine-associated neurotropic disease (YEL-AND)
    - Incidence is reduced if vaccine if administered to individuals older than 6 months
  - Increased risk for developing YEL-AVD: to note as potential contraindications for adverse events
    - Thymectomized people (treatment of thymoma)
      - Thymus disease
      - Possibility that an abnormal thymus is involved in the increased susceptibility of young women to YEL-AVD
      - Thymus disorders are listed as a contraindication in the vaccine insert
    - Elderly
      - Concentration in elderly men
      - ≥60 years was a consensus in both US and Brazil studies
      - Limitation- risk associated with age has been questioned
    - Women between ages 19-34
      - YEL-AVD can be fatal in women in their prime child-bearing years (association made in 2011)
    - People with autoimmune diseases
      - HIV infected people (viral load not CD4 count is a predictive of a poor response in vaccination
      - Possible association of autoimmune diseases and the increased risk of developing YEL-AVD has been noted
  - Estimated frequency of occurrence of YEL-AVD vary from 0 to 12 per 100,000 vaccinees
    - US vary from 0.3 to 0.4 per 100,000
  - Africa rate per 100,000 is 0.0043 for the Stamaril study (1993-2010) and 0.013 in the AEFI Africa study (2007-2010)
  - Estimates reported by endemic countries are much lower than the reporting system hosted by CDC
  - No indication that the rate differences for incidence of YEL-AVD are associated with different vaccines
  - Infants and children ≤ 11 years old
    - One fatal case in Brazil in a 10 month old
    - No cases of YEL-AVD in infants 9 months- ≤ 3 years old
    - Data does not support infants and children ≤ 11 years as a risk group
    - Increased risk in the more restricted age interval: 3-5 years

        - There is less than 5 cases reported in this age interval, not as strong data for an association
        - Rate is approximately 0.004 per 100,000 cases for the 3-5 year age group; rare cases
    - A Brazil study suggests that infants and children from 9 months to 2 years have the lowest risk, but there might be a slight increase for 3-5 year olds
    - Potential issue with vaccine administration- vaccinating millions in Sub-Sahara Africa is difficult enough, accurate surveillance fore adverse events would be "virtually impossible"
    - Limitations
        - Insufficient data available to evaluate a given case using the Brighton Collaboration working group definition for viscerotropic disease
        - Not all cases included had evidence by RT-PRC of virus or culture
        - Other cases not included due to atypical symptoms and absence of virological confirmation
        - Whether the lack of cases can be due to under-reporting or lack of individuals with increased susceptibility to the vaccine is unknown
        - Limitation on the YEL-AVD cases as the cases were obtained from passive surveillance, not confirmed
        - Brazil cases reported belong to risk groups
        - African cases that were not virologically confirmed and not included, belong to non-risk groups

Fernandes et. al 2007

- Type of study
    - Analysis of surveillance and reporting data for yellow fever vaccine and adverse events following immunization

- Objectives
    - Present an analysis of notified adverse events following immunization (AEFI) cases following yellow fever vaccination held in a municipality
    - Sought to expand the analysis to the local level, particularly during the mass vaccination campaign
    - Interested in aseptic meningitis for which the association with yellow fever vaccine is still unclear

- Design
    - AEFI cases attributed to yellow fever vaccine notified in Juiz de For a city from January 1999 to December 2005
    - Mass vaccination campaign from 1999-2001, resulted in 34 million doses applied
        - 1999 children between 9 months and 5 years old
    - Data source were
        - AEFI national surveillance system notification forms
        - SINAN investigation forms for meningitis (notifiable diseases)
        - Records of administered doses of yellow fever vaccine

- Specific Results in relation with the query (include limitation of the study)
    - Adverse events following immunization (AEFI)
    - Revaccination is safer with regards to adverse events associated with viremia
    - Incidence of post-vaccination encephalitis was estimated as 0.5-4.0/1000 in infants less than 6 months old
        - Encephalitis is characterized by the onset, 7-21 days after vaccination, of fever and variable neurological signs associated to altered cerebral spinal fluid test
    - 92% of doses were administered to children under 14 years of age (1999 campaign)
    - Most AEFI occurred in 15-59 year age group (60%)
    - Notification rate was similar in the 15-59 age group (9.4 per 100,00 doses) and the younger than 5 years age group (8.0 per 100,000 doses)
    - No difference in distribution of cases by gender
    - Systemic events accounted for 87.3% of notifications
    - Clinical manifestations included
        - Fever, vomiting, headache, myalgia, meningismus, and arthralgia
    - Increment in rate of aseptic meningitis (10.1 per 100,000 inhabitants; 3.87 per 100,000 doses) was observed in 2001 during the vaccination campaign
        - 50% of the total notified cases were in individuals older than 15 years old
    - Limitations
        - Passive surveillance
            - Under- and over-notification
            - Completion of notification form and data sources
            - Poorly defined cases
            - Inaccurate estimation of denominators
        - Vaccine coverage reached 98.8% in 2001 when the most severe AEFI reported with yellow fever vaccination was aseptic meningitis
            - Due to the high proportion of the population being vaccinated, even a coincident outbreak of this diseases from other causes could have been likely attributed to the vaccine
        - Healthcare workers' perception of the existence of an association between yellow fever vaccine and neurological events may have misled both detection and notification of cases
        - Temporal association between adverse events and vaccination is necessary, but insufficient to analyze causality
        - No clinical or laboratory confirmation of suspected cases to support causality
        - Vaccination campaigns and introduction of a new vaccination strategy may also influence the notification profiles

Martins et. al. 2014

- Type of study
    - Observational analysis using adverse events data reported to the National Surveillance System

- Objectives
  - To describe and analyze the neurological cases following administration of YFV-17DD in the Brazilian population from 2007- 2012 with estimation of rates of adverse events

- Design
  - Brazilian population 2007-2012 time period
  - Analyzed the whole country and the state of Rio Grande do Sul
  - Surveillance of adverse events following immunization has been conducted in Brazil by the National Immunization Program since 1998
  - Neurotropic disease cases were all classified as meningoencephalitis
  - Confirmed neurotropic disease cases were included in the analysis

- Specific Results in relation with the query (include limitation of the study)
  - Out of the 67 adverse events, 82.1% were neurotropic, 14.9% neurological autoimmune diseases, and 3% combined disease
    - Neurological autoimmune diseases included Guillain-Barre syndrome and Acute Disseminated Encephalomyelitis cases
  - Global rate of adverse events following YFV 1st dose in Brazil from 2007 to 2012 was 0.20 neurological adverse events per 100,000 doses
    - Total rate neurotropic cases was 0.17 per 100,000 doses
  - Rates for neurological autoimmune disease after the first dose is 0.03 per 100,000 and after the booster dose is 0.01 per 100,000 doses
  - Lowest rate of neurotropic disease occurred in the age groups: less than 1 year and 1-4 years
  - Highest rate of neurotropic disease occurred in the age group 5-9 years (2.66 per 100,000 vaccine doses)
    - Risk was 2.7 times higher for this age group compared to the reference group (15-59 age)
    - 2009 for whole country and state of Rio Grande du Sol
  - Most neurotropic cases were after the firs vaccine dose
  - Overall rates were higher in Rio Grande du Sol than the national rate
  - The neurological adverse events have in general good prognosis, they should not contraindicate the use of YFV in face of risk of infection by yellow fever virus
  - Limitations
    - Using passive surveillance data poses a limitation in the analysis
    - Cases that did not comply with definitions (neurotropic diseases) were not included
    - Higher rates of reported cases in 2009 and 2010 could be due to intensification in the passive surveillance system and training for detection of neurological events
    - Evaluation of risk by age group is difficult as the number of cases is small for neurological autoimmune diseases
    - Rates for children varies from different studies

        - 0.5 to 4.0 per 1,000 dosed in children younger than 9 months
        - 0.4 per 100,000 doses from 1-18 years
        - This articles shows a higher rate for children 5-9 years
    - Misclassification of cases due to flavivirus cross-reactivity, tests for other flavivirus were not always done

Thomas et. al. 2012

- Type of study
    - Systematic review

- Objectives
    - To conduct a systematic review of adverse events associated with yellow fever vaccination in vulnerable populations (infants and children, pregnant women, HIV positive patients, and elderly people 60 years and older)

- Design
    - Systematic review of adverse events associated with YF vaccination and serious adverse events, which included neurotropic disease, viscerotropic disease, anaphylaxis/hypersensitivity, and other life-threatening events
    - Searched electronic databases for reports of single studies and systematic reviews
    - Used Cochrane Library, MEDLINE, EMBASE, BIOSIS Previews, Global Health, CAB Abstracts, and Lilacs Database of Latin America and Caribbean Literature
    - Results from active surveillance vs. passive surveillance are presented separately
        - Active- randomized clinical trials

- Specific Results in relation with the query (include limitation of the study)
    - Studies that used active surveillance identified no serious adverse events in infants/children or pregnant females
    - Infant and children results
        - Active surveillance
            - Peru-
                - No serious adverse events were attributed to YFV were reported
                - 50% reported minor adverse reactions, mostly fever and upper respiratory symptoms
                - No local reaction at the injection site were reported
            - Ghana-
                - Infants received the 17D vaccine at either 6 or 9 months
                - No serious adverse reactions were noted
                - Non-serious adverse reactions were mostly fever and upper respiratory symptoms
            - Randomized study children 4-8 and 12-24 months-
                - Received either 17D vaccine, measles vaccine, or both

        - No serious adverse events were noted and minor adverse events included fever with low rates of upper respiratory or injection site symptoms
        - Similar reactions in both age groups and groups for 17D vaccine only or in combination with measles vaccine
    - Passive surveillance
        - Cameroon-
            - Infants were vaccinated with 17D vaccine
            - Look at the medical chart for any reactions at the 30th day after vaccination
            - No serious or minor adverse events were identified
- Infant transmission after maternal vaccination with YFV has been reported (via breastfeeding)
    - Three cases the mothers received the first YFV during the infant's first month of life and were breastfeeding
- Overall they reported on four randomized trials of infants and children
    - Two with low risk of bias
    - Two with moderate risk of bias
- Main minor adverse events were fever and upper respiratory tract symptoms, with similar rates across studies
- Limitations
    - Small numbers of patients assessed should be taken into consideration when interpreting risk estimates for rare events
    - In the randomized control studies in infants, not all infants were seronegative at baseline, which possibly reduces the number who might have had adverse reactions

Thomas et. al. 2011

- Type of study
    - Systematic review

- Objectives
    - Identify the rate of serious adverse events attributed to yellow fever vaccination with 17D and 17DD strains reported in active and passive surveillance data

- Design
    - Searched 9 electronic databases for peer review and grey literature
    - Published literature on adverse events associated with yellow fever
    - Serious adverse events included YEL-AND, YEL-AVD, anaphylaxis/hypersensitivity, and other life threating events
    - Passive surveillance systems included- US VAERS, Australian database, Brazilian system, UK (ARILVAX), and Swiss database

- Specific Results in relation with the query (include limitation of the study)
    - Identified 4 studies in children and infants for active surveillance studies

- Identified 2 studies in children and infants for passive surveillance studies
- 17D and 17DD YF vaccines have proven to be safe and highly effective against an illness with high potential mortality rate
- Anaphylaxis is 0.009-2.1 events per million vaccinations or equivalent, at most one anaphylactic event is expected in every 480,000- 105 million vaccinations (general data, not stratified by age)
- Hypersensitivity is between 6.4 and 14.3 expected events per million vaccinations, or equivalent, expected one case of hypersensitivity in every 70,000-150,000 vaccinations
- Viscerotropic and neurologic disease, expected internal rate is between 0 and 1.39 events per million doses, or equivalent, at most one event per 720,000
- Children studies reported no serious adverse events
    - 1.67 expected serious adverse events per 1,000 vaccinations (little data to make conclusions)
- US VAERS
    - Events in children <15 years were excluded as no adequate estimates of the numbers of persons who received yellow fever vaccine in these groups were available
    - Estimated 11.1 systemic adverse events per million doses
    - Rate of 6.6 for YEL-AVD and YEL-AND cases per million doses
    - 2000-2006 study suggested the rate of serious adverse events to be 15.6 per million doses
- Australia, Brazil, UK, and Switzerland
    - Systemic adverse events were defined as occurring within 2 weeks of vaccination
    - No serious neurological disease cases were identified and only one fatal case of YEL-AVD
    - Rate for severe neurological diseases was 0/210,656 and 1/210,656 for YEL-AVD
    - 17DD administered in Brazil
        - 9 cases/million doses for hypersensitivity
        - 0.23 cases/million doses for anaphylactic shock
        - 0.84/million doses for yellow fever vaccine-associated neurological disease
        - 0.19/million doses administered for viscetropic cases
    - UK
        - 34 serious adverse events per million doses
    - Switzerland
        - 8 weeks after immunization
        - 5.5 cases/100,000 doses
        - 14.6 cases per million for neurologic events
        - 40 cases per million for serious events not neurological
    - Overall-
        - 11.1 systemic adverse events, 6.6 YEL-AVD and YEL-AND cases, and 15.6 serious adverse events per million

  - Passive surveillance
    - Serious AEFIs rate of 0.51 cases/million
      - Study heavily weighted by Brazilian data
    - Senegal study reported 2.67,326 infants vaccinated with 17D reported encephalitis possibly attributed to 17D, but no confirmatory tests were conducted
    - Children studies
      - No AEFI were proven
      - Data heavily weighted by Nigerian study
  - Limitations
    - Numbers are heavily weighted by Brazilian data- active surveillance data
    - UK data strongly influenced the passive surveillance results
    - Each country (where the study was conducted) used different definitions, protocols, surveillance mechanisms for the initial reporting of cases and strategies for clinical and laboratory follow up cases
    - Infant and children active surveillance study had little data to make conclusions from estimated rates
    - Difficulty in interpreting the results from all studies due to sometimes administration of other vaccines, variation in the completeness of their active and passive surveillance methods, multiple other pathogens that can present as encephalitis, hepatitis, and variations in ability to test if yellow fever vaccine was implicated
    - Rural or remote areas may have under-reporting or no reporting of serious adverse reactions following vaccination
    - Many studies report rates for yellow fever vaccine in combination with other vaccines, making interpretation difficult
    - Difference definitions were used for serious adverse events
    - Quality of data, application, and supervision of surveillance mechanisms to identify cases varied among studies
    - Differences in availability of laboratory tests

Breugelmans et. al. 2013

- Type of study
  - Systematic analysis

- Objectives
  - To conduct a systematic analysis of all AEFIs reported during the vaccination campaigns and to estimate the incidence of YF vaccine-associated AEFIs

- Design
  - 2007-2010 active surveillance of serious AEFIs
  - African countries: Benin, Cameroon, Guinea, Liberia, Mali, Senegal, Sierra Leone, and Togo
  - Large-scare implementation of YF vaccine (17D) and established vaccine pharmacovigilance systems

        - 17D-204 and 17DD YF sub-strain vaccines were used
    - Used available clinical and laboratory data for the YF vaccine-associated AEFIs applied he Brighton criteria
    - Data for each country was collected was entered into country-specific databases and developed locally
        - Unified database was created to allow comparative analysis and country-specific databases were reviewed and merged

- Specific Results in relation with the query (include limitation of the study)
    - 5% AEFIs classified as serious, of these 13% as YF vaccine reaction, including 50% hypersensitivity reactions, 27% YEL-AND and 23% YEL-AVD
    - Incidence per 100,000 vaccine doses administered was 8.2 for all reported AEFI, 0.43 for any serious AEFI, 0.058 for YF vaccine related AEFI, 0.029 hypersensitivity reactions, 0.016 for YEL-AND, and 0.013 for YEL-AVD
    - The eight different countries did not find an incidence of YF vaccine associated AEFIs that was higher than previously reported
        - Reinforcing the safety of YF vaccine
    - Rates reported for travelers (US and Europe) are 15-fold higher than the rates reported in this study
        - The results from this study are comparable with results from previous YF AEFI study conducted as emergency vaccination campaign (Ivory Coast)
        - Similar results in Brazil study, another YF endemic country
    - Strengths
        - Different teams in the eight countries initiated extensive efforts to find YF AEFIs and yet the rates were not greater than the ones previously reported from the literature
    - Systematic analysis reinforce understanding of the safety profile of YF vaccine and support continued use of attenuated YFV during mass preventive campaigns in YF endemic areas
    - Limitations
        - Cultural issues affected evaluation (example was autopsies)
        - Subjects live in YF endemic areas and may have been naturally acquired immunity against wild-type YF and cross-protection from exposure to other circulating flaviviruses such as dengue and West Nile
            - Leads to lower rates of reported YEL-AVD and YEL-AND
        - Underreporting can also explain the lower AEFI incidence
        - None of the YF vaccine-associated cases had YF testing on sample tissues
        - Samples were missing for 96% of patients

- Risk factors that can predispose to adverse events associated with YF vaccination in children aged 6-24 months old

Although there are limited data on safety and immunogenicity of YF vaccine when used in HIV infected children, YF vaccine may be administered to all clinically well children. HIV testing is not a prerequisite for vaccination. (WHO 2013)

- Contraindications to administering YF vaccine in children aged 6-24 months old

The vaccine is not recommended for those aged 6–8 months, except during epidemics when the risk of infection with the YF virus may be very high. Other contraindications for YF vaccination are severe hypersensitivity to egg antigens and severe immunodeficiency (WHO 2013).

- Evidence showing reversion to virulence with live attenuated YF vaccine?
  Beck et.al. 2014.

  A major research article, the first comparison of a live RNA viral vaccine strain to its wild-type parental strain by deep sequencing is presented using as a model the yellow fever virus (YFV) live vaccine strain 17D-204 and its wild-type parental strain, Asibi. All of the live attenuated vaccines in use today were derived empirically, and understanding of the molecular basis of attenuation is often rudimentary. Despite the production of over 550 million doses of vaccine in the last 70 years, understanding of how the vaccine is attenuated or how the protective immune response is elicited are very limited. Deep sequencing offers the opportunity to investigate population structures of live attenuated vaccine strains, contributions of these features to attenuation and stability, and the potential of reversion to virulence. Methods: The YFV 17D-204 vaccine genome was compared to that of the parental strain Asibi by massively parallel methods. Variability was compared on multiple scales of the viral genomes. A modeled exploration of small-frequency variants was performed to reconstruct plausible regions of mutational plasticity. The wild-type Asibi virus was found to consist of diverse quasispecies, as would be expected of a RNA virus. By contrast, the 17D-204 vaccine strain population was homogeneous, and very limited evidence was found for the existence of the wild-type nucleotide identity within the vaccine population

  Chan et al 2001.

  A research letter describes a man vaccinated with the 17D204 strain of yellow fever virus, who subsequently died of yellow fever. On Jan 23, 2001, a 56-year-old man, living in Australia, was given a single dose of 0·5 mL of 17D-204 yellow fever vaccine (Stamaril, batch T5222-1, expiry Jan 23, 2003, manufactured in France by Aventis Pasteur and distributed in Australia by CSL Ltd), together with 0·5 mL of quadrivalent meningococcal vaccine (Mencevax ACWY, SmithKline Beecham, Victoria, Australia) by subcutaneous injection. Stamaril is available as a single dose vial and was reconstituted just before administration. Sequencing of the NS5-3_ untranslated region showed that the virus isolated from the patient was identical to the vaccine strain of the same batch, and different from wild-type virus. Both viruses contained a mutation, although the association of this mutation with virulence is unknown. A necropsy was done 36 h after death. Serum samples obtained on Jan 31, Feb 1, and post mortem on Feb 4, together with tissue samples were inoculated into cell cultures of mammalian cell lines. The patient samples were handled independent of any 17D204 vaccine strain; after all patient samples had been cultured, the 17D204 strain was cultured from a vaccine vial of the same batch that the patient had received. The cultures were incubated for

up to 8 days. The hepatic histopathology and immunohistochemistry were consistent with yellow fever virus infection, and virus was isolated from multiple tissues. Although the vaccine is known to cause a transient, short-lived viraemia, it should not cause a sustained viraemia or abnormalities of hepatic function.

Xie et. al. 1998

Research paper to assess whether 17D vaccine virus mutates following the normal course of immunization. Six consenting healthy volunteers received a 17D-204 vaccine manufactured in the United States of America (17D-204-USA) by subcutaneous injection. The vaccinees were bled at day 5 post-inoculation during the peak viremia (Freestone,1995). The sera were separated, stored at _70°C and named serum viruses 1–6, respectively. The serum viruses and a dose of the 17D-204-USA vaccine, batch c4L51152 were each given one passage in monkey kidney Vero cell monolayers at 37°C. After 7 days of incubation, the viruses were harvested. Total nucleic acids were extracted from cell culture supernatant using phenol: chloroform: isoamyl alcohol (25:24:1). Paper describes the RT–PCR and sequencing procedures and Passage of a 17D infectious clone-deri6ed 6irus in cell culture. The results provided on comparison of nucleotide and amino acid sequences between serum viruses and 17D-204 -USA vaccine, analysis of virus population in serum virus 5 and Sequence study of the eighth passage derivative of an infectious clone-derived virus. Results suggest that 17D vaccine virus is very stable following passage in the human body as a normal course of vaccination. The majority of virions in the virus population were found to accumulate only one or two nucleotide mutations in the genome of more than 10000 nucleotides. All but one of these mutations were silent. 17D vaccine virus accumulates mutations at a very low frequency and may explain in part the excellent safety record of 17D vaccine

- Safety and efficacy of co-administration YF vaccine with other vaccines administered between 6-24 months of age e.g. MR?

WHO 2013

From the available data, there are no safety concerns with the co-administration of YF vaccine and the polio (live and inactivated), cholera, diphtheria, hepatitis A, hepatitis B, influenza, rubella, pertussis, tetanus, typhoid, Bacillus Calmette-Guérin (BCG), cholera, measles, and mumps vaccines. However, the data have significant limitations: most studies were inadequately powered, many did not include all potential target populations, and none involved participants from special populations.

YF_Efficacy_Coadmin_Bull.WHO.1973.v48_Ruben

Objective: To measure the serologic responses to smallpox, DPT, yellow fever, and measles vaccines when given by jet injector at four separate sites and followe5d after two months by a second dose of DPT.

Methodology: Children 6 months to 2 years of age were selected from three separate villages in Daura Emirate in North Central State, Nigeria. Subjects in each village were randomly assigned to one

of four study groups: Group 0 received placebo, group SMY received smallpox, measles, and yellow fever vaccines; group SMYT received smallpox, measles, yellow fever, and DPT vaccines; and group T received DPT vaccine. The two groups receiving DPT were given a booster dose at 2 months. At the conclusion of the study, all children who had received placebo or DPT alone were vaccinated with smallpox and measles vaccines. Blood samples were taken before immunization and 3 months after the initial vaccine administration.

Positive response to injected antigens was defined by the following criteria:
Measles - if Haemagglutination Inhibition (HI) antibody increased from < 5 to >5.
Yellow fever - if the neutralization test converted from negative to positive.
Diphtheria and tetanus - if antitoxin levels increased from <0.01 units/ml to >0.01 units/ml.
Pertussis - if agglutinins increased from < 8 to > 8.

Results: pre-immunization serologic titres of the study subjects. Diphtheria was the only disease to which the children had any substantial pre-study protection: 20% had antitoxin levels of 0.01 or greater. For all other antigens, 94-100% of the study population were classified as susceptible. No smallpox vaccination scars were found.
Post immunisation rates: the incidence rates for major reactions and seroconversion were similar for all vaccine groups except for the SMYT group which showed a significantly lower measles rate (67.5 %) than the SMY group (83%) (x^2= 4.51, P = <0.05). In the SMY and SMYT groups, the measles seroconversion rates were, as expected, lower in children under 9 months of age: 64% and 59%, respectively. In children 9 months and older, measles conversion rates for the SMY group (89.5%) were greater than for the SMYT group (70.9%) (X2= 5.51, P = <0.025).

Yvonnet 1986

Objective: To compare the immune responses of Senegalese children to the separate or simultaneous injections of yellow fever and hepatitis B vaccines.
Methodology: Five groups of infants were formed.
Group I (the control group) consisted of infants who were neither vaccinated with yellow fever nor with hepatitis B vaccines.
Group II infants were immunized with hepatitis B and diphteria/tetanus/pertussis/ polio (DTP-polio) vaccines according to a protocol of three doses at 6-month intervals. At the third session of vaccination, they received hepatitis B, DTP-polio, measles, and yellow fever vaccines.
Group III infants were given the same vaccines as infants in group 11, but according to a protocol of 3-month intervals. In group IV, the infants were vaccinated with DTP-polio, yellow fever, and measles vaccines.
Group V infants were given hepatitis B vaccines according to another protocol, at 2-or 6-month intervals.
All the infants were from the Fatick area in Senegal. Vaccines were given simultaneously, but at separate sites.
Blood samples were taken before yellow fever vaccine administration (mean age 18.3 to 26.2 months depending on the group), and also 2 months later.
Yellow fever neutralization tests were performed by a plaque reduction technique in PS pig kidney cell culture, using the 17 D 204 yellow fever strain. Cell monolayers were inoculated with a pre-

incubated mixture of serum and virus, containing 100 plaque-forming units. A 90-100% reduction in plaques, compared to the controls, was considered positive.
Results: No evidence of untoward reactions was obtained during the study. Infants from the control group (Group I) had no evidence of seroconversion to yellow fever during this 2-month period, indicating that natural infection did not occur during the study.
Four infants had antibodies against yellow fever virus, on the very day of yellow fever vaccine injection, and in five cases, the sera were toxic for the cells used in the test for the determination of yellow fever antibodies. Results from such infants were excluded.
The rate of seroconversion ranged from 92.4 to 93.5% in the case of infants who received the yellow fever vaccine with (groups II and III), or without (group IV), the hepatitis B vaccine booster injection). Moreover, the yellow fever antibody geometric mean titers were lower (p = 0.02) in infants who received the two vaccines.

Antibodies to Yellow Fever Virus two months after vaccination

		Yellow fever antibodies		
	No. tested	No.	Percentage	Geometric mean titer
Group I	34	0	0	0
Group II	59	54	91.5	19.4
Group III	46	43	93.5	23.6
Group IV	78	73	93.6	31.8

Conclusion: Since no unfavorable side reactions were observed during the study, it is concluded from the results obtained that hepatitis B and yellow fever vaccines can be administered simultaneously

Fisker et. al 2014.

Objective: To investigate whether co-administration of pentavalent vaccine with MV and yellow fever vaccine is associated with increased mortality as is the case when of inactivated diphtheria–tetanus–pertussis (DTP) vaccine is co administered with live attenuated measles vaccine (MV)

Method: Conducted a randomised placebo-controlled trial of vitamin A at routine vaccination contacts among children aged 6–23 months in urban and rural Guinea-Bissau. In the present study, we included 2331 children randomised to placebo who received live vaccines only (MV or MV + YF) or a combination of live and inactivated vaccines (MV + DTP or MV + YF + pentavalent). Mortality was compared in Cox proportional hazards models stratified for urban/rural enrolment adjusted for age and unevenly distributed baseline factors. While DTP was still used 685 children received MV only and 358 MV + DTP; following the change in programme, 940 received MV + YF only and 348 MV + YF + pentavalent.

Sample population: The study took place in the urban and rural areas surveyed through the health and demographic surveillance system (HDSS) of the BHP in Guinea-Bissau. Children who had been randomized to placebo in a trial comparing vitamin A vs. placebo at routine vaccination contacts after 6 months of age entered the present study if they received MV, MV + YF, MV + DTP or MV + YF + pentavalent vaccine at enrolment.

Results: During the 12 months of follow-up 44 deaths occurred: 19 among the children receiving live vaccines only and 25 among children who received a combination of live and inactivated vaccines. Censoring for accident deaths and subsequent vaccines, the mortality rate was 44.0 per 1000 person years (PYRS) within the 6 months after enrollment for the combined live and inactivated vaccines group and 10.5/1000 PYRS in the live vaccine only group, yielding a crude Mortality Rate Ratio of 4.16 (1.58–10.9) when adjusting for age and stratifying by place of enrolment. Controlled for background characteristics which differed between the two groups, children who received a combination of live and inactivated vaccines had a threefold higher mortality than children who received live vaccines only. The negative effect of combined live and inactivated vaccines was also observed for pentavalent + MV + YF compared with MV + YF.

Limitations: observational study, sampled population was limited to children that did not receive Vit A, as this has been shown to interact with measles vaccine. The follow up period was limited to 12 months due to numerous immunisation campaigns during the study period, which could have had a cofounding effect.

Clarke et. al. 2016

Objective: To examine the safety and immunogenicity of IPV given alongside the measles–rubella and yellow fever vaccines at 9 months and when given as a full or fractional dose using needle and syringe or disposable-syringe jet injector.

Method: A phase 4, randomised, non-inferiority trial at three periurban government clinics in west Gambia. Infants aged 9–10 months who had already received oral poliovirus vaccine were randomly assigned to receive the IPV, measles–rubella, and yellow fever vaccines, singularly or in combination.

1504 were enrolled into one of seven groups for vaccine interference and one of four groups for fractional dosing and alternative route of administration

At visit one, infants received the IPV, measles–rubella, and yellow fever vaccines either singularly, in combinations of two, or all three vaccines given together. The measles–rubella and yellow fever vaccines were administered as single 0·5 mL intramuscular injections into the left thigh, and the IPV as a single 0·5 mL intramuscular injection into the right thigh using a 23G/25 mm needle.

At visit two, those infants who had not received IPV at visit one received the vaccine into the right thigh either as a full-dose (0·5 mL) intramuscular injection using a 23G/25 mm needle; as a fractional-dose (0·1 mL) intradermal injection using a 26G/10 mm needle; as a full dose (0·5 mL) using an intramuscular disposable-syringe jet injector or as a fractional dose (0·1 mL) using an intradermal disposable-syringe jet injector.

Infants were observed for 30 min after vaccination and immediate reactogenicity data were collected.

Reactogenicity data were also collected during home visits done on days one to three after vaccinations in which routes of IPV administration were investigated, and on day three after other vaccinations. Data on adverse events and serious adverse events were collected throughout the study.

Results: The rubella and yellow fever antibody titres were reduced by co-administration but the seroconversion rates achieved non-inferiority in both cases (rubella, –4·5% [95% CI –9·5 to –0·1]; yellow fever, 1·2% [–2·9 to 5·5]). Measles and poliovirus responses were unaffected (measles, 6·8% [95% CI –1·4 to 14·9]; poliovirus serotype 1, 1·6% [–6·7 to 4·7]; serotype 2, 0·0% [–2·1 to 2·1]; serotype 3, 0·0% [–3·8 to 3·9]). Poliovirus sero-prevalence was universally high (>97%) after vaccination, but the antibody titres generated by fractional intradermal doses of IPV did not achieve non-inferiority compared with full dose. The number of infants who seroconverted or had a four-fold rise in titres was also lower by the intradermal route.
All local reactogenicity was mild and had resolved by the day three home visit. All systemic reactogenicity was mild or moderate and there were no notable differences related to treatment group.

All vaccinations were well tolerated, with a low level of local and systemic reactogenicity being recorded overall. At the day three home visit after visit one, redness, swelling, or tenderness occurred in nine infants after IPV, six infants after measles–rubella, and five infants after yellow fever vaccine administration.

A total of 36 serious adverse events occurred in 35 infants enrolled in the trial. Three infants died, two of whom were hospitalised at the time. None of the deaths were deemed related to vaccination by the data safety and monitoring board. One serious adverse event was defined as possibly related to yellow fever vaccination. The infant developed a significant rash within 24 h of vaccination, although contact dermatitis related to an antiseptic wash was ultimately judged to be more likely.

Limitations: the study was undertaken in a trivalent OPV primed population rather than a population primed with bivalent OPV and IPV, safety data was not collected in a blinded fashion and the trial design did not include a second randomisation step at visit two. Thus, the possibility of some residual effect of the vaccines administered at visit one on the responses to IPV administered at visit two is acknowledged.

CollabGroup 2007

Objectives: (1) to compare the immunogenicity and reactogenicity of two yellow fever vaccines: 17DD (licensed product) and 17D-213/77 (investigational product) in children aged 9–23 months; (2) to assess the effect of simultaneous administration of yellow fever and the measles–mumps–rubella vaccines; and (3) to investigate the interference of maternal antibodies in the response to yellow fever vaccination.

Method: a multicentric, randomized, double-blind, prospective study to test the hypothesis of difference in the immunogenicity and reactogenicity of 17DD and WHO 17D-213/77 yellow fever vaccine substrains applied simultaneously or with a 30-day interval of measles–mumps–rubella (MMR) vaccination. The study was conducted in four Brazilian states (Sao Paulo, Minas Gerais, Mato Grosso do Sul and Bras´ılia-Distrito Federal) in public health centers where yellow fever and MMR vaccination are part of routine practice, targeting healthy children aged between 9 and 23-months old presenting for routine vaccination. A two-section questionnaire was applied: pre- and post-vaccination (applied 30 days after vaccination) with records of social, demographical and clinical data.
A 4mL sample of blood was collected to measure antibodies (measles, rubella, mumps, dengue fever and yellow fever) on the vaccination day and 30 days after vaccination (Figs. 1 and 2). On the

vaccination day, mothers of children under 1 year of age were requested to provide a blood sample to measure maternal antibodies against yellow fever.
All volunteers who received the vaccine were included in the safety analysis, Investigators asked parents about the occurrence of events following vaccination at the second visit and a standardized form filled by the parents, describing the events occurred during the first 10 days after vaccination collected. Serious adverse events were reported immediately.
Sample size: with 650 children in each comparison group differences as small as 0.3 in mean log10 in yellow fever antibody titres could be detected with 80% power. For adverse events found in 5% of subjects in one group this sample size had 82% power to detect 5% difference
Results: study was on going, had no results section

CollabGroup 2015

Results: from above described study
Seroconversion: post hoc analysis was conducted and showed 66.2% seroconversion for YF in 68 children who received simultaneous YF and MMR vaccines and 82.6% in children who did not receive the MMR vaccine (only 8 children received the 2 vaccines on different days).
Adverse events - A total of 25.9% and 25.5% of children who received the 17D-213/77 and 17DD vaccines, respectively, presented signs or symptoms, either systemically or at the injection site, regardless of the presumed association with vaccination. Of the 505 children with some type of adverse reaction, 38.6% (17D-213/77) and 39.8% (17DD) received medical care. Fever was the most common adverse event (16.8% and 15.8% in the 17D-213/77 and 17DD vaccines, respectively). Of the
children who had fever, 44.2% in the 17DD group and 40.6% in the 17D-213/77 group received medical care (not necessarily only due to fever). Vomiting was reported in 3.1% of children, with no significant difference between the two groups. Two severe events temporally associated with vaccination were reported. Both achieved complete clinical remission was observed a few days after treatment. A causality assessment based on WHO classification (WHO 2013b) indicated inconsistent causal association to immunisation in both cases.

Limitations: The inaccuracy in the proportion of seropositivity results from the application of cut-off points in the titres and misclassifications in both pre and post-vaccination tests.
The proportion of seroconversion after excluding seropositive individuals before vaccination was also affected by the limitations of seropositivity classification

- What is the safety profile (i.e. adverse events/side effects, Risk factors and contraindications) of Yellow Fever vaccination in children aged <2 years?

In clinical trials, mild adverse events, such as headache, myalgia, low-grade fever, discomfort at the injection site, pruritus, urticaria and rash were reported by 25% of vaccinees.28 Female vaccinees report more local adverse events than males, while the incidence of systemic adverse events is higher in males. Serious adverse events following immunization (AEFI) with YF vaccine fall into 3 categories: 1. Immediate severe hypersensitivity or anaphylactic reactions. Anaphylactic reactions have been estimated to occur in 0.8 per 100 000 vaccinations, most commonly in people with allergies to eggs or gelatine. 2. YF vaccine-associated neurologic disease (YELAND), a group of neurologic conditions due to either direct viral invasion of the central nervous system by the vaccine virus resulting in meningitis or encephalitis, or to an autoimmune reaction resulting in conditions such as Guillain-Barre syndrome or acute disseminated encephalomyelitis. 3. YF vaccine-associated viscerotropic disease (YELAVD) which is caused by replication and dissemination of the vaccine virus in a manner similar to the natural virus. YEL-AVD cases typically develop multi-organ system dysfunction or failure and >60% of cases have been fatal. To date, all reported and published cases of

YEL-AND and YEL-AVD have been described in primary vaccinees with a reported rate for YEL-AND of 0.25–0.8 per 100 000 vaccine doses and for YEL-AVD of 0.25 to 0.4 per 100 000 vaccine doses. A report on adverse reactions during preventive mass YF vaccination campaigns in 8 West African countries carried out in 2007–2010 found lower rates of AEFI than those observed in studies of travellers.31 In those 8 countries, the reporting rate for YEL-AND was 0.016 per 100 000 doses of vaccine administered, the YEL-AVD rate was 0.013 per 100 000 doses, and the hypersensitivity reaction rate was 0.029 per 100 000 doses. Documentation of a high rate of YEL-AND in young infants during the 1960s led to institution of age <6 months as a contraindication for YF vaccination. The risk of YEL-AND is inversely proportional to age.20 For this reason vaccination is not recommended for infants aged 6–8 months except during epidemics when the risk of YF virus transmission may be very high (WHO 2013)

Immunogenicity is usually unaffected when YF vaccine is co-administered with other vaccines. The most notable exception was identified in a study of simultaneous administration of YF vaccine and the combined measles, mumps, and rubella vaccine (MMR) to children 12–23 months of age. The study found a significant decrease in the seroconversion rates and geometric mean titres obtained against YF, mumps, and rubella when the vaccines were co-administered. No decreases were noted in the immune response to measles. Separating MMR and YF vaccine administration by 30 days mitigated the effect. (WHO 2013)

ii. Efficacy and effectiveness

b. Duration of protection of YF vaccine when administered in children either 6 months, 9 months, 12 months or 15 months of age

Belmusto-Worn 2005

- Type of study
  - Randomized, double-blind, phase III vaccine trial in Sullana in northern Peru in a pediatric population

- Objectives
  - To determine the safety, tolerability, and efficacy, by measurement of neutralizing antibody responses, of two YF vaccines (Arilvax and YF-Vax) and to assess the consistency in production of three different lots of Arilvax
  - Demonstrate non-inferiority in immunogenicity of Arilvax compared with TF-Vax

- Design
  - Healthy children 9 months- 10 years of age
  - Safety and efficacy by measurement of geometric mean neutralizing antibody triter response
  - Two yellow fever vaccines (17D vaccines Arilvax and YF-Vax)
  - Sullana lies outside the YF enzootic area and YF vaccination shortages have continued to exist; study population can be exposed to urban outbreaks
  - 2:1 ratio of Arilvax to YF-Vax was followed
  - Vaccinations were conducted between May and November 2002
  - All subjects received a 31 day follow up

- Immunity was determined by neutralizing antibodies (principal mediator of immunity)
  - Correlate of protection from disease in non-human primates
- Sera collected on days and 31—tested for neutralizing antibodies
- Day 1 sera was also tested for pre-existing immunity to dengue virus serotypes 1, 2, 3, and 4 by ELISA and plaque-reduction neutralization test
- Seroconversion to YF virus was defined as a log10 neutralizing index $\geq$ 0.7 (LNI)
  - Virus titer of a mixture of serum and virus between baseline and post-immunization samples
  - Represents the antibody titer required to protect against lethal challenge
- Primary efficacy analysis consisted of comparing the proportion of subjects who seroconverted to YF virus 30 days post-vaccination in the two vaccine groups
- Age groups: 9-18 months, > 18-36 months, >36-60 months, an d60 months plus one day to 10 years
- Secondary analysis entailed the comparison of geometric mean titers of the two vaccines
- Looked at whether antibodies to YF or dengue at baseline differed with respect to the incidence of adverse events in the two vaccine groups

Efficacy results

- Specific Results in relation with the query (include limitation of the study)
  - Seroconversion was higher in Arilvax 94.9% than in YF-Vax 90.6% recipients
  - Post-vaccination neutralization indices were similar in both vaccines
  - Adverse events reported similar in both vaccines; similar number of subjects reported at least one adverse event in both group
    - Mild adverse events and resolved without treatment
    - No treatment-related serious adverse events were reported
  - Both vaccines are highly immunogenic and well-tolerated
  - In Peru YF has been included in the EPI of the MOH since 2000 and is recommended for all children beginning at 9 months of age
  - Clinical consistency and homogeneity was seen in the three Arilvax lots
  - No difference found for the pre-existing prevalence of YF antibodies (4.1% vs. 3.0%) or antibody to dengue (14.3% vs. 15%) between Arilvax and YF-Vax, respectively
    - 94.9% Arilvax seroconverted
    - 90.6% YF-Vax seroconverted
  - Arilvax seroconversion rate was statistically non-inferior to that of YF-Vax
  - Arilvax produced a higher response than YF-Vax
    - All age groups had higher seroconversion rates and non-inferiority between treatment groups
    - Difference between seroconversion rates for the two vaccines was most striking in the lowest age groups
    - Seroconversion rates at day 31 by age group
    - 9-18 months: 95.8% Arilvax vs. 88.5% YF-Vax
    - >18-36 months: 94.6% Arilvax vs. 86.2% YF-Vax
    - No different detected between gender

- Antibody titer response showed no difference in mean neutralizing index between the two vaccines at day 31
  - No difference either between the two vaccines when looking at the four age groups
- None of the host factors (sex and gender) had a statistically significant impact of the YF antibody seroconversion rate or the mean YF neutralizing index antibody titers.

Gottuzo et. al. 2013

Objective: to assess the need for a booster dose every 10 years based on the efficacy profile and the available evidence on duration of immunity in residents of disease endemic areas and in travelers.

Method: a systematic review of the protective efficacy and duration of immunity of YF vaccine in residents of disease-endemic areas and in travelers to assess the need for a booster in these two settings and in selected populations (human immunodeficiency virus–infected persons, infants, children, pregnant women, and severely malnourished persons). To be included in this review, studies could address either efficacy, duration of immunity, or both. Studies that assessed duration of immunity but had a shorter than 10-year-follow-up period after vaccination were excluded.

Thirty-six studies and 22 reports were included. Identified 12 studies of immunogenicity, 8 of duration of immunity, 8 of vaccine response in infants and children, 7 of human-immunodeficiency virus–infected persons, 2 of pregnant women, and 1 of severely malnourished children.

Results:

Immunigenicity: Twelve studies in 11 articles addressed the efficacy of YF vaccine in terms of immunogenicity. Seroconversion rates were consistently > 90% in 9 of 10 studies. Only one study reported a 75% seroconversion rate six months after a mass vaccination campaign. The study identified two large RCTs that used two YF 17 D vaccines (ArilvaxÒ and YF-VAXÒ) and LNI as the method to identify neutralizing antibodies. Belmusto-Worn and others reported seroconversion rates of 90.6–94.9% among 1,107 healthy children. Monath and others found seroconversion rates of 98.6–99.3% among 1,440 healthy adults by using the same two vaccines. After antibody kinetic studies, Monath also reported that protective levels of neutralizing antibodies were found.

Regarding need for boosters: Rosenzweig and others reported results on 9 of 24 persons who were revaccinated within eight years of primary immunization. The titers of revaccinees did not differ from
those who had received only one dose. Another study monitored early and late events of immune system activation after primary and secondary YF vaccination in 17 healthy persons, 5 of whom had been vaccinated once at least ten years) earlier. The authors reported that revaccination was followed by a minor and transient increase

in neutralizing antibodies that disappeared seven months after the primary challenge.

Duration of protection: Eight studies addressed the duration of immunity 10 years after YF vaccination.

The percentage of persons with neutralizing antibodies at a protective level ranged from 74.5–100%.

Poland and others found that neutralizing antibodies persisted > 30 years in 80.6% of veterans of the Second World War.

Immune response in specific populations:

Infants and children. Eight included studies addressed the immunogenic response to YF vaccine in infants and children. Two old and small studies found no significant difference between children and adults regarding neutralizing antibodies or duration of immunity five years after primary vaccination.

However, more recent studies have not supported these observations. Children may not develop an immunologic response as effectively as adults or may lose immunity more rapidly. However, these studies have methodologic limitations, including use of an intraperitoneal protection test for young mice, which was later found to be less sensitive than newer techniques or the use of old vaccination records to recruit persons.

HIV positive: The recent study of Sidibe and others 52 was conducted in a YF-endemic area in Mali and reported that 92% (76 of 83) of HIV patients had neutralizing antibody titers > 1:20 nine months after a mass immunization campaign. Studies suggest that viral load inversely correlates with the immune response to YF vaccine: the lower the viral load at the time of vaccination, the stronger the immune response. The search did not identify any study addressing the response to YF vaccine booster in HIV-infected patients. However, one study showed that a booster effect was noted in only 3 of 9 patients with baseline immunity.

Pregnancy: Only two studies addressed the immunogenicity of YF vaccine in pregnant women. These studies reported contrasting results; they showed high seroconversion rates in women vaccinated early in their pregnancy versus low seropositivity after vaccination in their third trimester.

Severe Malnutrition: Only one small study showed that protein malnutrition was associated with impaired antibody response to YF vaccine and reported that only 1 of 8 persons with kwashiorkor seroconverted after vaccination compared with 5 of 6 controls. The role of cellular immunity in this population was not explored. The search could not identify any report that addressed the duration of immunity to YF vaccine in malnourished children.

CollabGroup 2015

Objective: To estimate and compare the seroconversion rates and antibody titres against YF 30 or more days after vaccination with substrains 17DD and WHO 17D-213/77 in children aged nine-23 months. Also estimated and compared immunogenicity of the vaccines against YF in subgroups of children whose mothers were either seropositive (and did not receive the vaccine after delivery) or

seronegative for YF and in subgroups of children who were vaccinated against measles, rubella and mumps up to 15 or more days apart from the YF vaccine. Also assessed the frequency of adverse events in the first 30 days after vaccination.
Method: Mothers and caretakers of children eligible for YF vaccination were invited to participate in the study when they spontaneously attended the selected public health care facilities. Children aged nine-23 months without a history of YF vaccination available for blood sample collection 30 days after vaccination. Enrolment considered the contraindications to the vaccine: severe malnutrition, transient or permanent immunosuppression induced by diseases, immunosuppressive drugs, radiotherapy (topical or inhaled corticosteroids for less than two weeks did not lead to exclusion from the study, but these factors were recorded in the questionnaire), therapy with immunoglobulin or other blood products, administration of experimental vaccine 60 days before the study or an administration scheduled within 60 days after the study, history of hypersensitivity to chicken eggs (and their derivatives) or gelatin, chronic or acute severe diseases and fever (axillary temperature of 37.5ºC or higher) on the day of vaccination. 981 children received 17D 213/77, and 985 received 17DD
Results: Immune response intensity was slightly higher with 17DD than WHO 17D 213/77, however, the magnitude of the difference between the two types of vaccines was small and not statistically significant in any of the outcomes considered in the study. The GMTs were 3.223 mIU/ML (2.935-3.540, 95% CL) and 2.516 mIU/ML (2.291-2.763 95% CL) for 17 DD and 17D 213/77 respectively. The proportion of sero converted children (seronegative to seropositive) and children presenting four fold increases over pre vaccination titres were similar in the subgroups of maternal serological status. Similarly, the proportions of post-vaccination seropositivity and seroconversion of individuals who were seronegative before vaccination were lower in the age group of 12 months or older than in the age group of eight-11 months. As the combined vaccine against measles, mumps and rubella (MMR) was recommended at 12 months, a post hoc analysis was conducted and showed 66.2% seroconversion for YF in 68 children who received simultaneous YF and MMR vaccines and 82.6% in children who did not receive the MMR vaccine (only 8 children received the 2 vaccines on different days).
Limitation: The data from this study are not conclusive regarding the interference of maternal immunity on the immune response to the YF vaccine. Interference from other vaccines applied simultaneously, particularly those from live attenuated viruses, has been suggested in several studies cited above.

Osinusi 1990
Objective: to study the side effects of, and percentage of seroconversion following vaccination with 17D Yellow Fever vaccine in children less than one year old in Nigeria.
Methodology: 77 healthy children were randomly recruited at an infant welfare clinic. They had to have completed BCG, DPT 3 and poliomyelitis inoculation. Children had blood drawn for pre-vaccination testing, then given 0.5 ml of 17D

yellow fever vaccine subcutaneously. Follow ups or AEFIs were made on day 2 and 10 following vaccination, using a standardized questionnaire.
2nd blood specimens were collected from each child 6 weeks after inoculation. Neutralization tests were carried out on paired sera from 20 of the subjects, using 2-3 day old Swiss suckling mice, which were subjected to the constant virus, constant serum technique. 0.1 ml of undiluted serum inactivated at 56 oC for 30 minutes and 0.1 ml of virus suspension were inoculated intracerebrally in a litter of suckling mice. Mortality rates of 0/6, 0/5, 1/6, and 1/5 were considered positive, rates of 2/6, and 2/5 were regarded as partial positive and 6/6, 5/6, 4/6, 3/6, 5/5, 4/5, and 3/5 considered negative.
Results: Of the 77 vaccinees, 15.6% had fever within 48 hours of inoculation and while 12.9% have fever within 10 days post vaccination. There was no episode of febrile convulsions and no feature suggestive of encephalitis.
The 20 from the neutralisation tests showed positive in one child before and 13 (65%) children after vaccination, a sero-conversion rate of 60%. In addition, 2 others showed evidence of partial positivity after vaccination. There was no relationship between the outcome of the test and the sex or nutritional status of the children.

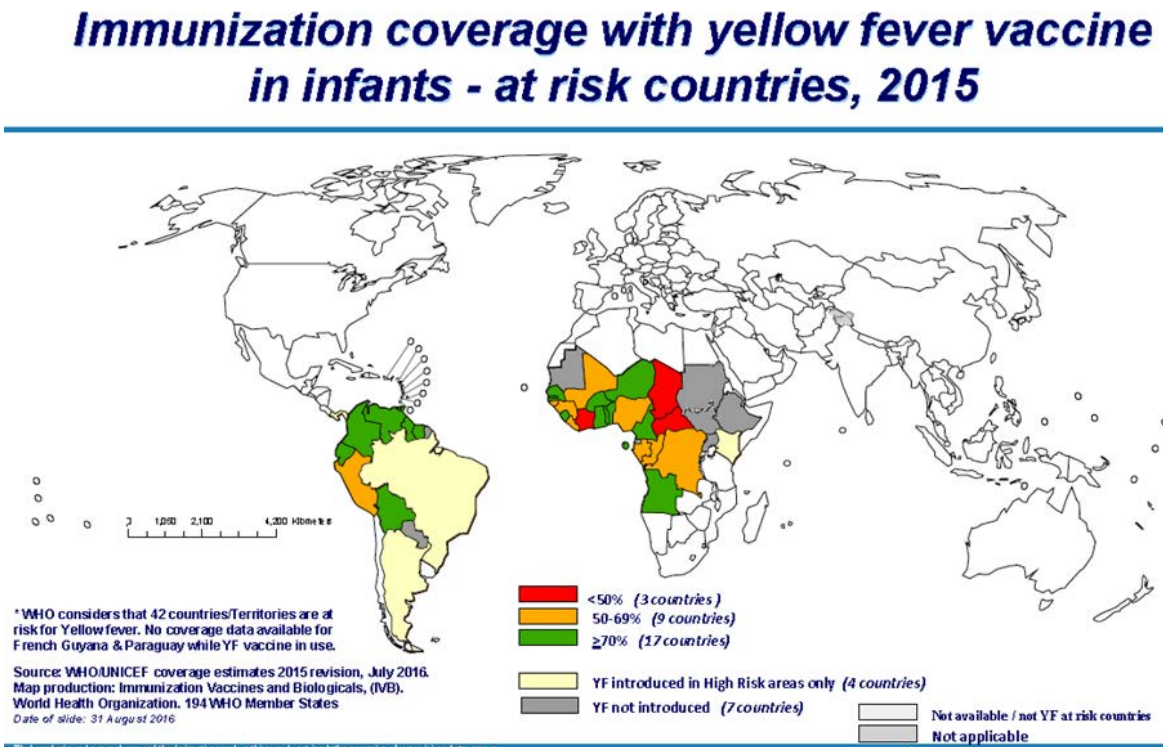
- Coverage of YF vaccine in developing countries where it has been introduced in routine immunization schedules
  WHO 2016a
  Global Strategy to Eliminate Yellow Fever Epidemics
  - In 2015, median coverage in 22 African countries with YF in their routine immunization programme was 70%
  - Vaccine coverage greater than 80%, with a 60-80% security threshold, are necessary to interrupt autochthonous transmission (human-mosquito-human) of YF virus within a community and ensure that sporadic unvaccinated cases do not generate secondary cases
  - When well implemented by strong health systems, YF routine immunization in the EPI can provide sufficient population immunity. However, it takes about 30 years to build the population immunity to adequate levels to potentially stop large scale outbreaks
  - If recently or insufficiently implemented, routine immunization alone does not represent a safe approach to controlling the risk of YF epidemics as recently demonstrated in Angola: Angola has implemented YF routine immunization since 1999. Between 2004 and 2015, WHO and UNICEF estimated that national vaccination coverage for YF ranged from 40% to 72%, with a 57% average
  - In West Africa: Vaccinations strategies combining preventive mass vaccination campaigns and routine immunization were successful at eliminating the risk of YF epidemics on a long-term basis. More than 150 million individuals were protected against YF between 2007 and 2015 in the 13 countries at highest risk for YF in Africa. No YF epidemic has been recorded in those countries

- In countries where YF has been introduced into routine immunization schedules what have been their successes and challenges?

WHO, 2016

Routine immunization: obstacles to progress

  - Vaccine supplies: A major block to progress has been the limited vaccine supply. Between 2013 and 2015, 15 countries among the 34 that introduced the YF vaccine into their routine immunization programmes reported a YF vaccine stock-out at national level, with consequences for national coverage.
  - Regional and country buy-in: due to competing vaccine introduction priorities and limited political will, no new countries have introduced the YF vaccine into their national routine immunization programme since 2008
  - Other reasons for low coverage: weak vaccine management; inadequate or overly rigid vaccination practices (e-g no vaccination after 11 months, unwillingness to open a 10 or 20-dose vial for one child)



i. Vaccine characteristics

- Recommended optimal vaccination schedule (dosage, age, booster) to protect the unvaccinated individual against YF?

WHO 2016b

General goal and strategy for the use of YF vaccine

- Yellow fever vaccination is carried out for 3 reasons: to protect populations living in areas subject to endemic and epidemic disease; to protect travellers visiting these areas; and to prevent international spread by minimizing the risk of importation of the virus by viraemic travellers.
- A single dose of YF vaccine is sufficient to confer sustained life-long protective immunity against YF disease; a booster dose is not necessary.
- In view of the ongoing transmission of YF virus, and the proven efficacy and safety of YF vaccination, WHO recommends that all endemic countries should introduce YF vaccine into their routine immunization programs.

  Endemic countries. It is recommended that the YF vaccine be given to children at age 9–12 months at the same time as the measles vaccine in YF-endemic countries.

  - Preventive mass vaccination campaigns are recommended for inhabitants of areas at risk of YF where there is low vaccination coverage.

- Characteristics or attributes of the YF vaccine that allow it to be aligned with the current EPI schedule?

  WHO recommends that the YF vaccine be given to children at age 9–12 months at the same time as the measles vaccine in YF-endemic countries (WHO 2013).

- Presentations and formulations for YF vaccine (e.g. diluents, doses per vial etc.)

  WHO 2013

  - All the current commercially available YF vaccines are live attenuated viral vaccines from the 17D lineage, developed more than 80 years ago by empirical passage in tissue culture, principally chicken embryo.
  - This attenuated vaccine virus exists in 2 sub-strains (17D-204 and 17DD), of which both sub-strains are used in vaccines prepared by culturing the virus in embryonated eggs. The vaccine contains sorbitol and/or gelatine as a stabilizer and is lyophilized. No preservative is added. The following conditions for storage and handling are recommended unless specific conditions in the labelling statement permit otherwise: lyophilized vaccine should be stored and kept at 2–8 °C and reconstituted immediately before use with the sterile diluent provided by the manufacturer. After reconstitution, most YF vaccines should be kept on ice, protected from sunlight, and discarded after 1–6 hours (see the manufacturers' product insert for specific details) or at the end of the vaccination session, whichever comes first.

- According to current WHO recommendations on quality, safety and efficacy of live attenuated YF vaccines, the immunizing dose recommended for use should not be less than 3.0 log10 international units (IU).
- YF vaccines are given as a single dose (0.5 ml) The vaccination site is usually the lateral aspect of the upper part of the arm or the anterolateral aspect of the thigh in babies and very young children.

Yellow Fever vaccine (Sinofi 2016 – Sanofi Manufacturers insert)	
Presentation	YF-VAX®, Yellow Fever Vaccine, for subcutaneous use, contains sorbitol and gelatin as a stabilizer, is lyophilized, and is hermetically sealed under nitrogen. No preservative is added. Each vial of vaccine is supplied with a separate vial of sterile diluent, which contains Sodium Chloride Injection USP – without a preservative. 1Dose: Vaccine vial, 1 Dose (NDC 49281-915-58) supplied in a package of 5 vials (NDC 49281-915-01). Diluent vial, 0.6 mL (NDC 49281-912-59) supplied separately in a package of 5 vials (NDC 49281-912-05). 5 Dose: Vaccine vial, 5 Dose (NDC 49281-915-68) supplied in a package of 1 vial (NDC 49281-915-05).Diluent vial, 3 mL (NDC 49281-912-69) supplied separately in a package of 1 vial (NDC 49281-912-10). Store at 2° to 8°C (35° to 46°F).
Formulation	YF-VAX is formulated to contain not less than 4.74 log10 plaque forming units (PFU) per 0.5 mL dose throughout 10 the life of the product
Dosage and Administration	Administer a single subcutaneous injection of 0.5 mL of reconstituted vaccine. Use YF-VAX within 60 minutes of reconstituting the single dose or multi-dose vial

- Guidelines for administration of YF vaccine with other vaccines administered to children aged 6-24 months of age e.g. storage, site etc.

  WHO 2013.
  The following conditions for storage and handling are recommended unless specific conditions in the labelling statement permit otherwise: lyophilized vaccine should be stored and kept at 2–8 °C and reconstituted immediately before use with the sterile diluent provided by the manufacturer. After reconstitution, most YF vaccines should be kept on ice, protected from sunlight, and discarded after 1–6 or at the end of the vaccination session, whichever comes first.

According to current WHO recommendations on quality, safety and efficacy 17 of live attenuated YF vaccines, the immunizing dose recommended for use should not be less than 3.0 log10 international units (IU). YF vaccines are given as a single dose (0.5 ml) and the manufacturers recommend that the vaccine be injected either subcutaneously or intramuscularly. The vaccination site is usually the lateral aspect of the upper part of the arm or the anterolateral aspect of the thigh in babies and very young children.

Separating MMR and YF vaccine administration by 30 days is recommended to mitigate the effect of a significant decrease in the seroconversion rates and geometric mean titres obtained against YF, mumps, and rubella when the vaccines were co-administered. Some manufacturers recommend that injected cholera or typhoid vaccines should not be administered simultaneously with the YF vaccine. Manufacturers also list febrile illness, pregnancy and debilitation as contraindications.

- Additional logistical and cold chain requirements for the immunization program to introduce YF vaccine into routine immunization for the whole country
  No data found. A readiness study needs to be conducted before introduction.

c. The disease

i. Burden of disease

- Current prevalence of YF in the whole population in Uganda.

WHO 2012. REPORT OF YELLOW FEVER RISK ASSESSMENT IN UGANDA, 2012

Before the 2010 outbreak in Northern Uganda, the last human case of YF was reported in 1971. Available literature indicates that human cases of YF occurred in Uganda in 1941[5], 1952[6], 1959, 1964[7] and 1971. Apart from 1941 when more than one case of YF occurred (though only one case was confirmed), the other cases occurred singly. While suspected YF cases continued to be reported to the formal health system (11-110 suspected cases per year countrywide), no case of human YF infection had been confirmed in Uganda during this period (1972-2009). During the 2010 outbreak, a total of 11 cases of YF were confirmed from 5 districts including: Abim (4 cases), Agago (2 cases), Kitgum (2 cases), Lamwo (1 case) and Pader (2 cases). Nine (9) other districts in Northern Uganda reported suspected cases meeting the surveillance case definition of YF. The districts include Kaabong, Kotido, Arua, Lira, Gulu, Nebbi, Napak, Dokolo and Yumbe. Nonetheless, laboratory tests remained negative for YF from these districts. Overall, a total of 272 suspected YF cases including 58 deaths (CFR 21.3%) were reported from the 14 districts as of 10 March 2011.

WHO WEBSITE 2016

From 26 March to 18 April 2016, 30 cumulative suspected cases, including 7 deaths, were reported from Masaka, Rukungiri, Ntungamo, Bukumansimbi, Kalungu, Lyantonde, and Rakai. Of these, 6 cases and 2 deaths were confirmed in Masaka district (5 cases), and

Rukungiri district (1 case). The mean age of the cases is 23 years old. The majority of cases are male. The cases do not have any history of travel outside of Uganda.

- Case fatality rate from the yellow fever

  WHO 2012. REPORT OF YELLOW FEVER RISK ASSESSMENT IN UGANDA, 2012

  A CFR of 21.3% was reported in the 2011 outbreak in northern Uganda.

  WHO 2013

  According to WHO estimates from the early 1990s, 200, 000 cases of YF, with 30 000 deaths, are expected globally each year, with 90% occurring in Africa, a CFR of 15 %.

- Potential of a YF epidemic occurring in Uganda and East Africa

  Cummings et. al. 2014

  A review of emerging and re-emerging epidemic prone diseases among settling nomadic pastoralists in Uganda; discussed the traditional burden of epidemic-prone diseases among nomadic pastoralists, discuss the forces driving settlement of a formerly nomadic population, and describe the emergence and re-emergence of cholera, hepatitis E, meningococcal meningitis, and yellow fever in Karamoja, Uganda. In the Karamoja region of north-eastern Uganda, where livelihoods have customarily been maintained through nomadic pastoralism, epidemic-prone diseases were historically uncommon. However, over the past decade, the region has been affected by multiple outbreaks of communicable diseases. In 2010, yellow fever re-emerged in Uganda and greater than 40% of the subsequent cases were located in Karamoja. In 2010 and 2011, Karamoja was affected by an outbreak of yellow fever, marking the disease's reemergence in Uganda since the early 1970s. Increased sedentism of a previously unexposed and largely unvaccinated population, especially near forests, likely contributed to a high-risk environment for yellow fever transmission. The index case in Karamoja repeatedly entered the forest, suggesting sylvatic transmission. Within the affected districts in Karamoja, urban transmission was also likely. The presence of open water storage vessels for domestic mosquito breeding in overpopulated manyattas and municipalities likely contributed to a setting favorable for person-to-person spread of yellow fever. Serologic data collected during the yellow fever outbreak also demonstrated limited natural or vaccine-induced immunity to yellow fever virus, further increasing the vulnerability of the population. The transition to sedentism among nomadic pastoralists in Uganda has contributed to the emergence and re-emergence of epidemic-prone diseases such a , yellow fever.

  Farnon et. al. 2010

  Report results of a Household-Based Sero-Epidemiologic Survey after a Yellow Fever Epidemic, in Sudan (2005) to assess YF vaccine coverage and to better define the epidemiology of the outbreak in an index village. the results of this investigation suggest that CHIKV and YFV contributed to febrile illness in Kortalla during this outbreak. Sporadic YF epidemics have been reported in eastern Africa since 1940, when the first documented YF epidemic in the region occurred also in the Nuba Mountains of Sudan. A smaller YF epidemic

in Sudan occurred in 1959 in the Blue Nile and Upper Nile states bordering Ethiopia, followed by a large outbreak in Ethiopia during 1960–1962. Sylvatic YF outbreaks have occurred in Kenya in 1992–1993 and in the Imatong Mountains of southern Sudan in 2003.

Bagonza et. al. 2013

A survey to estimate yellow fever vaccination coverage in Pader district and determine the reasons for non-vaccination to recommend possible mop-up actions, guide future vaccination efforts and contribute to the control of yellow fever in the country. In December 2010, the Ugandan Ministry of Health (MOH) declared a Yellow fever outbreak based on nine laboratory confirmed samples from the five districts of Abim, Agago, Kitgum, Pader and Lamwo in northern Uganda. This part of Uganda, home to game reserves and national parks, borders South Sudan and Kenya where previous cases of yellow fever have been reported. This was the largest ever recorded yellow fever outbreak in the country with an overall attack rate of 13 cases per 100,000 population based on confirmed cases. Previous yellow fever outbreaks in Uganda had fewer or single cases. For about 40 years now, no yellow fever cases had been reported in Uganda.

Study design: yellow fever vaccination coverage through a cluster survey based on the methodology recommended by World Health Organization for determining vaccination coverages of routine EPI vaccines; excluded the following from the study population: Individuals and children less than 5 years whose parents or caregivers were absent by the time of the survey. This survey was conducted 3 months after the massive emergency vaccination campaigns. Considered two main outcomes: vaccination status documented by the vaccination card (card only) and also by considering verbal reports of vaccination (card and history or recall).

Survey instruments: modified WHO cluster survey forms for yellow fever vaccination for children and adults.

Results: The overall yellow fever vaccination coverage in Pader district was 96.1% (95% CI 94.3 - 97.8) with a card retention rate of 51.6%. The other affected districts also reported high vaccination coverage estimates: Abim 95.4%, Agago 97.5%, Kitgum 97.8% and Lamwo 97.1%.However, a high vaccination coverage doesn't necessarily mean that the country is not at risk since Uganda borders South Sudan which experiences sporadic yellow fever outbreaks. Larger outbreaks had been reported in East Africa, with attack rates (cases per 100,000 persons) of 6,800 in Sudan and 27.4 in Kenya. Pader district is found in northern Uganda and this region borders South Sudan which is prone to sporadic yellow fever outbreaks.

Wamala et. al. 2012.

A case-series investigation in which the response teams conducted epidemiological and laboratory investigations on suspect cases. The cases identified were line-listed and a data analysis was undertaken regularly to guide the outbreak response November 2010. the Uganda Ministry of Health received reports of an outbreak of a fatal, febrile, hemorrhagic illness in northern Uganda. Molecular sequencing in one of the confirmed cases revealed 92% homology to the YF virus strain Couma (Ethiopia), belonging to the East African genotype.

Onyango et.al. 2004

Study on the genetic characterization of yellow fever virus isolates from an outbreak of the disease in southern Sudan in 2003.
The Study During the first week of May 2003, the Early Warning and Response Network, established in 1999 in southern Sudan, reported an outbreak of fatal hemorrhagic fever of unknown etiology in the Imatong region of Torit County, which is near the Ugandan border. Blood samples collected from Sarianga, Itohom, Lenyleny, Tarafafa, Lofi, and Locomo villages were tested at the Kenya Medical Research Institute (KEMRI), in Nairobi, where yellow fever virus was identified as the causative agent of the outbreak. A consensus sequence was established by aligning the sequences obtained from the Sudan 2003 outbreak of yellow fever with sequences obtained from GenBank for yellow fever isolates from previous outbreaks of the virus in Africa. The sequences from GenBank were selected to represent the five distinct genotypes circulating in Africa. The tree (Figure) shows that the virus circulating during the recent outbreak in southern Sudan was closely related to an isolate from an outbreak in Kenya in 1993 that belonged to the East African genotype. The recent Sudan isolates clustered with the East African isolates

Conclusions

Outbreaks of yellow fever virus have frequently been reported from areas within West Africa since the 18th century, with far fewer outbreaks being identified in East Africa. Serologic evidence for the presence of yellow fever virus in Sudan, Kenya, Uganda, and Tanzania was first reported in 1936. However, not until 1940 was the first epidemic confirmed in East Africa, in central Sudan. Sporadic cases were identified annually in East Africa until 1959, when an outbreak was recorded in the Blue Nile region of Sudan and subsequently in the neighbouring region of Ethiopia. From 1960 to 1962, the largest outbreak to date in Africa occurred in southwest Ethiopia.
Additional serologic studies confirmed that yellow fever activity was widespread in Uganda, Somalia, Ethiopia, and Kenya. Although two possible cases of yellow fever in Kenya were reported in 1943 (7), not until 1992–1993 was a large outbreak confirmed in the Rift Valley province of Kenya. Subsequent sporadic isolations of virus have been made in East Africa since then, but no large epidemics were recognized until the outbreak in southern Sudan in 2003. Originally, researchers speculated that outbreaks in East Africa were less frequent and smaller than the large outbreaks recorded in West Africa because they were the result of virus's being introduced into the area at the time of the outbreak. However, the genetic data suggest that yellow fever virus is endemic in East and Central Africa, with outbreaks occurring as a result of favorable environmental conditions. The fact that the isolate from Sudan were closely related to an isolate obtained 10 years ago in Kenya supports the contention that yellow fever is endemic in East Africa and has the potential to cause large outbreaks when conditions favor transmission to humans.

Markoff. 2013

Perspective on Yellow Fever Outbreak in South Sudan: On November 16, 2012, the Weekly Epidemiological Record of the World Health Organization (WHO) reported that an outbreak

of yellow fever was under way in Sudan. As of January 16, the Centers for Disease Control and Prevention (CDC) confirmed that 849 cases and171 deaths had been reported. Most suspected cases have occurred in Central, South, and West Darfur.

Ellis and Barrett. 2008

Review describes the natural history of YF in East Africa and discusses findings relative to outbreaks and more recent research developments elsewhere in Africa, for clarifying the ecology and epidemiology of YF in East Africa, equating historical findings and highlighting results that may be useful indicators of disease risk. East Africa is particularly vulnerable to the emergence of vector-borne diseases as evidenced by the largest epidemic of YF reported worldwide (Ethiopia 1960–1962) and more recent outbreaks of YF (Kenya 1992–1993, Sudan 2003, Sudan 2005), dengue (Somalia 2005), Chikungunya (Kenya 2005), Rift Valley fever (Kenya, Somalia, Sudan, Tanzania 2006-2007) and O'nyong-nyong (Uganda 1997) [11–18]. The greatest public health threat in regard to YF in East Africa is the potential emergence of YF in urban areas in which dense populations of unvaccinated humans and vector populations often exist.

Kebede et.al. 2010

Review examined the major epidemics reported to WHO/AFRO from 2003 until 2007, with the objective of describing the trends of epidemics and progress of EPR-related activities in the African region. The review examined the epidemic preparedness and response (EPR) activities to these outbreaks at the national and regional levels since the launch of the IDSR strategy in 1998. The summary (e.g. frequency, affected population and reported outcomes) of commonly occurring outbreaks reported to WHO/AFRO in the region from 2003 to 2007

Methods:

- A review of documents and reports obtained from WHO/AFRO. WHO inter-country team. WHO Country Offices and partners
- Meetings and discussions with WHO/IDSR focal people and partners involved in EPR
- Literature review on epidemic outbreaks and response interventions in the African region

YFever: During the last 10 years, multiple outbreaks were reported mainly from Liberia (seven outbreaks), Guinea (five outbreaks), Cote d'Ivoire (five outbreaks), Burkina Faso (five outbreaks) and Ghana (three outbreaks). During 2006-2007, a total of 477 suspected yellow fever cases and 32 deaths (CFR 7%) were reported from 13 countries, among which, seven countries (Cameroon, Central African Republic, Cote d'Ivoire, Guinea, Mali, Senegal and Togo) had confirmed outbreaks. However, there is a concern of gross underreporting in the region. The last decade had seen increased outbreaks of yellow fever due to accelerated urbanization with high population density, rise of rapid global transpo1i and communication links and the prohibitive cost of vaccines to implement mass preventive campaigns.

Risk and contributing factors to recurrent disease outbreaks: The main factors responsible for the above epidemics include high population density and environmental factors that promote breeding of disease transmitting vectors. These factors are commonly associated with the long-standing civil unrest in many countries of the region that lead to poverty and overcrowding in addition to poor public health systems.

Sang and Dunster. 2001.

Review the trend in arbovirus outbreaks and activity in Kenya in the last ten years. Sources: published reports of past outbreak investigations and more recent data available at the Arbovirology and Viral heamorrhagic fevers reference centre, Centre for Virus Research , Nairobi. Selected studies: Past and recent outbreaks and active transmission reports of arboviruses : YF, Rift Valley Fever, Dengue and Criean Congo Haemorragic fever.
Results: there is increased frequency of outbreaks and detection of arbovirus activity on humans and vectors in the last ten years including re-emergence of YF virus as a public health concern in Kenya. Environmental factors affect the emergence and re-emergence of arboviruses in Kenya: what governs the emergence and re-emergence of arboviruses as a health threat is complex but five important variables may influence this rate: vectors, virus, wild vertebrate host, human and environmental factors. Environmental factors have a most profound effect on the rate of rate of emergence of arbovirus disease by altering vector dynamics and ecology. The presence of human settlements as a consequence of economic prospects from irrigation schemes increases the chances of promoting colonies of mosquitoes that are highly adapted to feeding and breeding close to human settlements including important vectors in the transmission of yellow fever.

- Population at risk of acquiring YF infection in Uganda

WHO 2012. REPORT OF YELLOW FEVER RISK ASSESSMENT IN UGANDA, 2012

The naturally acquired yellow fever immunity was found to increase with age among the Ugandan population sampled during the Yellow Fever Risk Assessment.
Naturally acquired YF virus immunity by age group.

Age group	*n/N*	*(%)*	*[95% CI]*
< 15 years	1/132	(0.75)	[0,0002-0,041]
15-39 years	7/311	(2.25)	[0,009-0,045]
40-64 years	6/111	(5.40)	[0,02-0,11]
65+ years	1/35	(2.85)	[0,0007-0,14]
Total	15 /585	(2.56)	

ii. Clinical characteristics of the disease in the country

- Sequelae and long term complications of YF infection
[WHO YF position paper, Medical texts]

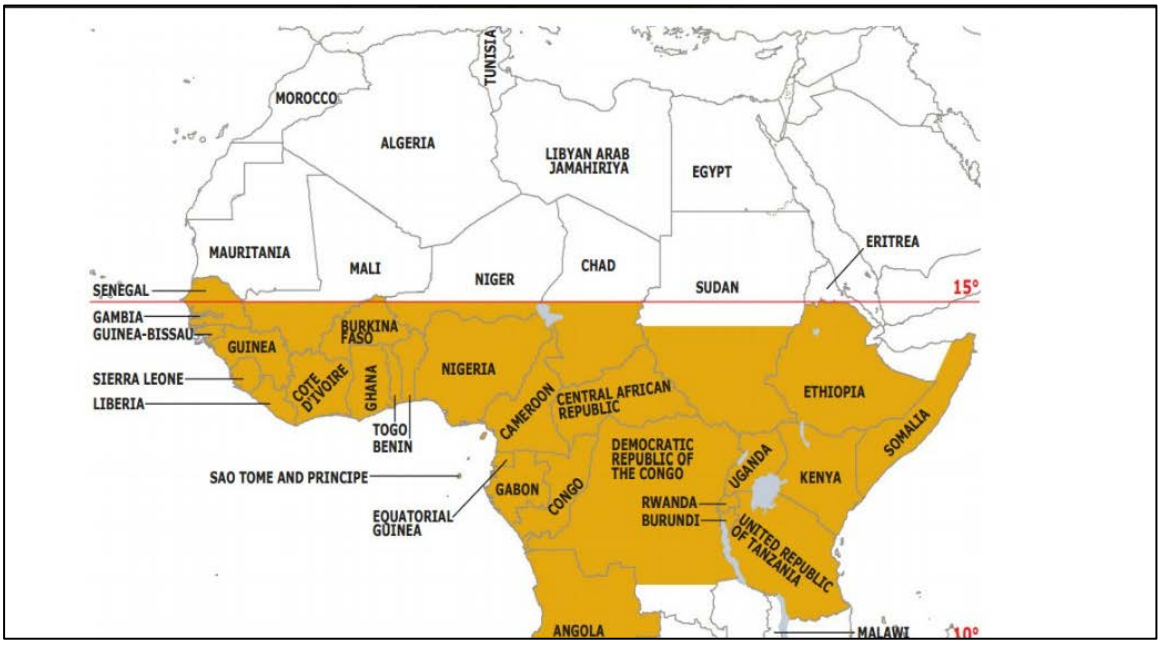
WHO 2013

- Infection with the YF virus can be asymptomatic or cause a wide spectrum of disease, from mild symptoms to severe illness with bleeding, jaundice and, ultimately, death.

- Physical symptoms usually appear 3–6 days after a bite from an infected mosquito. YF virus first replicates in the site of inoculation, after which it spreads to the lymph nodes. It then travels to the liver, spleen, bone marrow, kidneys and myocardium but rarely spreads to the brain, exhibiting viscerotropic, rather than neurotropic, affinity.
- Typically, the disease onset is abrupt, with fever, muscle pain, particularly backache, headache, shivering, loss of appetite, and nausea or vomiting. Congestion of the conjunctivae and face are common, as well as relative bradycardia in the presence of fever. The patient is usually viraemic during this period, which lasts for approximately 3–6 days.
- In approximately 15% of infected persons, the illness recurs in more severe form after a brief remission of 2–24 hours. Symptoms include fever, nausea, vomiting, epigastric pain, jaundice, renal insufficiency, and cardiovascular instability. A bleeding diathesis can occur causing gastrointestinal bleeding, haematuria, skin petechiae, ecchymoses, epistaxis, and bleeding from the gums and needle-puncture sites. Physical findings include scleral and dermal jaundice, haemorrhages at different sites and epigastric tenderness without hepatic enlargement. The haemorrhagic manifestations are caused by reduced synthesis of clotting factors as well as by a consumptive coagulopathy.
- About 20%–50% of patients with hepato-renal failure die, usually 7–10 days after the onset of disease. Patients surviving YF may experience prolonged weakness and fatigue, but healing of the liver and kidney injuries is usually complete.

iii. Regional and international considerations

- WHO's current position on YF vaccine for the Region/Uganda
  WHO 2013
  Uganda is situated in the "Yellow Fever belt" of Africa and is considered a country at risk of Yellow Fever virus transmission. WHO recommends that all endemic countries should introduce YF vaccine into their routine immunization programmes.
  Map showing Yellow Fever endemic zones in Africa



Source WHO website http://www.who.int/emergencies/yellow-fever/maps/en/

- Prevalence and distribution of YF infection/epidemics in the region/neighbouring countries?
  WHO website http://www.who.int/csr/don/archive/disease/yellow_fever/en/

  South Sudan

  In 2012, an outbreak of yellow fever in Darfur region of Sudan resulted in 849 suspected cases including 171 deaths (case fatality rate 20%). Around five million people were vaccinated against YF in the five states of Darfur in response to this outbreak. In 2005, a yellow fever outbreak was also reported from the South-Kordofan state, a place with high nomadic population. During that outbreak, 615 suspected cases including 183 death (CFR: 30%) were reported.

  DRC

  As of 31 May 2016, a total of 700 suspected cases, including 63 deaths, had been reported from all the provinces by the national surveillance system. A total of 52 cases were laboratory-confirmed for YF.

  On 12 March 2014, 2 events of yellow fever were reported in the North and in the South of DRC. Six laboratory-confirmed cases with yellow fever virus infection were reported. Of these, 3 were from Bondo health zone[1], Orientale Province, 2 from Buta health zone, Orientale Province and 1 from Kikondja health zone, Katanga Province. In total 139 suspected, probable and confirmed cases, including 6 deaths were reported.

  6 June 2013 -laboratory confirmation of six cases in the country.

  Kenya

  Between 15 and 18 March 2016, the National IHR Focal Point of Kenya notified WHO of 2 imported cases of yellow fever (YF). Both cases are male Kenyan nationals, in their early 30s, working in Luanda, Angola. Both travelled while symptomatic and none were vaccinated against yellow fever prior to traveling to Angola. Reverse transcription polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA) were performed on

samples of both cases by the Kenya Medical Research Institute (KEMRI). RT-PCR was negative for the two cases; however, samples from both cases tested positive for anti-YF IgM antibody.

Ethiopia

Laboratory confirmation of six cases in the country on 7 May 2013

- Likelihood of YF outbreak in the region/neighbouring country developing into a pandemic and crossing into Uganda.

  WHO 2013

  Pandemic potential for Yellow fever in Africa was demonstrated in 2012, a major outbreak occurred in Darfur, Sudan, where by the end of December 2012, 847 suspected cases of YF, including 171 deaths, had been reported. The outbreak spread to Chad where 139 suspected cases and 9 deaths were reported in December 2012.

  WHO 2012: REPORT OF YELLOW FEVER RISK ASSESSMENT IN UGANDA, 2012

  Findings from the 2012 assessment showed that the presence of uninfected vectors and low population immunity is indicative of low risk of YF outbreaks nationwide; however the risk of YF could dramatically increase if the YF infection is introduced in the mosquito population and the vectors adopt more anthropophilic biting behavior.

d. Economic and operational considerations

i. Vaccine related cost and resource use

- Cost of expanding YF vaccine into routine immunization schedule for all children in the country aged 6-24 months

  The WHO 2017 Immunisation Financing sustainability report put the total cost of New Vaccine introduction of Rota and Yellow Fever at $378.7m. (WHO 2016b). An estimate of costs made by Healthnet Consult 2017 put the cost of YFV introduction at $2.6- 3.5 million.

ii. Economic impact

- Cost-effectiveness of routine YF vaccination to all children in Uganda vs. to only children in high risk areas

  Monath and Nasidi 1993.

  A study, investigating the cost-effectiveness of introducing YF vaccine into Nigeria's immunization programme, estimated that after 15–18 years, routine immunization would be 7- to 8-fold more efficient than emergency outbreak control in preventing cases and deaths. A cost–effectiveness analysis covering 23 African countries at risk of YF, carried out to inform the development of the YF vaccine stockpile in 2005, found that adding preventive campaigns to complement routine YF immunization programmes is cost-effective, especially if the countries at highest risk are the focus of such prevention campaigns. The major cost

drivers are human resources, programme management, social mobilization and transportation rather than price of the vaccine itself.

Objective: to assess the cost-effectiveness of preventive yellow fever vaccination versus emergency mass vaccination campaigns for epidemic control in Nigeria.

Methodology: The effects of including yellow fever l7D vaccine in the Expanded Program of Immunization (EPI) on the immune status of the Nigerian population was studied under conservative assumptions of vaccine coverage and efficacy. The model defined the age-specific prevalence of immunity resulting from vaccination of infants and from natural endemic infection beginning in 1991 and extending over a time horizon of 35 years. The data were used to predict the number of cases and deaths during hypothetical epidemics in 2006 and 2026, representing the historic periodicity of epidemics. A second model was used to demonstrate that a 60% prevalence of immunity would preclude epidemic yellow fever transmission; under base case assumptions, this prevalence would be reached after 18 years of initiating routine yellow fever vaccination in the Guinea savannah zone, the region most often affected by epidemics. Using assumptions based on data from other African countries, the cost of adding yellow fever vaccine to the existing EPI was estimated as $0.65 per fully immunized child, whereas the cost of emergency vaccination in the face of an epidemic was estimated as 7.84/person. Vaccine coverage rates achievable by the EPI were modelled on recent successes with measles vaccine, and began in 199 1 at 60%. The effective vaccine coverage rate in an emergency campaign was taken as 10%, based on recent experience.

Results: For an epidemic of moderate size in 2006 (morbidity similar to the documented outbreak in 1987), the cost-effectiveness of emergency mass immunization for control of hypothetical yellow fever epidemics was two-fold higher ($381/case and $1,904/death prevented) than that of the EPI ($763/case and $3,817/death prevented). However, despite its higher cost, the efficiency of the EPI was seven-fold greater in terms of cases and deaths prevented. In large epidemics, such as that occurring over successive years (1986 -1991) in Nigeria, cost effectiveness of the EPI exceeded that of emergency control.

*Cost-effectiveness of emergency versus routine vaccination for prevention of yellow fever in hypothetical epidemics in 2006 and 2026 affecting large and small population groups in Nigeria. Costs and benefits are discounted at 5%**

Time horizon and affected population	Measure	Cost	Cases prevented	Deaths prevented	Cost/case prevented	Cost/death prevented
1991–2006						
16 million	EPI	$19,824,734	103,888	20,778	$191	$954
	Emergency	$5,811,525	15,255	3,052	$381	$1,904
1 million	EPI	$19,824,734	6,493	1,299	$3,053	$15,266
	Emergency	$363,220	953	191	$381	$1,904
1991–2026						
16 million	EPI	$48,445,125	158,848	31,770	$305	$1,525
	Emergency	$7,894,875	20,476	4,096	$386	$1,927
1 million	EPI	$48,445,125	9,928	1,986	$4,880	$24,398
	Emergency	$493,430	1,280	256	$386	$1,927

* EPI = Expanded Program of Immunization.

Assumptions: A number of assumptions were used to define the hypothethical impact of the EPI on immunity of the population. 1) Yellow fever vaccine would be administered only during the first year of life, at the same time as measles vaccine. The model therefore ignores

the potential for increasing coverage by the use of alternative delivery strategies, such as mass campaigns, and vaccination of older children through routine services provided by fixed centers and outreach teams. 2) The unimmunized population would continue to be naturally infected at the same rates of endemic virus transmission, regardless of the level of herd immunity induced by the vaccine.

Cost of immunisation used: The average cost of fully immunizing a child during EPI campaigns (as opposed to routine immunization) in Africa has been estimated as $15.08 plus the cost of vaccines used. The costs of delivering a single vaccine (e.g., yellow fever) during a mass campaign (as opposed to all EPI vaccines) may be estimated as approximately 50% of those associated with delivery of multiple vaccines (Batson A, World Health Organization, unpublished data), or $7.54 per immunized person, plus the cost of vaccine and wastage ($0.30), or $7.84. This cost per immunized person is used to estimate the cost of emergency interventions during future epidemics.

e. Health Policy and programmatic issues

i. Feasibility

- Can the current global pipeline for YF vaccine meet the annual needs for Uganda if it is expanded into routine immunization of all children aged 6-24 months?

UNICEF WEBISTE https://www.unicef.org/supply/files/YF_number_3_Supply_Update.pdf
Yellow fever vaccine (YFV) supply through UNICEF remains constrained due to limited production capacity. Despite the return of two manufacturers from temporary suspension, the high demand currently generated from the yellow fever outbreak in Angola, in addition to potential increased outbreak response requirements in other geographic regions, outweigh supply.

The demand in response to the current YF outbreak in Angola could negatively impact the supply availability for some routine immunization programme activities. UNICEF anticipates a constrained global production capacity to persist through 2017.

UNICEF has long – term arrangements (LTAs) with four YFV suppliers to cover emergency stockpile, routine immunization, and preventative campaign requirements. During 2015, UNICEF increased total aggregate award is to suppliers to reach approximately 98 million doses for 2016-2017. However, whereas supply can meet emergency stockpile and routine requirements, it is insufficient to meet all preventive campaign demands which increased the total demand through UNICEF to 109 million doses.

Once preventive campaigns in many African high and medium risk endemic countries have been completed, the pressure on YFV supply should ease, such that current production capacity will be sufficient to cover the needs of routine immunization programmes and any emergency outbreak responses.

- Does Uganda qualify as a priority country according to its risk profile?

  WHO 2016a
  Uganda was ranked 4th in the proposed priority ranking for African countries at high Risk of YF, behind Nigeria, Ghana and Sudan.

  UNICEF WEBISTE https://www.unicef.org/supply/files/YF_number_3_Supply_Update.pdf
  When the vaccine supply is insufficient to cover the countries' requirements for all immunization activities, vaccine demand is prioritised for outbreak response followed by routine immunization programmes. Any remaining quantities are then made available to meet preventative campaign demand.

- National coverage of vaccines being administered to children aged 6-24 months in Uganda?

Vaccine	Timing	Coverage %	Vaccine	Timing	Coverage %
Pneumococcal 1	6 weeks	86.5	Polio 3	14 weeks	65.8
Pneumococcal 2	10 weeks	77.0	BCG	Birth	96.3
Pneumococcal 3	14 weeks	62.2	DPT 1	6 weeks	94.9
Polio 0	Birth	79.5	DPT 2	10 weeks	89.9
Polio 1	6 weeks	94.5	DPT 3	14 weeks	78.6
Polio 2	10 weeks	86.2	Measles	9 months	80

Data source: Uganda Bureau of Statistics: Uganda Demographic Health Survey 2016

- Coverage of YF vaccine in areas of Uganda where it is part of routine immunization.

WHO 2012: REPORT OF YELLOW FEVER RISK ASSESSMENT IN UGANDA, 2012

YF is currently not part of Uganda's routine immunisation program. Reactive campaign vaccinations carried out following the 2011 outbreak in Northern Uganda had a coverage of 80.1%.

ii. Affordability and sustainability

- Uganda's investment plan for immunization services over the next 10 years
- Does the investment plan have the capacity to include YF vaccine as part of the routine immunization for all children countrywide?
- Possibility of partner funding YF vaccine to be expanded into routine immunization of all children countrywide.

  Ministry of Health 2017
  It was estimated that a total of $802 million dollars is required to introduce Rotavirus and Yellow Fever Vaccines into Uganda's routine Immunisation program of a five year period 2016/17-2020/21. There is an estimate funding gap of $62 million to finance the already existing vaccines in the routine immunisation schedule.

  Gavi Website. http://www.gavi.org/results/countries-approved-for-support/
  Yellow Fever Vaccine is not among the approved GAVI Supported vaccines for Uganda.

iii. Ability to evaluate

- Immunization program's ability to carry out AEFI monitoring for vaccines administered to children aged 6-24 months?

Ministry of Health 2014: UGANDA Combined EPI Review

Uganda has an AEFI system in place with a designated national committee. The Uganda combined EPI review 2014, reported that AEFI guidelines were available in 34% of facilities visited.

IV. Discussion

Disease Burden

a) Uganda has experienced two yellow fever outbreaks in the recent past, in 2010 and 2016. The Case Fatality Ration in the 2010 outbreak was 21.3%, higher than the WHO overall global estimate of 15%. A WHO Yellow Fever Risk Assessment 2012, carried out following an outbreak in northern Uganda in 2010 reported that Uganda is vulnerable to Yellow Fever sporadic outbreaks given its location in the Yellow Fever Belt (recent large outbreaks reported in neighbouring countries: South Sudan, Kenya and Democratic Republic of Congo), an YF naïve population with low natural immunity, and presence of potential vector carriers. With the high mobility of persons across country borders, an importation of Yellow Fever could lead to rapid spread in the country. Also, presence of a few individuals with acquired natural immunity indicates a prevalence within the country.

b) The disease is difficult to detect clinically diagnose, with many mild cases mistaken for common jaundice, or malaria, however severe conditions have no clear treatment protocol and cases of renal-hepato disease having a high fatality rate of 20 -50%.

Vaccine characteristics, safety, efficacy and effectiveness

a) Evidence shows no serious adverse events related to yellow fever vaccination in individuals over 8 months of age. Mild reactions include fevers with low rates of upper respiratory symptoms or injection site symptoms, although WHO recommends that the vaccine should not administered to children aged 6-8 months, except during epidemics, when the risk of infection may be very high.

b) Yellow fever live virus vaccine can cause severe, often fatal, multi-systemic illness, yellow fever vaccine-associated viscerotropic disease (YEL-AVD). Predominantly a neurological disease termed yellow fever vaccine-associated neurotropic disease (YEL-AND). Incidence is reduced if vaccine if administered to individuals older than 6 months, and increased risk for in Thymectomized individuals (treatment of thymoma), Thymus disease, severe malnutrition and severely immunocompromised, although WHO states that HIV testing should not be a prerequisite before immunizing children. Evidence showed no risk of reversion to virulence.

c) Co-administration with measles vaccine was shown in one study (Fisker) to increase mortality and affect efficacy of the yellow fever vaccine. One study showed a significant decrease in the seroconversion rates and geometric mean titres obtained against Yellow Fever, Mumps, and Rubella when the vaccines were co-administered. No decreases were noted in the immune response to Measles.

d) Evidence shows that a single dose offers more than 30 years of protection, possibly life, and hence no need for booster doses.

Issue on Economic Considerations for Yellow Fever Vaccine

a) Vaccines by their nature are almost always cost-effective. Therefore the key consideration for Uganda when deciding on new vaccine introduction is affordability and sustainability in view of other competing health priorities.

b) Comparison of cost effectiveness/ cost benefit of Yellow Fever Vaccine in routine schedule versus targeted reactive campaigns: Evidence from Nigeria showed that the routine schedule approach was 7-8 times more cost effective in the long run. Whereas WHO fully meets the cost of reactive campaigns (*actual figures from recent campaigns to be obtained from Dr. Kisakye*), with no fiscal costs to the government, the cost of lives lost in the epidemics needs to be taken into account. Also, with low card retention as evidenced in Uganda's recent reactive vaccination campaign in northern Uganda (51.6%), the possibility of wastage through multiple vaccinations is high.

   Using the PCV introduction costs as reported in the WHO 2016 Immunisation Costing Study (WHO 2016B) and the UNICEF website quoted price per dose of Yellow fever vaccine ($1.18) it was calculated that it would cost Uganda a rough estimate of $1.6 m to introduce a Yellow Fever vaccine to the immunisation program, assuming 5.6 million doses required per year. Given the relatively low purchase price per dose compared to PCV ($ 4..03), and that Yellow Fever is a one dose schedule vaccine, the major cost drivers are human resources, program management, social mobilization and transportation rather than price of the vaccine itself. Yellow Fever is not listed on the Gavi supported new vaccine introduction list for Uganda, therefore all/most costs for its introduction into the routine schedule would be borne by government. It is hence imperative to demonstrate the additional lives saved by introduction of Yellow Fever vaccine in routine schedule in order justify the cost, and show the competitive advantage over other new vaccines yet to be introduced, and other health interventions in general, competing for the same fiscal space.

Issue on Health Policy and Programmatic aspects of Yellow Fever vaccine in routine schedule

a) Uganda is considered as a Yellow Fever endemic country. According to the WHO Global Strategy to eliminate YF (EYE) www.who.int/immunization/sage/meetings/2016/october/2_EYE_Strategy.pdf, all babies aged 9-24 months in Yellow Fever endemic countries should be given one dose of yellow fever vaccine as part of the routine immunisation schedule and ensure that high coverage is

achieved. In Africa, as of September 2016, five out of the 27 countries had not yet done so (Ethiopia, Kenya, South Sudan, Sudan and Uganda).

b) Yellow Fever vaccine is recommended for routine vaccination of children aged 9 – 24 months. The current schedule of routine immunisation for children ends at 9 months with administration of a measles vaccine. With co-administration of Yellow Fever vaccine with measles containing vaccine associated with increased mortality and lower efficacy for yellow fever vaccine, the routine immunisation schedule would need to be extended to vaccine babies at 12 months against Yellow Fever. The upside is that it would ensure a good efficacy outcome, and provide an opportunity for overall child wellness check at 1 year mark. The low side is there is the risk of drop out, although, single dose vaccines, like the current schedule have a national coverage of over 80%. With an 80% coverage, herd immunity would confer protection to unvaccinated children.

c) Global yellow fever vaccine demand outstripped supply in 2016. UNICEF has long – term arrangements (LTAs) with four YFV suppliers to cover emergency stockpile, routine immunization, and preventative campaign requirements. During 2015, UNICEF increased total aggregate award is to suppliers to reach approximately 98 million doses for 2016-2017. However, whereas supply could meet emergency stockpile and routine requirements, it was insufficient to meet all preventive campaign demands which increased the total demand through UNICEF to 109 million doses. The average price of a 10-dose Yellow Fever Vaccine vial increased from US$ 0.50 in 2001 to an average price of US$ 1.04 in 2015, representing an increase of 100% over the 14-year time period. UNICEF anticipates the WAP of Yellow Fever Vaccine to reach US$1.10 per dose over 2016-2017 given continued supply constraints and prior trends. According to the WHO EYE strategy, Uganda was ranked 4th in the proposed priority ranking for African countries at high Risk of Yellow Fever, behind Nigeria, Ghana and Sudan, putting it in a good competitive space for supply. WHO approval for administration of fractional doses, that is currently under a formal approval review process will also ease up on the vaccine demand.

V. Proposed recommendation (s) /options

a) Introduction of a Yellow Fever Vaccine in Uganda's routine immunisation schedule at 12 months of age. This would be recommended if Government has fiscal space to ensure its sustainable financial support.

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II. Annexes

1. Advise Request Letter from Ministry of Health

Telephone: General Lines: 340874/ 231563/9
Permanent Secretary's Office: 256 - 41 - 340872
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THE REPUBLIC OF UGANDA

Ministry of Health
P.O. Box 7272
Kampala
Uganda

IN ANY CORRESPONDENCE ON
THIS SUBJECT PLEASE QUOTE NO: **ADM:215/306/01**

22nd June 2016

Dr. Nelson Sewankambo,
Chairperson for NITAG Uganda,

RE: REQUEST TO NITAG TO ADVICE THE IMMUNIZATION PROGRAM TO PRIORITIZE WHICH NEW VACCINES SHOULD BE INTRODUCED

The goal of immunization program is to ensure that every child and high-risk group is fully vaccinated with high quality and effective vaccines against the target diseases according to recommended strategies through five operational components: vaccine supply and quality, logistics, service delivery, surveillance, advocacy and communication.

SAGE has made several recommendations to countries to introduce new vaccines into their routine immunization program following evidence presented to them to show that they are effective and efficacious. Over the last three years, Uganda has introduced three new vaccines into the routine immunization program and plans to introduce yellow fever vaccine, Measles and Rubella Vaccine including second dose, Men A and Tetanus Diptheria(Td) Vaccine.
However along the way the program has observed some challenges and anticipates more to come as more new vaccines are introduced into the routine immunization program. Among these challenges, includes fulfilling co financing requirements for the recently introduced vaccine affecting the performance of new vaccine introduction

In line with the WHO recommendation, Uganda established the NITAG to provide evidence based advice to the Ministry of Health on immunization.

The purpose of this letter is therefore to request the NITAG to provide guidance on which new vaccine Uganda's immunization program should prioritize in order of importance in the next five years. Your response will highly be appreciated preferably by end of 2016.

Prof. Anthony K. Mbonye
FOR DIRECTOR GENERAL HEALTH SERVICES

Cc: The Permanent Secretary, Ministry of Uganda
Cc: The Director Health Services, Clinical and Community
Cc: Commissioner Health Services, National Disease Control
Cc: The Program Manager, UNEPI

2. List of Working Group Members

a) Assoc. Prof. Jesca Nakavuma -Core member, vaccinology(Chair)
b) Prof. Sarah Kiguli – Core member, Pediatrics
c) Ms. Charlotte Muheki Zikusooka – Core member, Health Economist
d) Dr. Emmanuel Mugisha –Liaison member, PATH
e) Dr. Annet Kisakye – Liaison member,WHO
f) Prof. Ponsiano Ocama – co-opted expert (Hepatologist)

3. Recommendation Framework

Attached as Excel Document.

Uganda Immunization Technical Advisory Group

Recommendation on Hep B vaccination at birth

Uganda Immunization Technical Advisory Group

Recommendation on Hep B vaccination at birth:

SHOULD A BIRTH DOSE OF HEPATITIS B VACCINE BE INTRODUCED INTO UGANDA'S ROUTINE IMMUNIZATION SCHEDULE?

SEPTEMBER 2017

Contents

Executive summary

The Ministry of Health asked the Uganda National Technical Advisory Group (UNITAG) to make recommendations on the prioritization of various new vaccines to introduce to the routine immunisation schedule. Challenges to the immunisation program's vaccine introduction efforts such as low coverage and limited financing prompted this request. The five new vaccines proposed for introduction are: Hepatitis B birth dose, Yellow Fever, Meningococcal A, 2nd dose of measles containing vaccine and a switch from Tetanus Toxoid to Tetanus diphtheria.

The vaccine considered in this dossier is the Hepatitis B birth dose. Hepatitis B Virus (HBV) is highly contagious and is transmitted by percutaneous and permucosal exposure to infected blood and other body fluids. Chronic HBV occurs in approximately 90% of persons infected perinatally, in 30% infected in early childhood and in 6% infected after 5 years of age. Persons with chronic HBV infection have a 15–25% risk of dying prematurely from HBV-related cirrhosis and Hepato-Cellular Carcinoma (HCC). The persistence of the antibodies associated with chronic HBV are the principal markers of risk for development of chronic liver disease and hepatocellular carcinoma later in life. Treatment is expensive and complicated by severe side effects. The WHO Position paper updated in 2009 recommends that all children receive the first dose of Hep B vaccine within 24 hours of birth. Uganda introduced Hepatitis B vaccine into its routine immunisation program in 2002, combined with Diphtheria, Whooping Cough, Tetanus, and Haemophilus influenza type B) commonly referred to as Pentavalent vaccine, administered at 6 weeks, 10 weeks and 14 weeks.

Data from the national sero survey conducted in 2009 suggested that the Hepatitis B burden in Uganda is high with about 1.5 to 3 million people chronically infected. The prevalence of Hep. B infection and the Hep. E antigen positive in pregnant women is high in certain settings in Uganda particularly in the northern and north eastern parts. The financial and human burdens of disease are high, since most patients diagnosed with liver cirrhosis and Hepato-cellular carcinoma die within months of diagnosis and those with Chronic infection must take antivirals their entire lives. Preliminary results from the 2016-2017 national sero-survey showed that the cohort born after the introduction of Hepatitis B vaccine into the routine schedule (0-14 years had significantly lower Hepatitis B infections (0.6%) than their older counterparts(15-49 years) who did not receive the vaccine (4.3%). The same positive public health impact of the Hep. B infants' vaccination on the decrease of level disease and HCC has been noted worldwide.

Evidence shows that administration of a Hep B birth-dose vaccine is safe and effective comparative to settings where no Hepatitis B vaccine is given at all. Evidence also shows that immunogenicity of the vaccine is not different whether it is first given at birth or 6 weeks of life and that there is good immune response regardless of whether the mother is Hep-B infected or not. A review of literature in the African setting showed that a birth dose did not result in significant additional protectiveness when given in combination with the existing schedule of 6, 10 and 14 weeks.

Administering a birth dose of Hep B shortly after a Health facility delivery was found to be highly cost effective in a study carried out in Mozambique, and it is estimated that the introduction of the Hep. B vaccine birth dose in Uganda would cost about 2.3-3.1 million dollars.

Programmatically, birth vaccine performance is high in Uganda, with BCG at 93% and OPV at 82%. Preliminary results from a pilot study in Tororo Referral Hospital showed significant programmatic

challenges in testing pregnant mothers for Hepatitis B and administering a birth dose vaccine to new borns within the first 24 hours after birth. To achieve Hep B high birth dose coverage, emphasis should be placed on ensuring an efficient vaccine delivery system; particularly, there would be a need to strengthen the Community Health Workers to reach the 30% of children not born in health facilities.

Based on the evidence, the UNITAG made the following recommendation:

UNITAG did not recommend addition of a Hepatitis B birth dose into Uganda's routine immunisation schedule. There is no high quality evidence to show additional value of birth dose in a setting where Hep B vaccine is routinely administered at 6, 10 and 14 weeks. More research is required in order to show the efficacy of the birth dose in a setting with Hep B vaccine administered at 6, 10, and 14 weeks.

1.Introduction

a.Context of the question

Ministry of Health requested Uganda National Immunisation Technical Advisory Group (UNITAG) for advice on which new vaccines Uganda should prioritise in the next five years for introduction into the routine immunisation schedule. This was prompted by challenges facing the immunisation program new vaccine introduction efforts including low coverage and limited financing. Five new vaccines were proposed for consideration including: Hepatitis B birth dose, Yellow Fever, Meningococcal A, 2nd dose of measles containing vaccine, and switch from Tetanus Toxoid to Tetanus diphtheria. (Annex 1)

b.General information on Hep B and vaccination

The hepatitis B virus (HBV) is a double-stranded, enveloped virus of the Hepadnaviridae family. The outcomes of HBV infection are age-dependent and include acute (clinically apparent) hepatitis B, chronic HBV infection, cirrhosis and Hepato-Cellular Carcinoma (HCC). Humans are the only reservoir of HBV. The virus is highly contagious and is transmitted by percutaneous and permucosal exposure to infected blood and other body fluids (i.e. semen and vaginal fluid). Common modes of transmission include mother-to-infant, child-to-child, unsafe injection practices, blood transfusions and sexual contact.

Acute hepatitis B occurs in approximately 1% of perinatal, 10% of early childhood (1–5 years old) and 30% of late (>5 years old) HBV infections. Fulminant hepatitis develops in 0.1–0.6% of acute hepatitis cases; mortality from fulminant hepatitis B is approximately 70%. The development of chronic HBV infection is inversely related to age and occurs in approximately 90% of persons infected perinatally, in 30% infected in early childhood and in 6% infected after 5 years of age. Persons with chronic HBV infection have a 15–25% risk of dying prematurely from HBV-related cirrhosis and HCC.
In serological terms, acute HBV infection is characterized by the presence of HBsAg and of IgM antibody to the core antigen, HBc (IgM anti-HBc). During the initial, highly replicative phase of infection, thus contagious, patients are also seropositive for the hepatitis B e-antigen (HBeAg). Antibody to HBsAg (anti-HBs) occurs after a few weeks and is followed by clearance of the HBsAg. Chronic infection is characterized by persistence (>6 months) of HBsAg (with or without concurrent HBeAg). Persistence of HBsAg is the principal marker of risk for development of chronic liver disease and hepatocellular carcinoma later in life. Long-term combined treatment with interferon alfa 2-b and modern nucleoside analogues may result in elimination of viral replication in 40–50% of cases with chronic HBV infection. This treatment is very expensive and often complicated by severe side-effects, induction of HBV mutants and high relapse rates.
(Source: WHO Position Paper)

Based on serological data, it was estimated that in 1995 more than 2 billion people globally had evidence of past or present HBV infection. In 2015 the global prevalence of HBV infection in the general population was estimated at 3.5% with about 257 million persons living with chronic HBV infection (who, 2017).The WHO position paper also states that since perinatal or early postnatal transmission is the most important source of chronic HBV infection globally, all

infants (including low birth weight and premature infants) should receive their first dose of hepatitis B vaccine as soon as possible after birth, ideally within 24 hours. If administration within 24 hours is not feasible, a late birth dose has some effectiveness. Although effectiveness declines progressively in the days after birth, after 7 days, a late birth dose can still be effective in preventing horizontal transmission and therefore remains beneficial. WHO recommends that all infants receive the late birth dose during the first contact with health-care providers at any time up to the time of the next dose of the primary schedule.

Uganda introduced Hepatitis B vaccine into its routine immunisation program in 2002, combined with Diphtheria, Whooping Cough, Tetanus, and Haemophilus influenza type B) commonly referred to as Pentavalent vaccine , administered at 6 weeks, 10 weeks and 14 weeks. The 2016 Uganda Demographic and Health Survey reports coverage as: Penta 1 (96.3%), Penta 2 (94.9%) and Penta 3 (89.9 %).

2.Methodology

a.Establishment of a Hep B birth dose working group

In line with the UNITAG Internal Procedures Manual, the UNITAG Chair in consultation with the Secretariat commissioned a working group to develop a Recommendation Framework on Hepatitis B birth dose introduction in Uganda's routine immunisation program, and conduct a systematic search, appraisal and synthesis of relevant evidence based on which, recommendations would be proposed. The Working Group was chaired by a core member, Vaccinologist, and comprised of the following UNITAG members: Paediatrician, Epidemiologist, Public Health expert, Health Economist, and a co-opted Hepatology specialist. List in annex 2. All members signed a declaration form stating that they had no known conflict of interest on the topic. The working group has met once to develop the Recommendation framework, and once to review the evidence and develop the technical dossier with proposed recommendation. . Minutes of the meetings in Annex 3.

b.Recommendation framework

The working group developed a recommendation framework, outlining the issues and specific data needed to inform a recommendation on Hep B vaccination at birth. The recommendation framework considered 4 categories of issues: 1) Disease burden (Burden of Hepatitis disease in Uganda) 2) Vaccine characteristics and immunization (efficacy and safety of available monovalent hepatitis vaccines at birth) 3) Programmatic and Economic Considerations and 4) Policy issues . A detailed Recommendation Framework is attached as Annex x

c.Evidence search and assessment

The Working group followed the steps outlined below in its evidence search and assessment:

•Step 1: Framing questions for the literature search

For each issue in the recommendation framework, the WG went further in specifying the specific data that are needed. For each data, queries were specified in the form of clear, unambiguous and structured questions before beginning the search work. Queries were categorised as those that required a systematic search in databases and those for which information could be found in

reference documents (WHO papers, text books, vaccine manufacturers' websites). These documents were used as source of background information. For systematic search of data, the queries were formulated to specify the specific outcomes of interest from the use of the intervention in the population considered as per UNITAG method of working for issuing evidence-based recommendation (using the PICO approach to search for evidence on the efficacy, effectiveness and safety of an intervention). Queries requiring systematic literature search proceeded to step 2. Grey literature (Ministry of Health Reports, Immunisation partner surveys, websites and unpublished local reports) and reference documents were looked for to answer background data queries.

•Step 2: Identifying relevant peer reviewed articles

Search strategies were developed to ensure that search terms covered all known terms relevant to the question. Multiple journal resources (Pubmed, Scopus, Embase and Cochrane) were searched with English language restriction to generate relevant title-abstracts. Inclusion and exclusion criteria were set for each query, to flow directly from the review question and was specified a priori. Articles obtained were screened (titles and abstracts) for relevance to the question. The search strategy and result was recorded, the report is available at the secretariat.

•Step 3: Assessing the quality of articles

Selected title abstracts were extracted in full text and subjected to review and if still relevant to the question, to a more refined quality assessment by use of a design-based quality checklists (CASP)[1] according to the study design. These detailed quality assessments were used for exploring for bias or flaws of the study by evaluating its methodological quality, certainty of results, and relevance to the question, hence ensuring quality of the evidence sustaining the recommendation. List of articles retrieved and assessed is also indicated in the search strategy and results report.

•Step 4: Summarizing the evidence

Selected full text articles were read and relevant findings under each query were summarised in a standard UNITAG working group outline report.

•Step 5: Interpreting the findings

The Working Group organized a one-day workshop for review of the evidence presented on each issue of the recommendation framework and, from sense-making of the overall body of evidence , propose recommendations to submit to the entire UNITAG for decisions. During the workshop the group worked on the write-up of the discussion section, analysing the findings with the view of joining the pieces together that will lead to the proposed recommendations

[1] http://www.casp-uk.net/casp-tools-checklists

3.. Presentation of the evidence

This section presents the evidence on the research questions for the specific issues indicated in the recommendation framework.

1)Vaccine and immunization characteristics

i.Safety

a)*Safety profile of Hep. B vaccine compared to other vaccines administered in new-born babies less than one week of age*.

In placebo-controlled studies, with the exception of local pain, reported events such as myalgia and transient fever have not been more frequent than in the placebo group (<10% in children, 30% in adults). Reports of severe anaphylactic reactions are very rare. (WHO 2017)

In a study carried out among neonates in South Africa, no apparent serious adverse effect resulted from giving the Hep B vaccine from birth onwards. (Prozesky et al, 1983)

In a study looking at safety of BCG given at birth, the side effects observed were keloids at the injection site and suppurative axillary lymphadenitis (Hawkridge et al, 2008)

b)Contraindications to administering Hepatitis B vaccine in new-borns less than one week of age

Hep B birth dose is not contra-indicated for any birth condition including low birth weight or HIV infection. (WHO, 2017)

c)Risk factors that predispose to adverse events of Hep. B vaccine when administered in the new-born less than one week of age

Hepatitis B vaccine is contraindicated for individuals with a history of allergic reactions to any of the vaccine's components. However at birth, no allergic history is available. (WHO 2017).

ii.Efficacy and effectiveness

a)*Immune response or immunogenicity or duration of protection of Hep. B vaccine when the first dose is given at birth compared to when given at 6 weeks of life in the region/Africa*

Schoub et al, 1991

Objective-To determine the efficacy of hepatitis B vaccine when added to the routine expanded programme on immunisation under field conditions in rural Africa.

Methodology-Infants were immunised according to two schedules-an early schedule at birth, 3 months, and 6 months and a later schedule to correspond with routine vaccination in the expanded programme on immunisation at 3 months, 4½/2 months, and 6 months. All hepatitis B virus markers were tested by radioimmunoassay (Abbott Laboratories, Chicago, Illinois), and antibodies to hepatitis B surface antigen were measured in mIU/ml using the WHO reference preparation as a standard. A positive titre was defined as having >10 mIU of antibodies. Data were analysed statistically using either a X' test or Fisher's exact test.

Setting-Venda, northern Transvaal, South, Africa, a self-governing region of 7460 squarekilometres varying from rural villages to small towns.
Subjects-The 1989 birth cohort of Venda.
Results
Analysis of the data accompanying the specimens showed that few of the infants received their doses of vaccine within the limits of either of the schedules: thus 1-6% (14 of 863) were vaccinated according to the early schedule and 5 0% (43) according to the late schedule; 93-4% (806) fell into the "unscheduled" group. This unscheduled group received vaccine as follows: first dose 0-224 (median 27) days after birth; second dose 1-215 (58) days after the first dose; the third dose 8-182 (49) days after the second dose. There was, however, no significant difference in the number who seroconverted to the surface antigen between the early schedule and the late schedule groups, (13/14 (930/0) V 42/43 (98%); p=0 43, Fisher's exact test), or between the scheduled and unscheduled groups (55/57 (97%) V 778/806 (97%); p=0-10, Fisher's exact test), or between those who were immunised in fixed clinics and by mobile teams (625/652 (96%) v 208/211 (99%); p=0-06, X' test).

Plymoth and Hainaut, 2009
Objective: briefly review the lessons of Hep B vaccination programmes and trials in high-endemicity regions, based on data gathered during 15–20 years of implementation.

In **Senegal**, a 9–12 year period of follow-up of infants immunized against Hepatitis B showed that HBsAg was detectable in 19% of infants from the control group compared to only 2% of immunized infants, corresponding to a protective efficacy of 88%. The results show that long-term protection against HBsAg carriage of Hepatitis B vaccination is very high and that a booster dose at school age does not significantly increase this protection.
South Africa implemented a vaccine against Hepatitis B virus into the EPI in April 1995. The HBV vaccine is given at 6, 10, and 14 weeks]. Two cohorts were followed up, consisting of 459 children born before the introduction of vaccination in 1995, and 1213 children born between 1 and 2 years after the introduction of the vaccination programme .At 12–24 month of age, the frequency of detection of HBV DNA was reduced from 6.5% in unvaccinated children to 0.3% in vaccinated children. There is evidence that HB infection can persist in the absence of any serological markers. This is the case for so-called ‘‘occult” infections as well as for infections by immune response escape mutant viruses.

The prospective study in **South Africa**, to determine whether universal vaccination of infants affect the prevalence of serologically negative infections as well as the emergence of escape mutants in a highly endemic context, showed that no unique amino-acid substitution were found within the major antigenic determinant of the S gene. Thus, universal vaccination reduced the frequency of serologically negative infection without leading to selection of immune escape variants.

A Field efficacy trials in **Gambia** was launched in 1986 with the objective of evaluating the efficacy of Hepatitis B vaccination in childhood for the prevention of HB infection, chronic liver disease and HCC in a population at high risk. HB vaccine was introduced in the EPI using a ‘‘stepped wedge” design. Recruitment started in July 1986. A 4-dose vaccine schedule was

used with the first dose given as soon as possible after birth (during the child's first attendance at a welfare clinic) and subsequent doses given at the ages of 2, 4 and 9 months. With the aim of evaluating the immunogenicity of the vaccine and its efficacy in preventing infection and chronic carriage, two subgroups of the study cohort have been studied in detail. Group 1 was a cohort of 1041 children, including approximately the first 250 HB-vaccinated children. These children have been followed-up annually (except for the 6th and 8th year). Group 2 consisted of two cross-sectional surveys, each including 800 unvaccinated subjects aged 4 and 9 years old. Vaccine efficacy did not significantly change over time, and was 84% against infection and 94% against chronic carriage at 9 years of age.

Taiwan experience

In Taiwan, studies reported that HCC mortality was 223-fold higher for HBsAg seropositive men than for those who were HBsAg-seronegative. Hep B vaccination was started. For the first two years, the programme covered only neonates born to mothers who were HBsAg carriers, where the infants received a 4-dose regimen of Hepatitis B vaccine The programme was extended to all neonates in July 1986, to preschool children in July 1987, to primary-school children in 1988, to middle-school children in 1989, and to adults in 1990, where a 3-dose regimen of Hepatitis B vaccine was given. In 1997, Chang et al. published the first report demonstrating a sharp decline of primary liver cancer in children vaccinated with Hepatitis B in Taiwan. In this report, they analysed the incidence of HCC in children from 1981 to 1994, using data on liver cancer in children from Taiwan's National Cancer Registry. They found that the average annual incidence of HCC in children 6–14 years of age declined from 0.70 per 100,000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994. The corresponding rates of mortality from hepatocellular carcinoma also decreased, since fatality rates for HCC are close to 100%.

Further studies on Taiwanese vaccinated subjects evaluated the long-term antibody persistence after vaccination and the vaccine efficacy in preventing chronic carriage status. In 15 year old subjects vaccinated at birth, despite a sharp decline in antibody titres observed with time, vaccine efficacy against chronic carriage was sustained and no booster vaccination was deemed necessary at this age. In a series of 1357 persons who were born after the implementation of the vaccination programme, only 9 (0.7%) became chronic carriers vs. 7% (39 of 559) observed in participants older than 15 years of age, who were born before the universal vaccination programme ($P < 0.001$. Among them, most were from families with a positive history of HBV infection and, in particular, had HBsAg carrier mothers. This observation suggests that a small proportion of newborns exposed to vertical transmission may acquire their infectious status before vaccination, despite the first dose being delivered before one week of age.

So far, the only data available on the effectiveness of HB vaccination against HCC are those from Taiwan. However, within the next few years, large vaccination trials in The Gambia will be in a position to provide comparative estimates of incidence of HCC in young adults born before or after the introduction of the vaccine. The public health impact of universal Hep B infants vaccination on the decrease of chronic liver disease and HCC is expected to be impressive.

Odusanya et al 2011.

Objective: to determine the effectiveness of the HB vaccine five to seven years post-introduction within a rural community in Nigeria.

Methodology

The study design was cross-sectional. Eligible children were either vaccinated subjects who had received at least two doses of HB vaccine or unvaccinated subjects (controls) who had not received HB vaccine. Following informed consent obtained from mothers/care givers, data was obtained using an interviewer-administered questionnaire. Venous blood was obtained to measure HB markers including hepatitis B surface antigen (HBsAg), and antibodies to the core (anti-HBc) and antibody to the hepatitis B surface (anti-HBs) antigens. HBVDNA was used to determine HB status. The HB vaccine is administered at birth, 6, 10 and 14 weeks of life.

822 subjects were eligible for analysis, 449 vaccinated and 373 controls. Majority of the subjects did not receive birth dose (261, 58%), 88% had at least 3 doses.

Results

Prevalence of anti-HBc was 43.2% in unvaccinated children compared to 10.5% in vaccinated children ($p < 0.001$). The rate of HBsAg was 11.8% in the unvaccinated group and 2% in the vaccinated group ($p < 0.001$). The vaccine effectiveness against anti-HBc was 84.6% (95% confidence interval 77.8, 89.3%) and the effectiveness against infection was 84.7% (95% confidence interval 68.2, 92.6%). Sixty-one percent of vaccinated subjects had protective antibodies ≥10 EIU/ml compared to 18% of controls ($p < 0.001$) and the geometric mean titers (GMT) were 19.96 and 7.28 EIU/ml respectively ($p < 0.001$). Vaccinated subjects were protected at least for five to seven years following HB vaccination.

HBV Markers in study subjects

Amongst vaccinated subjects, the HBsAg rate was comparable ($p = 0.74$) amongst those who received the HB vaccine dose at birth (3/188, 1.6%) and those who did not (6/261, 2.3%). Amongst vaccinated subjects 275 subjects (61%) had anti-HBs ≥10 EIU/ml compared to 18% of the controls ($p < 0.001$). Amongst the unvaccinated subjects ($n = 68$) who had anti-HBs ≥10 EIU/ml, only two (2.9%) were negative for anti-HBc.

Limitation: The study has some limitations. The study design did not to assess the value or added benefit of the HB vaccine birth dose. The markers of HB infection in these subjects were not determined at birth thus making it impossible to compare for trend in antibody response to vaccination and the natural history of the disease in unvaccinated subjects. It was also not always possible to distinguish between breakthrough infections after or during vaccination and pre-existing infections before vaccination, which might have underestimated vaccine effectiveness.

Barin et al, 1982

Objective: To assess whether the HB vaccine was as immunogenic in neonates as in older infants.

Methodology: 26 Senegalese babies were immunised within the first month of life as part of the programme. Titres of antibodies against HBsAg (anti-HBs) and the kinetics of the response to HB vaccine were compared with those previously obtained among older

Senegalese children. Of the 26 vaccinated neonates (15 boys, 11 girls), 14 were less than 5 days old and 12 were 20-30 days old when they received their first injection of HB vaccine. Before immunisation 3 infants (11-5%), were seronegative (negative for HBsAg, anti-HBs, and antibodies against hepatitis B core antigen [anti-HBc]), 16 (61 - 5%) were anti-HBc positive only, and 7 (26 - 9%) were anti-HBs positive. None was HBsAg positive (see table).
The HBV status of 21 of the mothers was known: 3 (14' 3%) were HBsAg positive at delivery (1 of them had twins), 6 (28' 6%) were anti-HBc positive only, and 12 (57 -1%) were anti-HBs positive Babies received three injections of HB vaccine (1 ml subcutaneously) separated by intervals of 1 month and a booster injection after 1 year. Blood samples were taken on the day of birth, or before the injection on the day of the first injection ofHB vaccine (To), or both, then on the day of the third injection), 2 months after the third injection (T4), and (for 12 children) at the time of the booster injection.

Results
The study established that the HB vaccine is safe and potent in both children and neonates. Moreover, it has shown that active immunisation against HBV can be induced in babies with passive immunity due to anti-HBs of maternal origin. Thus, for children born to mothers positive for HBsAg and HBeAg a combination of HB vaccine and HBIg started at birth may offer complete and long-lasting immunity, although the efficacy of this approach was yet to be tested.

Perrin et al 1986
Objective: to test efficacy of a 2 dose protocol, where newborns are vaccinated at birth and exactly 2 months later and a booster dose at 12 months of age.

Methodology: Newborns were randomly divided into vaccine and control groups. Vaccinated newborns were given two injections of hepatitis B vaccine: one at birth and another 2 months later. A booster dose was given at 12 months of age. The Vaccine used was from Pasteur Vaccins (Hevac B°). The HBsAg concentration was 5 microgams per dose. Blood samples were taken from the infants from both groups on the day of birth (TO), and at specific periods: 4 months (T4), 12 months (T12), and 24 months (T24). In addition, blood samples were obtained from the infants in the vaccine group at a period of 18 months (T18), i.e. 6 months after the booster dose had been administered. A blood sample was also obtained from the mother on the day of delivery.

Results: obtained show that two months after the second dose of HB vaccine, 96.8% of the vaccinated babies had anti-HBs; at the age of one year this figure had fallen to 83.8%. Six months after the booster dose, 95.6% were anti-HBs positive, with a geometric mean titre of 214 mlU ml. The anti-HBs responses were lower in terms of mean titre values in neonates who received the two dose protocol than in older children and in neonates who received three doses at one month intervals.
Vaccine efficacy was monitored during a two year period in neonates both immunized and non-immunized. Protective efficacy was found to be 100% if considering HBsAg positive events and 75% if considering all HBV events (HBsAg and or anti-HBc positive).

These clinical and experimental trials confirmed the finding that hepatitis B vaccine is immunogenic in newborns. However, results obtained with babies vaccinated with two doses at an interval of 2 months are not as good as those with three doses at intervals of one month.

Ekra et al, 2008

Objective: a non-randomized controlled trial comparing hepatitis B vaccination given at age 0, 6, and 14 weeks versus the current C^ote d'Ivoire schedule of 6, 10, and 14 weeks.

Methodology

Compared the difference in HBsAg positivity at age 9 months following a vaccine schedule starting at birth vs. 6 weeks. Pregnant women were enrolled February 2001- September 2002, at 4 participating health centers. Excluded infants had chronic or acute disease, received immunosuppressive therapy, could not receive vaccine, or received hep B vaccine other than the designated study vaccine.Blood samples were tested for antibodies against HBV core antigen (anti-HBc) and HBsAg. Vaccine used was Euvax B recombinant vaccine

Results

71.5% mothers had positive test (HBc test) for HBV infection at 6-8 weeks postpartum. HBsAg positive prevalence was 7.7%. 2mothers had acute infection, IgM anti-HBc positive

None of the infants tested at birth were tested positive, 9 infants in the 6-8 weeks were tested positive for HBsAg (born to HBeAg, HBsAg, and IgG anti-HBc positive mothers)

By age 9 moths 0.5% infants in both cohorts were positive for HBsAg and were all born to HBeAg-positive mothers. 9 month follow up birth cohort 77.5% and in the 6-week cohort 81.7% had protective anti-HBs levels. From HBeAg-positive mothers, 38% infants from the birth cohort and 59% infants from the 6-week cohort became HBsAg carriers despite appropriate vaccination. Calculated protective vaccine effectiveness at 9 months (assuming the 75% transmission from mother-to-infant) was 22% for the 6-week cohort and 50% for the birth cohort

Results suggest that either vaccine schedule will reduce overall transmission during infancy. Both vaccine schedules prevented most cases of infant HBV transmission, but additional studies are needed to verify the birth dose benefits

Limitations

-Did not look at perinatal transmission in the 6-week cohort so no comparisons can be made with the birth cohort

-Lost to follow up was 44% in the birth cohort and 23% in the 6-week cohort for the 9 months evaluation, can impact the calculations and/or conclusions of the study

-Sanofi Pasteur provided the funding for the current study, although did not have access to study database, possible conflict of interest

-Selection of immunization schedule was based on clinic not randomized, could be selective bias based on the location of the clinics (socioeconomics and education level)

-Assumed a 75% transmission rate in the absence of vaccination for the mother-to-infant transmission calculations

-Results from this study indicate vaccine failure rates may be the highest yet documented

-Lower antibody levels could be due to testing blood after three vaccines, at month 9 instead of the 1-3 month period other studies often test for sero-protection studies, limiting the possibility to compare the results from this study with other studies

-Accelerated schedule used in Cote d'Ivoire and Sub-Sahara Africa may not be as effective as the recommended schedule of 6 months dose or at least 16 weeks between first and third dose and 8 weeks between second and third dose.

b) efficacy of Hep. B vaccine in reducing the risk of Hep. B transmission and HCC when the 1st dose is given at birth (24 hours vs. 72 hours vs. 7 days of life) vs. 6 weeks?

Lee et al, 2006

Objective: To assess the beneficial and harmful effects of hepatitis B vaccines and hepatitis B immunoglobulin in newborn infants of HBsAgpositive mothers.

Methodology

Search methods

Trials were identified through The Cochrane Neonatal Group Controlled Trials Register, The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials in The Cochrane Library, MEDLINE, and EMBASE (until February 2004), authors of trials, and pharmaceutical companies.

Selection criteria

Randomised clinical trials comparing: plasma-derived vaccine (PDV) or recombinant vaccine (RV) versus no intervention, placebo, or other active vaccines; hepatitis B immunoglobulin versus no intervention, placebo, or other control immunoglobulin; as well as PDV or RV plus hepatitis B immunoglobulin versus no intervention, placebo, or other control vaccines or immunoglobulin.

40 references describing 29 randomised trials were included.

Results

Hepatitis B vaccines versus placebo or no intervention

Compared with placebo/no intervention, hepatitis B vaccination significantly decreased the risk of hepatitis B occurrence (RR 0.28, 95% CI 0.20 to 0.40, 4 trials). Subgroup analyses did not find a significant difference relating the mother's HBeAg status, or time of vaccine injection. Post hoc subgroup analysis according to vaccine schedules (0-1-6 months versus 0-1-2-6 or -12 months) showed no significant difference.

Recombinant Vaccine versus Plasma Derived Vaccine

Found no significant difference between RV and PDV on hepatitis B occurrence. Significantly fewer newborn infants on RV compared to PDV had anti-HBs less than 10 IU/L (RR 0.51, 95% CI 0.36 to 0.72, (trials)

PDV at birth versus PDV at one month

PDV administered for the first time at birth did not significantly differ from PDV administered for the first time at one month of age regarding the number of newborn infants having hepatitis B occurrence (RR 0.70, 95% CI 0.18 to 2.77, 1 trial).

One type of RV versus another type of RV with the same vaccination schedule

Different RV in terms of various manufacturers were assessed and no significant differences were found on hepatitis B occurrence or anti-HBs less than 10 IU/L.

In general, the review was unable to demonstrate significant differences among different doses, different schedules, and different forms of PDV and RV on hepatitis B occurrence. Furthermore, subgroup analyses did not show strong associations between timing of injection (within 12, 24, or 48 hours) and magnitude of effects.

Limitations
The number of newborn infants evaluated in these comparisons was small. Therefore, future trials ought to be much larger before equivalence or non-inferiority can be claimed.

c)Efficacy of Hep. B vaccine given at birth to babies born to mothers with HBsAg positive mothers vs. babies born to mothers with HBeAg positive in reducing the risk of Hep. B transmission?

Ekra et al 2008
Objective:
To compare the difference in HBsAg positivity at age 9 months following a vaccine schedule commencing at birth versus one commencing at age 6 weeks among infants from Abidjan, Cˆote d'Ivoire.

Methodology:
A non-randomized controlled trial conducted at four health centers in Abidjan. Pregnant women were enrolled between February 2001 and September 2002. Allocation of vaccination was by health center: infants born to mothers enrolled at two health centers were assigned arbitrarily to receive vaccine at birth, 6, and 14 weeks while infants born to mothers enrolled at the remaining two health centers received vaccine at 6, 10, and 14 weeks. Infants were excluded if they weighed less than 2500g, had known chronic or acute disease, received immunosuppressive therapy, could not receive vaccine on the assigned schedule for any reason, or had received a hepatitis B vaccine other than the designated study vaccine.
The birth cohort received vaccine at 0, 6, and 14 weeks while the 6-week cohort followed the standard infant immunization schedule in Cˆote d'Ivoire of 6, 10, and 14 weeks. Following application of exclusion criteria, the study analyzed 2230 mothers and 2242 infants (including 12 pairs of twins) in the birth cohort and 2155 mothers and 2167 infants in the 6-week cohort (including 12 pairs of twins).

Results
Mothers
Of the 4385 mothers evaluated at 6—8 weeks post-partum, 71.5% (3131/4385) had evidence of previous or current HBV infection. The prevalence of HBsAg positivity was 7.7%. The prevalence of HBeAg positivity was 1.1%. Among HBsAg-positive mothers, the overall prevalence of HBeAg positivity was 14.5% 14.6% (25/171) in the birth and 14.5% (24/166) in the 6-week cohorts.

Status at birth/ 6-8 weeks

None of the infants tested at birth were HBsAg positive. By contrast, nine of the infants tested at 6—8 weeks were HBsAg positive. All nine infants were born to mothers positive for HBeAg, HBsAg, and IgG anti-HBc antibody. Two of these nine women also had a positive IgM anti-HBc antibody suggestive of an acute infection.

The 6-week cohort had a vertical transmission prevalence of 0.4% (9/2167; 95% confidence interval [CI]: 0.1—0.7%), including 5.4% (9/166) among HBsAg-positive mothers (95% CI: 2.0—8.9%), 38% (9/24) among HBeAg-positive mothers (95% CI: 18.1—56.9), and 0% (0/142) among HBeAg negative mothers

Status at 9 months
Anti-HBs levels were available for 1887 birth and 1879 6-week cohort infants. Of these 1463 (77.5%) tested infants in the birth cohort and 1535 (81.7%) in the 6-week cohort had protective anti-HBs levels of more than 10 IU/l (prevalence ratio: 1.0; 95% confidence interval: 0.9—1.0).

9 (0.47%) tested infants in the birth cohort were HBsAg positive and 10 (0.53%) in the 6-week cohort were HBsAg positive (prevalence ratio: 0.90; 95% CI: 0.37—2.21) All 19 infants who were HBsAg positive at age 9 months were born to HBeAg-positive mothers.

Among HBeAg-positive mothers, 58.8% (10/17) of the 6-week cohort infants and 37.5% (9/24) of the birth cohort were HBsAg positive at age 9 months (prevalence ratio: 1.6; 95% CI: 0.83—3.0).

Controlling for maternal age, education, and marital status, the study found a relatively high association between assignment to the 6-week versus the birth cohort and becoming HBsAg positive at age 9 months, although this association was not statistically significant at the 95% confidence level (adjusted odds ratio, 2.7; 95% CI: 0.7—11.0).
Conclusions
Despite relatively high maternal infection prevalence, the study found that HBeAg negative women did not transmit virus to their infants and that only approximately 0.5% of the entire vaccinated infant cohort became infected. These findings suggest that either vaccine schedule will substantially reduce overall transmission during infancy. Despite these positive results, among infants of HBeAg positive women, 38% of the birth cohort and 59% of the 6-week cohort became HBsAg carriers despite appropriate vaccination.

Kang et al. 2015
Objective: Analyse Efficacy of antigen dosage on the hepatitis B vaccine response in infants born to hepatitis B-uninfected and hepatitis B-infected mothers

Methodology
A phase III, controlled, single-blinded clinical trial was conducted with 506 healthy newborns. The newborns were assigned to three groups based on maternal levels of HB surface antigen

(HBsAg) and HB e antigen (HBeAg): Group A, HBsAg negative; Group B, HBsAg positive and HBeAg negative; and Group C, HBsAg positive and HBeAg positive. Three doses of 10 or 5micro gram recombinant HB vaccine were randomly administered by 1:1 within 24 h after birth, at 1 month and at 6 months. Safety data and pre-and post-vaccination blood samples were collected.

Results

A total of 326, 93, and 87 subjects were included in Groups A, B, and C, respectively. Both dosages of HB vaccine were well tolerated by all subjects. The most common injection-site adverse reactions (ARs) and systemic ARs were pain and fever. After 1 month of the third dose, the Group A infants who received the 10 g HB vaccine achieved a higher geometric mean concentration (GMC) of HB surface antibody(anti-HBs) than those who received the 5 Micro grams dosage. Maternal anti-HBs sero status did not influence HB vaccine immunogenicity at either dosage. In contrast, there was no significant difference in the anti-HBs seroconversion rate, GMCs, or estimated vaccine efficacy (EVE) against perinatal transmission between Groups B and C, regardless of dosage. However, the seroconversion rate and EVE of the 5 g HB vaccine was lower in Group C than in Group B. Conclusions: Both dosages of the HB vaccine were well tolerated and elicited a good immune responsein infants of Group A, regardless of the maternal anti-HBs serostatus. EVE did not significantly differ between Groups B and C.

iii.Vaccine characteristics

a)Presentations and formulations of Hep. B monovalent vaccine

When immunizing against HBV at birth, only monovalent hepatitis B vaccine should be used: the other antigens found in combination vaccines are currently not approved for use at birth. (WHO 2017)

- Available monovalent HepB vaccines (see table 1)

Table 1: WHO prequalified Monovalent Hepatitis B vaccines (Presentation and Formulation)

Source	(Engerix –B - Manufacturer's insert)	(Recombivax HB - Manufacturer's insert)
Presentation	0.5-mL (10 mcg) single-dose vials and prefilled TIP-LOK® syringes 1-mL (20 mcg) single-dose vials and prefilled TIP-LOK syringes **NDC 58160-820-01** Vial in Package of 10 **NDC 58160-820-43** Syringe in Package of 10	0.5 mL (5 mcg) Pediatric/Adolescent single-dose vials and prefilled syringes **NDC 0006-4981-00** – box of ten 0.5-mL single-dose vials **NDC 0006-4093-09** – carton of six 0.5-mL prefilled single-dose Luer-Lok® syringes with tip caps **NDC 0006-4093-02** – carton of 10 prefilled single-dose Luer-Lok® syringes with tip caps
Formulation	contains the following excipients: Sodium chloride (9 mg/mL) and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/mL; sodium dihydrogen phosphate dihydrate, 0.71 mg/mL). formulated without preservatives.	Without Preservative contain approximately 0.5 mg of aluminum (provided as amorphous aluminum hydroxyphosphate sulfate, previously referred to as aluminum

	Store refrigerated between 2° and 8°C (36° and 46°F).	hydroxide) per mL of vaccine. hepatitis B surface antigen is adsorbed onto approximately 0.5 mg of aluminum (provided as amorphous aluminum hydroxyphosphate sulfate) per mL of vaccine. The vaccine contains <15 mcg/mL residual formaldehyde. Store vials and syringes at 2-8°C (36-46°F).

b)Recommended form of administration and dosage for Hep. B monovalent vaccine

- Vaccine dose and administration.

The vaccine is administered by intramuscular injection in the anterolateral aspect of the thigh (infants and children aged <2 years. Administration in the buttock is not recommended because this route of administration has been associated with decreased protective antibody levels as well as injury to the sciatic nerve. Intradermal administration is not -recommended because the immune response is less reliable, particularly in children (WHO 2017).

Table 2: WHO prequalified Monovalent Hepatitis B vaccines (Administration, Dosage and Formulation)

	REFERENCE – DOCHBBD-002 (Engerix –B - Manufacturer's insert)	REFERENCE – DOCHBBD-003 (Recombivax HB - Manufacturer's insert)
Administration	should be administered by intramuscular injection .The preferred administration site is the anterolateral aspect of the thigh for infants younger than 1 year	intramuscularly The anterolateral aspect of the thigh is the preferred site for intramuscular injection for infants younger than 1 year of age
Dosage and schedule	Primary immunization for infants (born of hepatitis B surface antigen [HBsAg]-negative or HBsAg-positive mothers), consists of a series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule Infants born to HBsAg-positive mothers should receive vaccine and hepatitis B immune globulin (HBIG) within 12 hours after birth	From birth: A series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule

c)Recommended schedule of Hep. B vaccine by WHO

Hepatitis B vaccination is recommended for all children worldwide. Reaching all children with at least 3 doses of hepatitis B vaccine should be the standard for all national immunization programmes. Importantly, all national programmes should include a monovalent hepatitis B vaccine birth dose.

WHO recommends hepatitis B vaccination of persons at high risk of HBV infection in older age groups and catch-up vaccination of unvaccinated cohorts if the necessary resources are available. (WHO 2017)

d)Additional logistical and cold chain requirements as a result of introducing Hep. B birth dose vaccine into routine immunization.

As with any new vaccine introduction, a readiness assessment should be done before possible introduction of a Hep B birth dose.

2)The disease

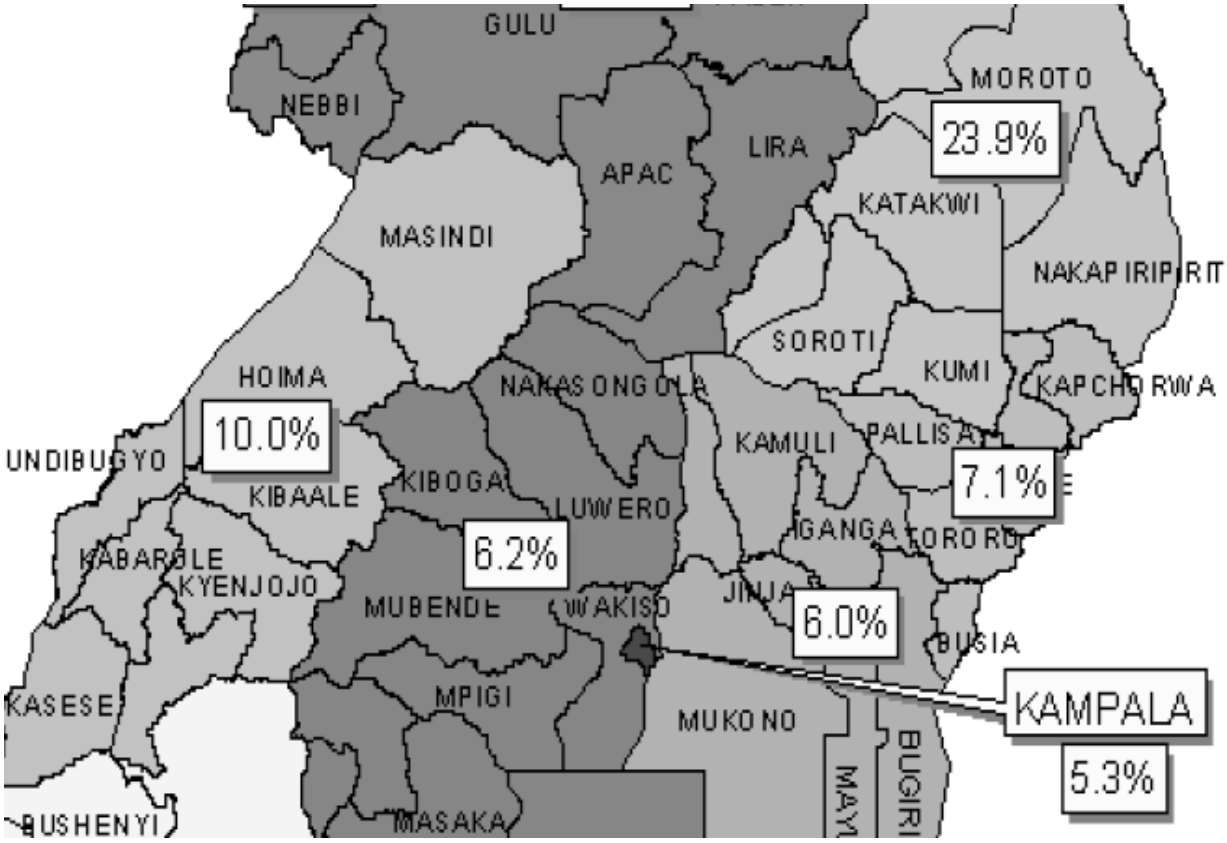
i.Burden of disease

a)Prevalence of Hep. B associated Chronic Hepatits and Hepatocellular carcinoma (HCC) in Uganda;

Ministry of Health, 2015a

Uganda is highly endemic for Hepatitis B with more than one half of the population having been exposed to HBV of whom averagely 10% are having chronic Hepatitis B. There is however a general variation in the distribution of HBV with the greater North of Uganda (Northwest, North Central and North east) having very high proportions of people with chronic HBV infection with population distribution ranging between 20% and 24%. The rest of the country is not spared as can be seen on the map below, from a national sero - survey study conducted in 2004

Recommendation on Hep B vaccination at birth



Source Ministry of Health National Hepatitis B Strategy (2015/2019)

Figure 1. Geographical Distribution of Hep. B infection in Uganda, 2004

b)Trend of HCC incidence in Uganda over the last 15 years; Trend of Hep B infection incidence over the last 15 years, Pattern of transmission, prevalence of ABsAg and HBe Ag positivity in pregnant women in Uganda

Currently, there is no standard reliable data system for Hepatitis B whether from facilities or Population based. (Ministry of Health, 2015a).

Causes of mortalities: cirrhosis 18th cause-166 000 Years of life lost; 1.10% ; percentage of change since 1990 = 54% (Ministry of Health 2015b)

Table 3: Hepatitis B associated Deaths in Uganda 2015

Child, adult, and vaccine-preventable disease mortality	**GBD 2015***
Cause-specific mortality: all ages (deaths per 100,000)	
Acute hepatitis B	1.2 (0.6-2.0)
Cirrhosis of the liver secondary to hepatitis B	2.3 (1.1-4.1)
Liver cancer secondary to hepatitis B	1.1 (0.5-1.9)

Source: EXTRACTED FROM GAVI FCE UGANDA COUNTRY REPORT 2016

*Figure 2: * Mortality based on Global Burden of Disease (GBD) 2015 estimates*

c)Epidemiological trend of Hep. B infection, Chronic Hepatitis and HCC been in Uganda over the last 15 years (post introduction of Hep. B vaccine in EPI)

Ministry of Health and Marco, 2006: HIV/AIDSSero-Behavioural Survey 2004-05

The 2004-05 Uganda HIV/AIDS Sero-Behavioural Survey (UHSBS) nationally representative, population-based survey designed to obtain national and sub-national data on the prevalence of HIV and other sexually transmitted infections (STIs) and their social and demographic variations in the country. One of the specific objectives was to determine the magnitude and distribution of hepatitis B infection.

One in ten Ugandan adults is infected with hepatitis B; residents of Northeast and North Central regions are particularly affected. Overall rates are slightly higher for men than women (12 and 9 percent, respectively). There is surprisingly little variation in infection by age group.

Bwogi et al.,2009

Analysis of the 2004-05 Uganda HIV/AIDS Sero-Behavioural Survey data showed that of the 5875 participants aged, 15-59 years systematically selected for HBV tests, 3072 (52.3% CI: 51.0 -53.6) were HBcAb positive, 1424 (53.6%) of the tested men and 1648 (51.2%) of the tested women meaning HBV infection was higher in men than in women, and much higher in the northeast, north central region and northwest (18.5 – 23.9%) than in other regions, with the lowest in the southwest (3.8%). The Karimojong, Langi and Acholi ethnic groups had the highest prevalence of current HBV infection, as high as 28.7% compared to 4.8% in the Baganda, and those with little or no education had a higher prevalence than the more educated. The likelihood of being infected declined with increasing wealth, with 15.7% infected in the lowest quantile compared to 6.8 % in the highest quantile. By age 15 -19 years, 40.0% (95% CI: 37.2 – 42.7) had been infected with HBV.

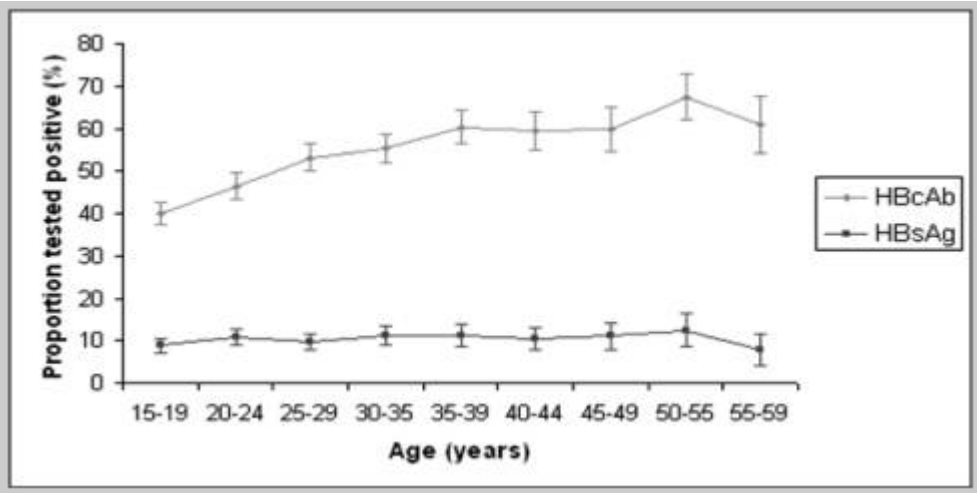


Figure 2 Proportion of adults with lifetime exposure (HBcAb) and current hepatitis B infection (HBsAg) by age, Uganda, 2005.
Source Bwogi et al, 2009

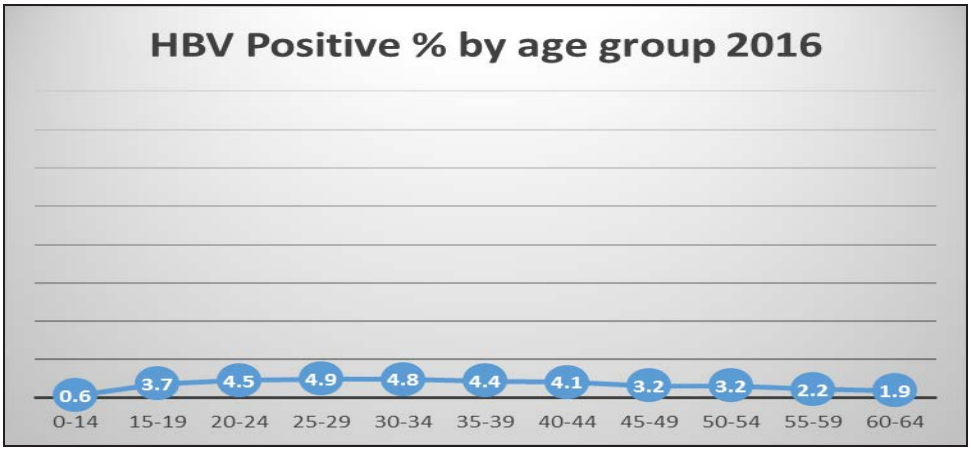


Figure 3: Proportion of surveyed individuals by age group that tested HBV positive
Source: Ministry of Health 2017. Preliminary Results of the 2016 Uganda Population HIV Impact Assessment (CONFIDENTIAL. DO NOT CIRCULATE UNTIL PUBLIC RELEASE)

d)Pattern of transmission of Hepatitis B infection in Uganda;

Ott et al, 2017

Objective: To evaluate trends of chronic HBV infection and assess patterns of change (Uganda)
Methodology: Retrospective study of a systematic review that consolidated data on Hep B infections. Applied a mathematical model (linear model) to ascertain trends of Hep B infection.

Results: Trending increase in prevalence of HBsAg antigen presence. Estimated rate of increase is 1.05%.

Limitations:
Model based issues (linear regression may not provide a trend of best fit)
Availability of data points for Uganda
Lack of consistent population selection (poor representation of infants or youth, high representation of ages 15-49)
Exclusion of potentially high-risk populations (migrants, refugees)

Teshale et al. 2015.

Objective of the Study: Assessment of the efficacy of application of Hep B vaccine at 6 weeks of age in transmission of disease compared to a birth dosage based off of the introduction of Hep B vaccine introduction in 2002.

Methodology: Non-blinded random sampling of population that had been tested in 2008 as part of an Hepatitis E outbreak in Uganda.

Results:
Total Population: 656
Overall Prevalence of Chronic Hepatitis B Infection (CHBI) based off of positive HBsAg and Anti-Hbc: 62 (9.4%)
Prevalence in 0-4: 0 (0%)
Prevalence in 5-9: 5 (7.6%)
Prevalence in all other age groups: 62 (14.9%)
Pertinent to the Query: Presumed reduction in lower ages was considered to be resulting from the introduction of the vaccine. However, no clear indices of how this would be affecting trends of Hep B prevalence.

Limitations:
Non-representative population sample since it was based off of a population that had been part of an Hep E epidemic

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Bwogi et al. 2009.
Objective: To determine baseline prevalence of Hepatitis B infections (HBV) in Uganda and determine risk factors.

Methodology: Conducted a sero-behavioural survey for Hep B as part of the regular HIV/AIDS sero-behavioural survey (UHSBS). Samples were selected based off a representative sampling of population clusters based off of the 2002 Population census. This selection was not proportional to population, but adjusted for by weight factors. Lifetime exposure to HBV was evaluated through lab tests on HBcAB and active infection based off of HBsAg presence.

Results:
Prevalence of Active HBV (positive HBcAB and positive HBsAg): 606/3072 (10.3%)
Significant predictors for Lifetime Exposure to Hep B (Positive HBcAB): male gender, Acholi or Langi ethnicity, Lugbara/Madi/Alur/Jopadhola men, religion (other than Catholic, Moslem, or Anglican, residence in Northeastern region in men & women, residence in Northwest region for women
Significant predictors for Active Hep B Infection (positive HBsAg): age >24, lower educational status, ethnic group (Iteso, Lugbara/Madi, Langi, Alur/Japadhola, Karimojong and Acholi, and also Basoga for women), region of residence (higher in the northeastern, north central, and northwestern regions and lower in the southwestern region and Kampala region for men), number of life-time sex partners, and for women, having HSV 2 or HIV infection

Limitations:
Did not consider non-seropositive Hepatitis B infections
Does not account for earlier age of mortality for Chronic Hep B carriers
Does not account for period in which patient has Hep B infection but no sero-markers

Pido and Kagimu, 2005

Objective: Assess seroprevalence of HBsAg and Anti-Hbc in clinical and preclinical students.

Methodology: Random sampling of medical students from two strata: the clinical and preclinical years at the Makerere University Medical School. Following sampling, questionnaires and blood samples were taken to determine prevalence and risk factors based off of HBsAg presence and answers to the questionnaire.

Results:
Prevalence of HBsAg positive students: 20/182 (11.0%)
Prevalence of anti-HBc positive students: 120/182 (65.9%)
Prevalence of anti-HBc positive students spikes between preclinical and clinical years from 50%-82.9%
Major risk factors include across both preclinical and clinical students: sexual relationships, unprotected exposure to patient fluids and needlestick injuries.

Limitations:
Occult infections were not assessed or controlled for

Bayo et al, 2014
Objective : Assessment of the prevalence of Hepatitis B infection (HBsAg) and Hepatitis E antigen (HBeAg) positive in pregnant women attending antenatal clinics in Northern Uganda.

Methodology: Pregnant women who attended the clinic on two days of the week (Mondays and Thursday) were recruited to the study by random sampling (every 5 people were asked). Upon acceptance of participation, blood samples were taken and questionnaires administered.

Results:
Prevalence of HBsAg: 11.8%
Prevalence of HBeAg (as a percentage of those with HBsAg): 14.9%
Risk Factors with no statistical significant in prediction of HBsAg positivity: scarification, number of sexual partners, history of blood transfusion, or polygamy
Risk Factor with high statistical significance in prediction of HBsAg positivity: age <20

Limitations:
Population was hospital based and had significant exposure to unprotected sexual intercourse
Lack of demonstration of chronicity of HBV through HBc antibodies.

Stabinski et al, 2011

Objective: To assess prevalence of HBV in a rural and HIV endemic location prior to the availability of Anti-Retrovirals (ARVs).

Methodology: Random sampling of participants already enrolled in the Rakai Community Cohort Study (RCCS). These participants' serological data and questionnaires response from 1998 were used based off of the RCCS data gathered at that point in time.

Results:
Prevalence of HBsAg and/or HBc Antibody positivity: 41%
Prevalence of HBsAg: 5%
Significant risk factors: 3< sexual partners, HIV positivity or syphillis positivity
Preliminary Conclusion of Paper: Horizontal transmission via sexual route is increasing

Limitations:
None stated.

e)Prevalence of HBsAg and HBeAg positivity in pregnant women in Uganda

Bayo et al. 2014
Objective of the Study: Assessment of the prevalence of Hepatitis B infection (HBsAg) and Hepatitis E antigen (HBeAg) positive in pregnant women attending antenatal clinics in Northern Uganda.
Methodology: Pregnant women who attended the clinic on two days of the week (Mondays and Thursday) were recruited to the study by random sampling (every 5 people were asked). Upon acceptance of participation, blood samples were taken and questionnaires administered.

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Prevalence of HBsAg: 11.8%
Prevalence of HBeAg (as a percentage of those with HBsAg): 14.9%
Risk Factors with no statistical significant in prediction of HBsAg positivity: scarification, number of sexual partners, history of blood transfusion, or polygamy
Risk Factor with high statistical significance in prediction of HBsAg positivity: age <20

Limitations:
Population was hospital based and had significant exposure to unprotected sexual intercourse
Lack of demonstration of chronicity of HBV through HBc antibodies.

ii.Use and cost of health care

a)Implications of Hep. B infection and HCC on the health care systems in Uganda i.e. on short and long term use of health care services

Approximately 3.5 million (10%) people out of the total population of 35 million are infected with the Hepatitis B virus. 30% (1,050,000) of those infected are chronically ill and require treatment.

Ministry of Health estimates that a total amount of UGX 1,143,828,017,548/- is required to cater for the Hepatitis B programme in the whole country. This is broken down as follows: Vaccines - 43,617,995,200/- , Laboratory reagents - 87,869,294,700/- , Programme Activities - 19,611,527,648/-, Medical/clinical equipment - 12,302,500,000/-, Antiviral drugs - 980,426,700,000/-

Government of Uganda allocated 10 billion shillings towards procurement of Vaccines, laboratory reagents and antiviral drugs for the treatment and prevention of Hepatitis B for the financial year 2015/16.

MoH Website: http://health.go.ug/content/ministerial-statement-hon-minister-health-parliament-progress-control-hepatitis-b-virus

In Africa, 55% of HCC is due to Hepatitis B. Compared to other regions, Hepatitis B HCC occurs at a much younger average age of 35 years. 3% patients in Africa receive treatment specifically for HCC. Mean HCC survival in Africa (excluding Egypt) is 2.5 months.
Yang et al, 2015

Treatment used for Chronic Hepatitis B in Uganda is as per WHO recommendation with lifelong administration of Tenofvir, which is currently going for 7 USD/month and Entecavir which is going for 50 USD/month.
WHO, 2015.

(Personal communication- Prof. Ponsiano Ocama –Hepatologist, Makerere University College of Health Sciences)

Government financing for essential medicines and health supplies (EMHS) stood at UGX 219 billion in 2013/14, translating into a public per capita medicine expenditure of about US$2.4. Out of this per capita spend (US$2.4), a larger proportion goes to HIV, TB and malaria commodities, while a smaller proportion of about US$1 goes to the rest of basic essential medicines.
Ministry of Health (2015c).

3)Economic and operational considerations

i.Vaccine related cost and resource use

a)Current cost of Hep. B monovalent vaccine in Uganda;

In single dose presentation:
Serum Institute of India Ltd = $0.420,
Shantha Biotechnics Ltd = $ 0.200

In ten dose presentation:
LG Life Sciences Ltd = $0.1750,
Serum institute of India Ltd = $0.200
UNICEF WEBSITE https://www.unicef.org/supply/files/HepB.pdf

b) Total cost (direct and indirect) of administering Hep. B vaccine per neonate at birth;
It was estimated that the cost of introduction of Hep B Birth into Uganda's routine immunisation schedule between 2017 and 2021 would be $ 2.6 -3.1 million per year. (Healthnet Consult, 2017)

c) Estimated cost of outreach programs to provide Hep. B birth dose vaccine for home deliveries;
Data is not available on what would be the cost of r Hep B outeach programs in Uganda.
Cost of outreach for introduction of PCV in Uganda was estimated at $79,703
WHO 2016 Costing of Immunisation in Uganda

d)Potential wastage rates if the currently available Hep. B vaccine is administered at birth

A study conducted in Indonesia comparing use of 5 dose and 10 dose vials with use of the HB Unijet devise, due to the Indonesian policy of discarding opened vials of vaccine at the end of a day, when used for outreach; the reported vaccine wastage rate was 70%. When used in monthly immunization sessions, as opposed to home visits, the hepatitis B wastage rates for Indonesia were 26% for 5-dose vials and 31% for 10-dose vials. (Levin et al. 2005)

ii.Vaccine affordability

a)Expected annual fiscal implications to the government if Hep. B vaccine is introduced at birth.
It was estimated that the cost of introduction of Hep B Birth into Uganda's routine immunisation schedule between 2017 and 2021 would be $ 2.6 -3.1 million per year. (Healthnet Consult, 2017)

iii.Economic impact on the immunization programme

a)Cost benefit to Uganda if Hep. B vaccine is administered at birth vs. current schedule

b)Cost effectiveness if Hep. B vaccine is administered at birth vs current schedule
Klingler and Mithinjayam, 2012
-Administering a birth dose of Hep B shortly after a Health facility delivery was found to be highly cost effective in a study carried out in Mozambique using the Markov model to analyze the costs and effects associated with avoiding perinatal transmission of Hepatitis B Virus (HBV) through a birth dose vaccination in addition to existing recommended vaccination schedule (6-10-14 week schedule)
The study assumed that an ICER (incremental cost-effectiveness ratio) smaller than 3x the GDP per capita is cost-effective. Cost effectiveness was highly sensitive to Prevalence of HBsAg among mothers and transition probability from chronic HBV to HCC and transition probability from chronic HBV to HCC and transition probability from chronic HBV to cirrhosis

4)Health Policy and programmatic issues

i.Feasibility

a) proportion of deliveries that occur in health facilities compared to home deliveries in Uganda

According to UDHS 2016, 73.4 % of live births were in a health facility in the 5 years preceding the survey, a higher figure than was estimated by HMIS. (**Uganda Bureau of Statistics (UBOS) and ICF. 2017**)

Kiyingi Herbert, 2015

A preliminary report of a CDC supported pilot project testing Hep B Antenatal Screening Integration and Immunization of Newborns (BASIIN) at Tororo Government Hospital (TGH) in Eastern Uganda made the following findings:

Preliminary analysis of timely HepB BD delivery among 2,069 newborns immunized during April 1 – October 12, inclusive, and having a filled in BASIIN newborn data collection sheet. Among these 1,989 (96.1%) were born at Tororo Government Hospital (TGH), 19 at other health facilities (1.0%), and 61 (2.9%) were born at home. Within this subset, the mean newborn age at administration of the HepB BD to the 1989 infants born in the TGH maternity ward was 21.1 hours (standard deviation [SD] 32.6 hours). This compared with 123.3 hours (SD 100.1 hours) after birth for the 19 infants born at a different health facility (not offering HepB BD) and 97.0 hours (SD 151.0 hours) for the 61 home births. Overall, 85.0% of infants born at TGH received the HepB BD during the first 24 hours of life.
However, while the mean time elapsed between birth and administration of the HepB BD for standard vaginal deliveries at TGH was 20.1 hours (SD 32.1 hours), with 86.8% vaccinated <24 hours after birth, the mean elapsed time between birth and receipt of HepB BD for infants born by cesarean section (C-section) was 40.3 hours (SD 37.0_hours). Only 51.0% of newborns delivered by C-section received the HepB BD during the first 24 hours of life, with another 36.0% receiving HepB BD at between 24 and 72 hours after birth.

Data analysis, observation and interviews revealed a variety of reasons for delayed delivery of HepB BD in the maternity ward at TGH. The HepB BD administration was appropriately delayed (later than 24 hours after birth) among infants with fever, dyspnea or birth asphyxia. However, despite having a specific, limited list of contraindications to follow, HepB BD was also delayed for any other condition that was “not normal.” Nursing students frequently administered the HepB BD; while students were trained at the beginning of BASIIN implementation, later groups of nursing students did not always receive full training on the HepB BD and their interpretation of indications for HepB BD delay/contraindications for the HepB BD was not always closely monitored. Some nursing students reported delaying delivering the HepB BD to later than 24 hours after birth if the newborn had difficulties breastfeeding or the mother’s condition was unstable. 49% of infants who were delivered via C-section received the HepB BD more than 24 hours after birth; importantly, these mothers may not hear the HepB BD counseling or be aware of the HepB BD until their day of discharge, usually at post-operative days 3-7 or the infant may not be brought to the immunization session the morning after birth because the mother is in recovery. HepB BD

was completely deferred for premature infants. Other newborns not brought to the immunization station either on the day of or day following birth, for reasons that were not reported, also had delayed HepB vaccination past 24 hours. Newborns delivered mid-morning just prior to the single routine immunization session frequently did not receive the HepB birth dose within 24 hours of birth. Newborns delivered on weekends were not always offered the HepB vaccine birth dose due to understaffing.

Due to recording failures, linkage of maternal antenatal HBsAg/HBV status with timely newborn receipt of the HepB BD was very limited and only available for 210 newborn/mother pairs: 199 delivered at TGH (94.8%); 2 (0.9%) delivered at outside health centers; and 9 (4.3%) delivered at home. Of these, eleven (11) (5.2%) were born to HBsAg-positive mothers; 10 (90.9%) of them received the HepB vaccine birth dose within the first 24 hours of life. Among the 199 (94.8%) born to HBsAg-negative mothers, 166 (83.4%) received the HepB vaccine birth dose within the first 24 hours of life.

b)Availability (and functionality) of immunization services through outreach programs

Ministry of Health 2015b-Health Sector Development Plan 2015-16_2019-20-1

–A health systems approach will be used to address the current challenges in health service delivery

–There is strong emphasis on health promotion, underlined by the introduction of ―Alert Villages‖ and ―model homes‖ through the Community Health Extension Workers (CHEW) Program

–**Service Delivery Systems:** HSDP will introduce and operationalize the concept of a 60-bed community hospital. The range of services and staffing requirement for the community hospital will be determined in future in the revised Essential Health Care package.

–Establishment of CHEW Program in 7,500 parishes in the Country

- ○6,000 CHEWs trained by mid term; 15,000 CHEWs trained end term;
- ○CHEWs functional in 3,000 parishes; in 7,500 parishes end of term

c)Proportion of new born babies that are reached through outreach programs for immunization services

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Health system delivery

The government of Uganda health system consists of the district health system (communities, Village Health Teams (VHTs or health centres: HCs I, II, III and IV and general hospitals, Regional Referral Hospitals (RRH) and National**- Ministry of Health 2010. The Second National Health Policy.**

EPI Service Delivery:

The 2010 EPI review reported that immunizations services were not always provided by qualified personnel due to low staffing levels of qualified health workers, competing health activities that are better funded as well as irregular and little outreach allowances, compared

to other health program allowances. Service delivery at outreach sites was also very irregular due to lack of PHC funds and transport, which resulted in high drop-out rates.

Strengths: Village health teams are involved in planning outreach immunization sessions, thereby strengthening the link between the service providers and the community.

Ministry of Health 2014.

d)Coverage and timeliness of other vaccines administered at birth in Uganda e.g. BCG, OPV?

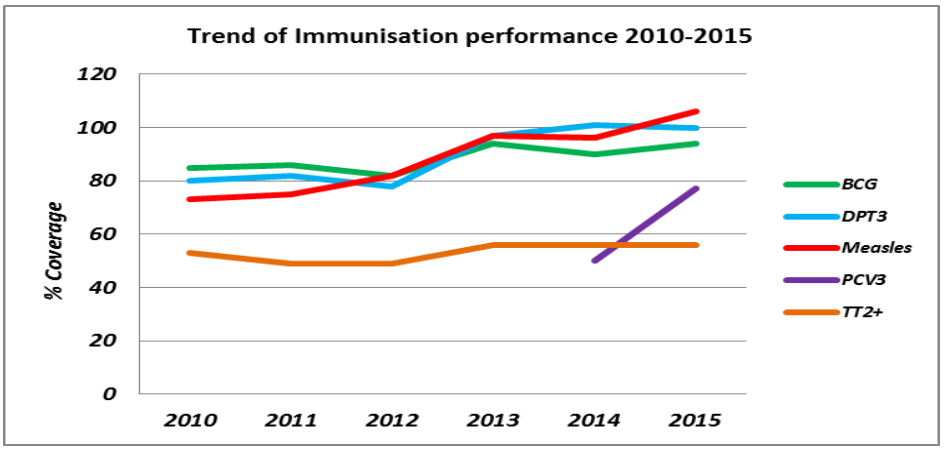

Figure 4 Trends in immunization performance from 2010 to 2015

Source: Ministry of Health 2016. Uganda National Expanded Program on Immunization Multi year plan 2016-2020

Despite the registered increase in immunization coverage, these estimates vary when compared to other surveys including the most recent household survey by the Gavi FCE and the WHO/UNICEF estimates. These variances are shown in table 4 below:

Table 4: Performance of birth dose vaccines in Uganda's Routine Immunisation Program.

Vaccine coverage	Most recent survey estimate*	WUENIC 2013 revision**	Self-reported coverage (WHO)***
BCG coverage	93.7%	93%	90%
OPV3 coverage	62.9%	82%	99%

*Most recent survey coverage estimates from 2011 DHS
**WHO/UNICEF estimates of National Immunization Coverage (WUENIC) 2014(2).
***WHO vaccine-preventable diseases monitoring system , 2014 global summary
****BCG, measles and three doses each of DPT and polio vaccine (excluding polio vaccine given at birth)

Source: Cited in Gavi FCE report 2015: ***Performance of Uganda's immunisation program-Gavi Full Country Evaluation-Uganda September 2016***

Coverage of birth dose vaccines for children aged 12-23 months (data based on child vaccination cards and mother's recall) according to Uganda Demographic Survey 2016.

BCG: 96.3%, Polio 0: 79.5% (UBOS and ICF 2017).

ii.Impact on resources

a)Additional human, technical, logistics and financial resources required for distribution of birth dose of Hep. B vaccine

Kiyingi 2016

Maternity ward EPI nurses and nursing students interviewed indicated that actual delivery of Hep B BD should not interrupt care, however, staff will still need to administer one additional vaccine and record its time and date in the newborn log book and on the infants immunisation card. The additional time required to prepare and administer the monovalent Hep B BD (from single dose vials) was estimated to between 15 seconds and 2 minutes. Maternity ward staff did note that this produced some additional waiting time for mothers of newborns at the immunisation area of the maternity ward. Similar to the experience in the ANC clinic, counselling and consenting mothers for their newborns to receive the Hep B BD required 3-12 additional minutes per newborn.
However, nursing students found administration of the Hep B BD to be easier than administration of the BCG vaccine.

iii.Ability to evaluate

Capability of the immunization program to carry out AEFI for vaccines administered at birth

Acute and chronic hepatitis B infection cases are routinely notified through public health surveillance systems with limited demographic information. These cases will be forwarded to Government's National Notifiable Diseases Surveillance System for collating and national reporting. Notifications of newly acquired hepatitis B underestimate the true incidence of the infection, while notifications of unspecified or chronic cases underestimate the burden of disease related to hepatitis B. This mechanism is also poor in reporting country of birth. (**Ministry of Health 2015a**)

iv.Acceptability

a) *Perception of the community on vaccines administered at birth*

A study conducted in two rural districts in Eastern Uganda found that community perceptions to neonatal interventions including vaccination depended on their affordability, compatibility with long held traditional beliefs like seclusion of mother and baby till the cord falls off, Health Worker Communication skills to alley misconceptions especially during antenatal, maternity and postnatal care, , and male partner support. (**Waiswa et al, 2008)**
These findings are similar to findings from other studies in Africa which showed the same factors affecting community perception and additional ones including: satisfaction with vaccination services (short waiting times, efficient staff), mothers' level of education, Community Health worker visits.
Oladokun and Adedokun, 2009.pdf
Kiddane et al, 2013

Influencers of Community perception include: traditional birth attendants, Community Health Workers, Older women in the family, mothers, mothers-in-law, aunts; drug shop attendants.

Nalwadda et al. 2015

Sharkey et al. 2016

Efficacy, safety of the vaccine, and severity of the disease did not have significant impact on perception.

Chambongo etal 2016

b)Average earliest time for which babies born outside health facilities are likely to be brought to the health facility

The time when mothers access postpartum care at the health facility is highly correlated to the babies' first contact at the health facility. Studies conducted in two rural districts in Uganda showed that untimely vaccination was correlated to increasing number of children per woman, delivery outside health facility, being unmarried and poverty (lowest wealth quartile).

Babirye et al. 2012

Similar studies carried out in different African countries to assess the timing and factors affecting the timing for first postpartum/postnatal care made the following findings:
A study in Nigeria showed sampling 155 infants has only 2 presented within 24 hours of birth, 66 (48.1%) presented within the first week. Mean presentation time was 9 days. Another study in Nigeria recorded only 10% of respondent having received postpartum care within the first 48 hours with a similar trend observed in Ethiopia.

Sadoh et al 2013.

Marchant et al. 2015

A study among the pastoralist community in Ethiopia found very low coverage for Polio 0, attributed to poor knowledge among the mothers of the correct timing, most births were facilitated by Traditional Birth attendants, who also had poor knowledge of birth dose.

Kiddane et al 2013

In Zimbabwe, 61% of new mothers sampled attended post-natal care, of which 80% presented within the 6 weeks of birth.

Sibanda et al, 2001

In Sierra Leone, for mothers delivering at a health facility, 79.4% received post-natal care within 2 days of birth, compared to 59.5% of those who had home deliveries. Reasons given for untimely post-natal attendance included distance to the health facility, limited options for transport, and social norms that prohibited travel shortly after birth.

At the district level, there are dedicated focal persons (District Health Educators) responsible for social mobilization and communications. Eighty nine percent (89%) of the health facilities visited in this review have established linkages with Village Health Teams (VHTs). The community focus groups revealed the VHTs to be a primary source of information regarding immunization at the community level.

Strengths

• There are focal persons (District Health Educators) for social mobilization and communications at district level.

• All villages have existing community structures, e.g. VHTs, Local Councils (LC1) who link the communities to health services.

• High demand for immunization services, as the community has trust in health care system.

Weaknesses

• VHT programme is based on " voluntarism" and therefore leads to varied support, affected by poor/inequitable remuneration (in form of stipends in cash or kind), and competing priorities with other programmes.

• Advocacy, communication and social mobilization activities for EPI tend to focus on campaign and new vaccine introductions and not on RI and community based disease surveillance. (Ministry of Health 2014).

v.Equity

a)*Performance of birth dose vaccines in hard to reach communities e.g. migrants, refugees etc*.

- 'immunisation equity assessment' was commissioned to support national stakeholders and district stakeholders to get a list of districts with inequities and high risk communities, identify barriers to access and use of immunisation in those communities, then come up with recommendations and actions
- This exercise was done in Uganda in September 2016 through a process of collecting views of EPI stakeholders and DHOs by key informant interviews, desk review of documents like UDHS report 2011and EPI Review 2015, analysis of UDHIS2 data, surveillance data and Secondary analysis of GAVI FCE house hold data from 19 districts. This was followed by a consensus building workshop in Iganga
- The 36 districts with immunization inequities contribute 53% of the under immunised children for DPT3 for the period 2013 to 2015. On the other hand, the identified 241 sub counties out of 1386 (17.4%) contribute 49% of the under immunised children for the period 2014 – 2015.
- The high risk communities / underserved communities identified were: urban poor settlements, migrants, ethnic minorities, some religious sects (especially Muslims, Bisaka sect and triple 6), upcoming town settlements, fishing communities, Refugee communities, remote rural, Island and mountainous communities
- The districts with immunization inequities were: Adjuman, Amudat, Amuria, Arua, Buikwe, Butalejja, Butambala, Buyende, Hoima, Ibanda, Isingiro, Jinja, Kaabong, Kaliro, Kalungu, Kamwenge, Kapchorwa, Kibaale, Kibuku, Kisoro, Kween, Kyankwanzi, Kyenjonjo, Manafa, Masindi, Mayuge, Mbarara, Moyo, Mubende, Nebbi, Pallisa, Rakai, Sembabule, Sheema, Wakiso and Yumbe. However, Kampala district was considered to be the 37th district with immunization inequities because it had the largest number of under immunized children for DPT3 for the period 2013 to 2015
- The social economic factors that cause immunization inequities in Uganda were: religion, tribe, maternal education, wealth quintile, place of child delivery, travel time and transportation costs to service delivery points..

Recommendation on Hep B vaccination at birth

- The system factors that were prevalent in districts and sub counties with immunization inequities were: Human resource challenges like DHT teams with weak leadership, absenteeism, non-transparency with funds and poor supervision, logistics issues like non-distribution of vaccines from district vaccine stores to lower health facilities and gas shortages
- Matrix for high risk communities and barriers

High risk communities	Barrier: HF (supply side)	Barrier: Community (demand side)
Urban Poor Settlements	There are few government facilities	Leaders do not attend immunization planning meetings eas and services are costly in private clinics
Migrants	Fixed Service delivery service points do not match mobility pattern of those communities -Lack of trained Village health teams	Rural Location ; Maternal Education (Primary education) - Inadequate mobilization due to limited facilitation to VHTs. -
Ethnic Minorities	- Health workers in such areas are largely non-qualified staff or nursing assistants	Where such communities live, there are impassable roads during the rainy seasons and too dusty during the dry spells
Religious groups	Poor Communication & Mobilisation strategies -Inadequate sensitization of the religious leaders	Religious beliefs and Misconceptions on immunisation on contents of the vaccine
Upcoming town settlements	Attitude as perceived by the parents towards health workers that they are rude, long waiting time for parents at facilities while the parents have little time	Low maternal education affects in such areas
Fishing Communities	Service delivery time not favouring their working patterns - Difficult to plan, locate and reach the fishing populations - Limited immunization Services/posts	Majority of the people sell their fish in the morning when immunisation services are being offered - They are mobile populations
Refugee communities	Failure to communicate due to language barrier	Lack of organised leadership structures in such communities - Lack of awareness on availability of service points
Remote rural, Islanders & mountain living communities	-Irregular and unreliable outreach sessions -Inadequate knowledge of the health workers; inadequate staffing in such areas -Rift valley escapements make transport difficult -Inadequate logistics for immunization -Poor road & building Infrastructure	high cost of travel from community to health centre, -Low education levels of care takers - District councils and sub county Local councils not prioritizing immunization service delivery -Low community awareness of

High risk communities	Barrier: HF (supply side)	Barrier: Community (demand side)
		benefits for immunisation

UNICEF 2016. Uganda Immunization Equity Assessment Report, September 2016; Communities and Districts Affected by Immunisation Inequities Report as of 29/9/2016

4.Discussion

Disease burden

a)There is sufficient local evidence to show that the Hepatitis B burden in Uganda is significantly high, especially in the northern region, with about 1.5 to 3 million people chronically infected. Specific at risk groups were: pregnant mothers (as the disease can be sexually contracted), children born to mothers who are careers or chronically infected (through vertical transmission), and children under 10 years susceptible to horizontal transmission. Most patients with Hepatitis infection contracted from the mother develop Hepato carcinoma complications around age 30 years, which is the productive age in Uganda.

b)The prevalence of Hepatitis B infection (HBsAg) and Hepatitis E antigen (HBeAg) positive in pregnant women was found to be high in certain settings in the Uganda in 2009: Prevalence of HBeAg 14.9%(as a percentage of those with HBsAg):

c)There is no convincing evidence on the trend of HCC incidence in Uganda and trend of Hep B infection incidence over the last 15 years, and patterns of change (after introduction of HepB vaccination)

d)The financial and human burden of management of the disease is high, considering that all patients diagonised with liver cirrhosis and Hepato-cellular carcinoma die within a few months of diagnosis, the cost of laboratory testing is expensive, and chronic sufferers are on treatment with antivirals for life. Sufferers are also subjected to social stigma.

e)A national sero survey was conducted in 2004 -2005, shortly after the introduction of Hepatitis B vaccine in Uganda's routine immunisation schedule in 2002 as part of pentavalent vaccine given at 6, 10 and 14 weeks of age. Preliminary results from the 2016-2017 national sero survey showed that the cohort that has been vaccinated using the Hepatitis B vaccine as part of Pentavalent since its introduction in 2002 (0-14yrs) has significantly lower prevalence than their unvaccinated counterparts. The impressive public health impact of universal Hep B infants vaccination on the decrease of chronic liver disease and HCC has been widely documented worldwide.

Vaccine Characteristics, safety, efficacy and effectiveness

a)Although most of the studies on vaccine safety, efficacy and effectiveness were carried out on small numbers/sample sizes, there is sufficient evidence to show that the vaccine is

safe and effective, with comparative safety profiles as other vaccines issued at birth, for example: BCG, and have no contra-indications when co-administered with other birth-dose vaccines.

b)There is evidence that Immune response or immunogenicity or duration of protection of Hep. B vaccine when the first dose is given at birth is weeks of life

c)Good immune response is elicited regardless of whether the mother is HepB-infected or not

d)No evidence was found to demonstrate difference in *efficacy of Hep. B vaccine in reducing the risk of Hep. B transmission and HCC when the 1st dose is given at different times after birth (24 hours vs. 72 hours vs. 7 days of life) vs. 6 weeks*

e)From the evidence gathered from African countries, whereas a birth dose showed better protective effects compared to no vaccination, it did not show a statistically significant additional protectiveness comparative to the existing schedule of 6, 10 and 14 weeks. Data on how effective the introduction of the hepatitis vaccine within the pentavalent vaccine has been on reducing the burden of Hepatitis B disease in Uganda would be useful to decide if additional protective measures are justifiable. This would be deduced from comparisons of the burden in the 2004/5 sero-survey report and that the 2016/7 sero-survey report for the vaccinated cohort, in view of the DPT3 coverage.

Economic Considerations

a)Vaccines by their nature are almost always cost-effective. Therefore the key consideration for Uganda when deciding on new vaccine introduction is affordability and sustainability in view of other competing health priorities.

b)Using a PCV introduction costs as reported in the WHO 2016 Immunisation Costing Study and the UNICEF website quoted price per dose of monovalent hepatitis vaccine, it was calculated that it would cost Uganda a rough estimate of $2.3 -3.0 million per year to introduce a Hep B birth dose into the immunisation program between 2017 and 2021.

c)Even with external donor support from international agencies e.g. Gavi Alliance, Government of Uganda still has to make a co-payment, and after graduation from Gavi support, Government will be expected to make a full payment.
It is therefore imperative to demonstrate the additional lives saved by introduction of a birth dose in order justify the cost, and show the competitive advantage over other new vaccines yet to be introduced, and other health interventions in general.

Health Policy and programmatic aspects

a)There is a global recommendation by WHO for all babies born in Hepatitis B endemic countries to be given a birth dose vaccine within 24 hours of birth or at first contact before the first 3 dose schedule is administered. Uganda is considered as a Hepatitis B endemic country, having a 10% national prevalence of Hep B infection in 2009.

b)The static unit mode of delivery is the standard method used for vaccination in Uganda, and the Hep B birth dose would be administered at health facilities as well. Evidence shows that

the number of health facility deliveries in Uganda are over 70%. In order to catch the remaining babies born outside the health facilities, and to help overcome some of the barriers to newborns accessing health facilities on time, there would be need to strengthen the Community Health Workers (CHEWS), who would identify, refer and encourage caregivers to take newborns for birth dose administration within the recommended time period. Strengthening of health worker knowledge and efficiency would also be key.

c)Performance of birth vaccines in Uganda is generally high with BCG coverage over 90% and Polio 0 over 70%. Discrepancies in birth dose coverages were most attributed to the vaccine supplies and delivery failures (stock outs, poorly trained and low motivated health workforce) than to vaccine hesitancy. The evidence presented from various studies in Africa supports this conclusion. Therefore in order for Hep B birth dose to perform well, emphasis should be placed on ensuring an efficient vaccine delivery system and a trained and motivated health workforce.

5.Proposed recommendation (s) /options

UNITAG recommendation regarding introduction of a Hepatitis B birth dose vaccine into Uganda's routine immunisation schedule is as follows:

UNITAG does not recommend addition of a Hepatitis B birth dose into Uganda's routine immunisation schedule. There is no high quality evidence to show additional value of birth dose in a setting where Hep B vaccine is routinely administered at 6, 10 and 14 weeks. More information is required in order to assess the added efficacy of the birth dose.

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7.Annexes

1.Advise Request Letter from Ministry of Health*

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THE REPUBLIC OF UGANDA

Ministry of Health
P.O. Box 7272
Kampala
Uganda

IN ANY CORRESPONDENCE ON
THIS SUBJECT PLEASE QUOTE NO **ADM:215/306/01**

22nd June 2016

Dr. Nelson Sewankambo,
Chairperson for NITAG Uganda,

RE: REQUEST TO NITAG TO ADVICE THE IMMUNIZATION PROGRAM TO PRIORITIZE WHICH NEW VACCINES SHOULD BE INTRODUCED

The goal of immunization program is to ensure that every child and high-risk group is fully vaccinated with high quality and effective vaccines against the target diseases according to recommended strategies through five operational components: vaccine supply and quality, logistics, service delivery, surveillance, advocacy and communication.

SAGE has made several recommendations to countries to introduce new vaccines into their routine immunization program following evidence presented to them to show that they are effective and efficacious. Over the last three years, Uganda has introduced three new vaccines into the routine immunization program and plans to introduce yellow fever vaccine, Measles and Rubella Vaccine including second dose, Men A and Tetanus Diptheria(Td) Vaccine.
However along the way the program has observed some challenges and anticipates more to come as more new vaccines are introduced into the routine immunization program. Among these challenges, includes fulfilling co financing requirements for the recently introduced vaccine affecting the performance of new vaccine introduction

In line with the WHO recommendation, Uganda established the NITAG to provide evidence based advice to the Ministry of Health on immunization.

The purpose of this letter is therefore to request the NITAG to provide guidance on which new vaccine Uganda's immunization program should prioritize in order of importance in the next five years. Your response will highly be appreciated preferably by end of 2016.

Prof. Anthony K. Mbonye
FOR DIRECTOR GENERAL HEALTH SERVICES

Cc: The Permanent Secretary, Ministry of Uganda
Cc: The Director Health Services, Clinical and Community
Cc: Commissioner Health Services, National Disease Control
Cc: The Program Manager, UNEPI

*Hepatitis B birth cose was not included in the official letter but communicated for addition from the Ministry at UNITAG Meeting on 21.07.2016. Ref: **MIN. 2: UNAS UNITAG: 6/2016**

2.List of Working Group Members:

i.Assoc. Prof. Jesca Nakavuma (Chair- and core member, Vaccinology)

ii.Prof. Sarah Kiguli – Core member, Pediatrics

iii.Ms. Charlotte Muheki Zikusooka – Core member, Health Economics

iv.Dr. Emmanuel Mugisha –Liaison member, PATH

v.Dr. Annet Kisakye – Liaison member,WHO

vi.Prof. Ponsiano Ocama – co-opted expert (Hepatologist)

3.Evidence search process and results

Attached as separate excel document

Uganda Immunization Technical Advisory Group

Recommendation on Tetanus vaccination in the routine immunization programme

Uganda Immunization Technical Advisory Group

Recommendation on Tetanus vaccination in the routine immunization programme:

WHAT IS THE BEST STRATEGY FOR UGANDA TO TRANSITION FROM TT TO TD IN ORDER TO SUSTAIN MNTE ELIMINATION AND ENSURE HIGH POPULATION IMMUNITY AGAINST TETANUS?

SEPTEMBER 2017

Contents

Executive summary

The Ministry of Health asked the Uganda National Technical Advisory Group (UNITAG) to make recommendations on the prioritization of various new vaccines to introduce to the routine immunisation schedule. Challenges to the immunisation program's vaccine introduction efforts such as low coverage and limited financing prompted this request. The five new vaccines proposed for introduction are: Hepatitis B birth dose, Yellow Fever, Meningococcal A, 2nd dose of measles containing vaccine and a switch from Tetanus Toxoid to Tetanus diphtheria.

The vaccine considered in this dossier is Tetanus diphtheria, specifically the switch from TT to Td, and the introduction of three booster doses in the routine immunisation schedule. Tetanus is an acute infectious disease caused by toxigenic strains of the bacterium *Clostridium tetani*. The spores of C. tetani are present in the environment irrespective of geographical location; they enter the body through contaminated skin wounds or tissue injuries including puncture wounds. The disease may occur at any age and case-fatality rates are high even where intensive care is available. The majority of reported tetanus cases are birth-associated, occurring among insufficiently vaccinated mothers and their newborn infants, following unhygienic deliveries and abortions, and poor postnatal hygiene and cord care practices. In the absence of medical intervention, the case-fatality rate approaches 100%. The most effective way of controlling tetanus is through immunisation.

Tetanus and Diphtheria vaccines are routinely administered to children at schedule of 6, 10 and 14 weeks, as part of DPT. Pregnant women are also given 2 doses of Tetanus toxoid, 4 weeks apart. Following new evidence on waning immunity of both Tetanus and diphtheria over time, WHO Strategic Advisory Group of Experts (SAGE), recommended addition of three booster doses of Tetanus diphtheria vaccine, preferably during the second year of life, between 4-7 years of age, and between 9-15 years of age, to achieve protection throughout reproductive age, probably lifelong protection.

A systematic rsearch of evidence suggests Uganda has the highest incidence of non-neonatal tetanus in sub-Saharan Africa, with more cases seen among females 5 years and older. Case fatality rates are very high ranging from 40 to 70%, even with good intensive care. Fatal cases die within 3 days of admission. Treatment costs of tetanus patients are very expensive, and taking care of those who live beyond 3 days is extremely costly, as the spasms related to stimulation dictate that patients should be isolated in quiet, dark intensive care spaces, which are lacking in most Ugandan hospitals.

Tetanus containing vaccines are effective and safe, with mild side effects like injection site pain and mild fevers commonly reported and major adverse events are extremely rare. The safety profile of TT and Td is comparable, both in children and pregnant women. Evidence suggests that diphtheria toxoid increases the immunogenicity of tetanus toxoid as well as other vaccine antigens, and has no counter-effect when co-administered with other vaccines, with the exception noted when Td was administered a month prior to PCV 13 and Men C vaccines which resulted in reduced reactogenicity of the two vaccines although titre levels remained above protective limits.

The costs per dose for Tt and Td are similar ranging from $0.07 to $0.09 per dose. Packaging volumes are similar too, with 10 dose vials, indicating that the financial implications of the switch may not be significant. The additional financial costs will be due to addition of three booster doses targeting box sexes. Td is highly cost effective in terms of lives saved, particularly for maternal tetanus immunization. Td is not listed among the vaccines supported by Gavi. Government of Uganda currently fully funds TT vaccination.

Recommendation on Tetanus vaccination in the routine immunization programme

Programmatically, the second year of life provides a platform for vaccination against several diseases including measles, and meningococcal A conjugate vaccines. The pre-adolescent and adolescent vaccination platform includes Child Days and HPV vaccination. Programmatic issues of concern to the booster doses include: high drop-out rates observed for vaccines administered to individuals over a year old, e.g. HPV, low coverage (55 %) of TT among Pregnant women (high coverage of booster doses would eventually eliminate need to vaccinate pregnant women), increased number of doses will present higher work burden to the health workers and require more cold chain space. Making it a requirement for full vaccination before school enrollment at the nursery, primary and high school, can help increase coverage among school going children.

Based on the evidence, the working group made the following recommendations:

a. Uganda should switch from TT to Td. This will not only strengthen the protection against tetanus, but also provide protection against diphtheria. This also goes with current worldwide trends and Uganda might be left behind if it does not make the switch.

b. Uganda should add 3 booster doses of Td to the routine immunization schedule at 24 months, 4–7 years of age; and 9–15 years of age. This will provide lifelong protection against tetanus as well address the low coverage problem with pregnant women and help maintain MNT elimination in the long term.

I. Introduction

a. Context of the question

The Ministry of Health (MoH) in Uganda through its Comprehensive Multiyear Plan 2016-2020, proposed to introduce five new vaccines into the routine immunisation program, one of which is Tetanus-diphtheria vaccine by 2018. This is following a recommendation by WHO Strategic Advisory Group of Experts (SAGE) made in 2016, in light of evidence showing waning immunity following the primary vaccination series against tetanus and diphtheria. SAGE recommended that the booster dose schedule should be adjusted to include three booster doses, giving a total of six doses to achieve protection throughout reproductive age, probably lifelong protection. These should be given preferably during the second year of life, between 4-7 years of age, and between 9-15 years of age. Ideally there should be at least a 4-5 year interval between doses. (WHO, 2016a).

The WHO position paper on diphtheria also notes the need for booster doses. Following the primary immunization series, the average duration of protection is about 10 years. Protective immunity may be boosted through exposure to circulating strains of toxi-genic C. diphtheria. Where natural boosting does not occur, booster doses of diphtheria toxoid beyond infancy and early school age are required to maintain protective immunity (WHO, 2006). WHO SAGE in April 2017 reviewed evidence of protective immunity following primary immunisation series and recommended that booster doses of diphtheria-containing vaccine should be given at: 12–23 months of age; 4–7 years of age; and 9–15 years of age (WHO, 2017a).

MoH requested Uganda National Immunisation Technical Advisory Group (UNITAG) for advice on which new vaccines Uganda should prioritise in the next five years, in view of challenges facing the immunisation program new vaccine introduction efforts including low coverage and limited financing. (Annex 1).

b. General information on the issue

Tetanus is an acute infectious disease caused by toxigenic strains of the bacterium *Clostridium tetani*. The spores of C. tetani are present in the environment irrespective of geographical location; they enter the body through contaminated skin wounds or tissue injuries including puncture wounds. The disease may occur at any age and case-fatality rates are high even where intensive care is available. In the absence of medical intervention, the case-fatality rate approaches 100%.

The majority of reported tetanus cases are birth-associated, occurring among insufficiently vaccinated mothers and their newborn infants, following unhygienic deliveries and abortions, and poor postnatal hygiene and cord care practices. Neonatal tetanus occurs when non-sterile instruments are used to cut the umbilical cord or when contaminated material is used to cover the umbilical stump. WHO estimates that in 2015, approximately 34,000 neonates died from neonatal tetanus globally. Even in countries that have reduced the burden of maternal and neonatal tetanus (MNT) through vaccination, a considerable proportion tetanus cases occur following injuries in children and adults.

Three clinical presentations are characteristic of tetanus infection: localized, cephalic, and generalized tetanus. Localized tetanus is uncommon; it is characterized by sustained contraction of the muscles in the same area as the injury site. Case-fatality rates for localized tetanus are < 1%. Cephalic tetanus is a rare form of the disease associated with ear infections (otitis media) or head lesions. It presents clinically as cranial nerve palsies. This form of tetanus has a short incubation period of only 1 to 2 days and a case-fatality rate of 15–30%. Cephalic tetanus can progress to generalized tetanus. Generalized tetanus occurs in > 80% of cases, presenting as a generalized spastic disease. Characteristic features of disease

onset are early spasms of the muscles of the jaw known as trismus or lockjaw (inability to open the mouth). Spasm of the facial muscles produces risus sardonicus, a distinctive facial expression that resembles a forced grin. Subsequently, sustained spasm of the muscles of the back leads to opisthotonos, the backward arching of the head, neck and spine, and to sudden generalized seizure-like spasms, frequently in response to stimuli. Spasm of the glottis may cause sudden death. In neonatal tetanus, generalized spasms are commonly preceded by the inability to suck or breastfeed and excessive crying. Case-fatality rates vary from 10% to70% depending on treatment, age and general health of the patient. Among patients in the youngest and oldest age groups without intensive care, case-fatality rates approach 100%.

The diagnosis of tetanus is primarily based on clinical features and does not depend on laboratory confirmation. Management of tetanus cases involves administration of human tetanus immune globulin (TIG) to prevent further progression of the disease by removing unbound tetanus toxin, but is unlikely to influence existing pathology. Antibiotics may also prevent further disease progression. Supportive care should be provided including keeping patients in a dark and quiet environment to reduce the risk of reflex spasms, and nasogastric feeding for newborn infants. To prevent the development of tetanus after contaminated wounds or tissue injury, all wounds should be cleaned and debrided promptly and appropriately. Passive immunization using TIG, preferably of human origin, is recommended for prophylaxis in the case of dirty wounds in incompletely vaccinated individuals and those with uncertain vaccination history. Age-appropriate TTCV booster doses are recommended for those with incomplete vaccination.

The WHO position paper on Tetanus vaccine (WHO, 2017b) recommends 3 doses for the primary series and an interval of at least 4 weeks between the doses for vaccination of infants against tetanus using Tetanus Toxoid (TT) containing vaccines. TT is available as a single-antigen vaccine and in combination vaccines to protect against other vaccine-preventable diseases. The pentavalent vaccine, which provides protection against diphtheria, tetanus, pertussis, Hib and hepatitis B (DTP-Hib-HepB), is the most commonly used childhood vaccine worldwide, but other pentavalent (DTaP-IPV/Hib) and hexavalent (DTaP-IPV/Hib-HepB) combinations are also available. In Uganda, pentavalent vaccine is currently administered at 6, 12, and 14 weeks.

Although tetanus antibody levels are high after 3 primary TTCV doses in infancy, they decline over time. A booster dose in the second year of life can rapidly increase antibody levels. WHO therefore revised its policy in 2017 to require 3-dose booster series prior to adolescence. For booster dosing, a tetanus-diphtheria combination with lower concentration of diphtheria antigen (d) is available. The 3 TTCV booster doses should be given at: 12–23 months of age; 4–7 years of age; and 9–15 years of age. Ideally, there should be at least 4 years between booster doses. Additionally, opportunities should be taken to provide or complete the full TTCV series for those who were not vaccinated, or incompletely vaccinated, during childhood. If tetanus vaccination is started during adolescence or adulthood, a total of only 5 appropriately spaced doses are required to obtain lifelong protection. Opportunities for catch up vaccination of adult males should be explored, e.g. at military recruitment and in advance of safe male circumcision.

In countries where MNTE has not yet been achieved, and in areas where MNT remains a public health concern, Women of Reproductive Age (WRA) should be immunised with 2 doses of TT containing vaccine 4 weeks apart. For women who received only the three primary doses during childhood and also 2 doses

during pregnancy, to provide lifelong protection, a sixth dose would be needed at least 1 year after the fifth dose. However, once high coverage with the 6-dose childhood and adolescent tetanus schedule has been realized, adult vaccinations will not be required as future cohorts of WRA and adult males will be protected against tetanus throughout their reproductive years and beyond.

II. Methodology

a. Establishment of a working group

In line with the UNITAG Internal Procedures Manual, the UNITAG Chair in consultation with the Secretariat commissioned a working group to develop a Recommendation Framework on Tetanus-diphtheria introduction in Uganda's routine immunisation program, and conduct a systematic search, appraisal and synthesis of relevant evidence based on which, recommendations would be proposed. The Working Group was chaired by a core-member, a Medical Microbiologist and comprised of the following UNITAG members: Health system specialist, Public health expert, vaccinologist, and a co-opted epidemiology specialist. List in annex 2. All members signed a declaration form stating that they had no known conflict of interest on the topic. The working group has met once to develop the Recommendation framework, and once to review the evidence and develop the technical dossier with proposed recommendation.

b. Recommendation framework

The working group developed a recommendation framework, outlining the issues and specific data needed to inform the best strategy for Uganda to transition from TT to Td in order to sustain MNTE and ensure high population immunity against tetanus. The recommendation framework considered 4 categories of issues: 1) Disease burden (Burden of Tetanus disease in Uganda) 2) Vaccine characteristics and immunization (efficacy and safety of available vaccines) 3) Economic impact and 4) Policy and programmatic considerations. A detailed Recommendation Framework is attached in the Annex 3.

c. Evidence search and assessment

The Working group followed the steps outlined below in its evidence search and assessment:

•Step 1: Framing questions for the literature search

For each issue in the recommendation framework, the WG went further in specifying the specific data that are needed. For each data, queries were specified in the form of clear, unambiguous and structured questions before beginning the search work. Queries were categorised as those that required a systematic search in databases and those for which information could be found in reference documents (WHO papers, text books, vaccine manufacturers' websites). These documents were used as source of background information. For systematic search of data, the queries were formulated to specify the specific outcomes of interest from the use of the intervention in the population considered as per UNITAG method of working for issuing evidence-based recommendation (using the PICO approach to search for evidence on the efficacy, effectiveness and safety of an intervention). Queries requiring systematic literature search proceeded to step 2, while grey literature (Ministry of Health Reports, Immunisation partner surveys, websites and unpublished local reports) were looked for to answer background data queries.

•Step 2: Identifying relevant peer reviewed articles

Search strategies were developed to ensure that search terms covered all known terms relevant to the question. Multiple journal resources (Pubmed, Scopus and Embase) were searched with English language restriction to generate relevant title-abstracts. Inclusion and exclusion criteria were set for each query, to flow directly from the review question and was specified a priori. Articles obtained were screened (titles and abstracts) for relevance to the question. The search strategy and result was recorded, the report is available at the secretariat.

•Step 3: Assessing the quality of articles

(Selected title abstracts were extracted in full text and subjected to review and, if still relevant to the question, to a more refined quality assessment by use of a design-based quality checklists (CASP)[1] according to the study design. These detailed quality assessments were used for exploring for bias or flaws of the study by evaluating its methodological quality, certainty of results, and relevance to the question, hence ensuring quality of the evidence sustaining the recommendation. List of articles retrieved and assessed is also indicated in the search strategy and results report.

•Step 4: Summarizing the evidence

Selected full text articles were read and relevant findings under each query were summarised in a standard UNITAG working group outline report.

•Step 5: Interpreting the findings

The Working Group organized a one-day workshop for review of the evidence presented on each issue of the recommendation framework and, from sense-making of the overall body of evidence, propose recommendations to submit to the entire UNITAG for decisions. During the workshop the group worked on the write-up of the discussion section, analysing the findings with the view of joining the pieces together that will lead to the proposed recommendations

III. Presentation of the evidence

This section presents the evidence on the research questions for the specific issues indicated in the recommendation framework

1. Vaccine and immunization characteristics

There is little data found on head-to-head comparison between TT and Td. The evidence presented from the WHO paper refers to Tetanus Toxoid Containing Vaccines (TTCV) with no specification on the formulation, TT or Td

i. Safety

a) *How does the safety profile (local, systemic & laboratory) of Td vaccine compare to TT administered in children above 5 years, adolescents and adults*? What are the risk factors or risk groups that can lead to adverse events of Td vaccine in children above 5 years, adolescents and adults?

Tetanus-diphtheria (Td, low-dose diphtheria toxoid) formulations are licensed for use from 5 years of age. TTCV are considered very safe. Mild local reactions are common after TTCV administration.

[1] http://www.casp-uk.net/casp-tools-checklists

However, more serious reactions are rare. The rates and severity are influenced by the number of prior doses, level of antibodies before booster vaccination, the type and quantity of adjuvant, and the presence of other substances such as preservatives. None of the combination vaccines have produced any adverse events that had not been observed with the individual components. Grading of evidence on the safety of TTCV (**PICO Question:** *In immunocompetent individuals, is there an increase in the incidence of serious adverse events following immunization with any dose of TTCV vaccine compared to not giving a TTCV vaccine?)* concluded from a review of 20 RCT Severe adverse events are extremely rare. TTCV using various presentations have demonstrated to be safe to use in immunocompetent individuals of various age and population groups including infants, children, adolescents, adults and pregnant women (WHO, 2017b).

Choi et. al. 2010

-Type of study

- Multicentre, non-randomized open label phase 4 study
- Objectives
  - To evaluate the immunogenicity and safety of diphtheria tetanus (Td) vaccine in adults over 40 years old who had never received a diphtheria tetanus pertussis vaccine
- Design
  - Adults in Korea who had not received DPT or Td vaccination were enrolled.
  - Td vaccine given intramuscularly three times. First dose administered after screening, second dose 4 weeks after first dose, third dose 5-6 months after second dose
  - Blood samples collected before injections, 4 weeks after first injection and 4 weeks after the third injection.
  - Subjects told to record adverse events that occurred within the two weeks after the vaccination. All subjects also monitored for additional 2 weeks. Adverse events that occurred during the 4-week study period were also recorded.
  - GMCs and sero-protection rates calculated with 95% CIs, for each antibody.
  - Incidence rate of adverse events and its 95% CI estimated and analysed.
- Results
  - 240 subjects completed three doses vaccination. Before vaccination, 33.9% and 96.7% of participants showed antibody levels of diphtheria and tetanus of less than .2 U/mL, respectively.
  - After first dose Td vaccination, 92.6% and 77.6% of participants showed antibody levels greater than .1 U/mL for diphtheria and tetanus.
  - After third dose, 99.6% and 100% of participants had antibody levels greater than .1 U/mL.
  - Mild adverse events developed In 41.7% of subjects. Most adverse events were mild and resolved within 7 days without hospitalization. No serious adverse events were found.

Jackson et. al. 2009

Type of Study

- Retrospective cohort study

- Objective
  - To estimate the risk of local reactions following Td vaccination in adolescents and young adults.
- Methods
  - Study cohort included managed care organizations members who had a Td vaccination recorded when they were 9-25 years old. Vaccination were identified from computer immunization records maintained by each MCO.
  - Study outcome was the chart confirmed medically attended local reaction and a secondary outcome was a chart confirmed medically attended illness.
  - Outcome events were identified by selected ICD-CM codes assigned to inpatient and outpatient medical encounters within 6 days following Td vaccination. Diagnosis codes consistent with immediate hypersensitivity reaction or which were specific indicators of adverse events assigned on days 0-6 were used to identify events. Cases were validated by medical record review.
  - Medically attended local reactions were defined by symptoms like inflammation, ulceration, erythema, swelling, etc. An illness possibly indicative of a hypersensitivity reaction was defined by symptoms consistent with urticarial, hives, wheezing, respiratory collapse, etc.
- Results
  - A total of 159 estimated medically attended local reactions and 61 of illnesses possibly indicative of a hypersensitivity were found.
  - Estimated risk of medically attended local reactions was 3.6 events per 10,000 td vaccinations, and as discussed in the study, uncommon following Td vaccinations.

Macko et. Al.1985

- Type of Study
  - Randomized double blind study
- Objective
  - To compare the morbidity of Tt with that of Td.
- Method
  - Patients over 16 years of age with broken skin or burns with full primary immunization for tetanus prophylaxis and who denied booster immunizations were randomized to receive either tetanus toxoid or tetanus-diphtheria toxoid.
  - Patients were asked about presence and severity of pain at injection site. Asked to categorize the pain as absent, mild, moderate or severe.
- Results
  - There were no differences between groups of individuals who received Td and Tt.
  - Results consistent with unpublished study that concluded that there was a significantly greater reaction rate for second doses of Td as compared to T alone, for both local and systematic reactions.

Salama et. al. 2009

- Type of Study
  - Randomized clinical trial

Recommendation on Tetanus vaccination in the routine immunization programme

- Objective
  - To compare the immunogenicity, reactogenicity and efficacy of TT and the Td in pregnant women in Egypt.
- Method
  - 131 Egyptian pregnant women enrolled at 20 weeks gestational age. Unimmunized women received two random doses of either TT or Td 8 weeks in between during pregnancy.
  - Interviews were done evaluating the occurrence of either local or systemic adverse effects. Events monitored included fever, malaise, headache, redness, etc.
  - Blood samples were obtained from the women at enrolment, 8 weeks post first dose, and 1 week after delivery.
  - Protective antibody levels were detected in the serum of 80-90% of the women after doses of TT
- Results
  - There were no differences in occurrence of fever, malaise, body ache and headache between the two treatment groups.
  - There was no difference in the post-delivery health between the two treatment groups.
  - Physiological jaundice seen more in the infants of mothers who received the TT vaccine.
  - Recommendation that the TT vaccine can be replaced by the Td vaccine

b) What the safety profile of Td *vaccine when combined with HPV as compared to administering Td vaccine alone? What the safety profile of Td vaccine when combined with MR (during campaign) as compared to administering Td vaccine alone?*

Co-administration of multiple inactivated and live-attenuated vaccines is safe and acceptable. Evidence also supports co-administration of TTCV booster doses with other vaccines administered during adolescence such as HPV and meningococcal conjugate vaccines (WHO 2017b)

c) Risk factors
  - Populations vulnerable to severe adverse events from Td vaccine

Bitragunta et. al. 2008

- Type of study
  - Non-random clinical trial
- Objective
  - To evaluate the immunogenicity and safety of a single dose of Td vaccine
- Methods
  - Non or partially immune children were administered Td vaccine intramuscularly
  - Children were observed for 30 min after vaccination for immediate adverse reactions. Information was further collected from health workers on the childrens' health 24-48 hrs post vaccination.
  - 6 weeks post vaccination, blood samples were obtained from the vaccinated children
- Results

- Common adverse events observed were pain at injection sites and fever
- Before vaccination, 25.3% and 37.7% were sero-protected against diphtheria and tetanus, respectively. After vaccination, sero-protection rates were 96.1% and 98.8%, respectively.
- Reduced potency diphtheria-tetanus toxoid is safe and immunogenic

Cassidy et. al. 2005

- Type of study
  - Random, unblended study
- Objective
  - To study the safety and immunogenicity of concomitant administration of Hepatitis B, Td, and MMR vaccines

- Methods
  - 11-12 year olds with DTP vaccinations and no Td boosters were enrolled and randomized into two groups. One group was given HB, MMR and Td on the first visit and the second and third dose of HB 1 and 6 months later. The other group was given the HB vaccine at initiation and then again at 1 and 6 months; they received the Td and MMR vaccines at 4.5 months
  - For tetanus, diphtheria and measles, mumps and rubella antigens, repeat levels were drawn 6 weeks post vaccination. For Hep. B, surface antibody titers were drawn 1 month after the third dose of the vaccine.

- Results
  - Increased boost effect for mumps seen in the concomitant group.
  - No serious adverse events in either group, the concomitant and the non-concomitant.
  - The concomitant administration of the three vaccines was as safe and immunogenic as the administration of HB vaccinations alone from Td and MMR.

Scheifele et. al. 1998

- Type of Study
  - Controlled sequential assessment of Td vaccine
- Objective
  - To assess the safety of Td boosters in Grade 6 Canadian students
- Methods
  - Grade 9 students given Td vaccine from single lot, students were observed 15 minutes after immunization to detect and treat any anaphylactic reactions
  - Grade 6 students given Td vaccine from another lot, given at the same time as a third dose of Hep. B vaccine.
  - Follow up visits made with students 48 h after post immunization. Interviews were completed to assess student well-being and injection site discomforts.
- Results
  - 96.4% of students in grade 6 and 90.3% in grade 9 said they were fine

  - there was no redness detected at the Td injection sites in 83.3 % of the Grade 6 students and 92.4% of the Grade 9 students
  - Td booster immunization are moderately reactogenic in adolescents.

Lee et. al. 2009

- Type of study
  - Multi-center, non-randomized open level phase 4 study
- Objective
  - To compare the immunogenicity and safety of Td vaccine between 11-12 yr olds and 13-18 yr olds in Korea.
- Methods
  - 132 pre-adolescents and 145 adolescents who had received DTaP 4-5 times and have not received DTaP or Td vaccine within the previous 5 years.
  - Single dose of Td vaccine was given to each group
  - Blood samples were collected before vaccination and 4 weeks after booster dose
  - Subjects' parents told to record local adverse events such as pain, redness, fatigue that occurred during the 2-week period post vaccination. All patients were further monitored for 2 weeks after.
  - Symptoms were graded on a scale of 0-3, 0 being absence of symptoms, and 3 representing a symptom that prevented normal activity.
- Results
  - Four weeks after vaccination, all subjects in both groups showed 100% immunogenicity. All subjects showed anti-D antibodies consistent with sero-protection
  - Pain at the injection site was the most common local adverse event. All of the adverse events reported were resolved with 7 days.
  - More local adverse events were observed in the pre-adolescent group than in the adolescent group.

d) *What are the contraindications to administering Td vaccine in children above 5 years, adolescents and adults?*

TTCVs are considered suitable for use in HIV-infected and immunocompromised persons (WHO 2017b).

ii. Efficacy and effectiveness

a) What is the immunogenicity (immune response to tetanus) of Td vaccine as compared to TT in children above 5 years, adolescents and adults?

In children, a 3-dose primary series of DTP induces an antibody titre above the minimum protective threshold, with a mean level above 0.2 IU/ml. A minimum interval of 4 weeks between TTCV doses is necessary to induce a sufficient immune response with an increase in tetanus-specific antibody levels.

The immune response to TTCVs tends to decrease with age. Comparative studies suggest that children tend to develop higher antibody levels than adults. However, in spite of a decrease in titre, most vaccinated adults achieve and maintain protective levels of tetanus-specific antibodies. In adults not previously vaccinated, a third dose 6–12 months after the first 2 doses induces production of high levels of long-lasting tetanus-specific antibodies (WHO 2017b)

b) *What is the duration of protection to tetanus of Td vaccine in children above 5 years, adolescents and adults as compared to* TT?

Antibody concentration, avidity and the duration of protection depend on a number of factors including the age of the vaccinees, the number of vaccine doses and interval between them. Data from serological studies suggest that a primary series of 3 TTCV doses in infancy plus a booster during the second year of life will provide 3–5 years of protection. A further booster dose (e.g. in early childhood) will provide protection into adolescence, and another booster during adolescence will induce immunity that lasts through much of adulthood, thus protecting women through their childbearing years. There is not enough evidence to compare the antibody levels for the duration of protection with specific tetanus vaccination schedules. Some experts consider 5 doses in childhood to be sufficient to confer long term protection based on the observation that most tetanus cases in developed countries occur in unvaccinated individuals and those who received <5 doses of TTCV. Some countries have reduced their tetanus vaccination schedule to include only 5 TTCV doses throughout the life course, with alternative primary and booster dose schedules. Evidence from a serological study in the USA demonstrated that a primary series administered at 2, 4 and 6 months followed by a booster dose at 18 months resulted in another antibody peak that provided protection through school entry. In the Netherlands, results from use of a 6-dose schedule of TTCVs in childhood with the last dose at 8 years of age demonstrated that tetanus immunity persisted for at least 20 years after the sixth dose, with a geometric mean titre (GMT) of 0.44 IU/ml in individuals aged 30–34 years. A regression analysis from this serological data predicted that protective antibody levels would persist until 90 years of age, with a GMT of 0.22 IU/ ml.38 Protective immunity persisting for 20–30 years after a sixth dose of TTCV has been suggested in several studies

Evidence from a systematic review on recent research findings and adolescent immunization policy in the USA indicated that a booster dose of Tdap or Td in adolescents and adults induced a robust humoral immune response to all vaccine antigens. Ten years after immunization, tetanus antibody levels still exceeded pre-immunization levels and remained protective (≥0.10 IU/ml) in ≥97% of adolescents and adults. (WHO 2017b)

Aboud_et. al. 2000

Study type: This was a cross-sectional study conducted from the end of June to the end of August 1997.

Study Objective: The objectives of this study were therefore to determine the anti-TT antibody levels, antibody avidity and distribution of anti-TT IgG subclasses in relation to age and sex in children aged 1–15 years in Dar es Salaam and Bagamoyo.

Methodology: study was undertaken to determine the serological response in children (aged 1–15 years) immunized with diphtheria-pertussis-tetanus vaccine (DPT) alone or with a tetanus

toxoid (TT) booster dose under the Expanded Programme on Immunization in Dar es Salaam and Bagamoyo, Tanzania. Using an ELISA technique, serum levels of anti-TT antibody, antibody avidity and anti-TT IgG subclasses were determined in 138 apparently healthy children.
In Tanzania, childhood immunization is conducted within the Expanded Programme on Immunization (EPI) which has been integrated into the Maternal and Child Health (MCH) clinics since 1975. DPT doses are given to infants at 4, 8 and 12 weeks of age. In addition, a TT booster dose is usually given to the child either during outreach services or following minor injury.
Of 68 children from Dar es Salaam, 38 were 1–5 years of age and 30 were 6–15 years.
Seventy children from Bagamoyo were recruited, 50 aged 1–5 years and 20 aged 6–15 years.
After recording general information, a history of the child's immunization with DPT and/or TT was obtained from the mothers or guardians, or extracted from MCH immunization records if available.
The anti-TT antibody level was estimated in all serum samples by indirect ELISA technique

Results: All children 1–5 years in Dar es Salaam and 68.6% of children in Bagamoyo had received a third dose of DPT by the 3rd month of life.
Among the older children, 22 (44%) had received one or two TT booster doses after primary immunization.
The majority of children aged 1–5 years, 36 (94.7%) in Dar es Salaam and 49 (98%) in Bagamoyo, had anti-TT antibody levels > 0.1 IU/ml (p . 0.1).
Among the older children, 16 (53.3%) in Dar es Salaam and 11 (55%) in Bagamoyo had anti-TT antibody levels $ 0.1 IU/ml (p . 0.1).

Table 1 summarises the results

Characteristics		No.	Mean anti-TT antibody
Residence			
1–5 y	Dar es Salaam	38	0.86
	Bagamoyo	50	0.78
6–15 y	Dar es Salaam	30	0.45
	Bagamoyo	20	0.22
Age (yrs)			
1–5		88	0.82
6–10		15	0.13
11–15		35	0.46
Gender			
1–5 y	Boys	42	0.87
	Girls	46	0.78
6–15 y	Boys	23	0.35
	Girls	27	0.36
Third DPT dose by 3rd month			
1–5 y	Not completed	19	0.87
	Completed	69	0.81
6–15 y	Not completed	3	0.11
	Completed	47	0.38
TT booster dose(s)			
None		28	0.09
1–2		22	0.69
Time after vaccination			
< 4 y		92	0.87
4–9 y		23	0.29
10 + y		23	0.17

Table 2 shows Multivariate logistic regression analysis among children aged 1–15 years with non-protective anti-TT antibody levels

Independent variable	No.	Antibody <0.1 IU/ml (%)
TT booster dose(s)		
Reference: 0	116	23 (19.8)
1–2	22	3 (13.6)
Time after vaccination (yrs)		
Reference: <4	92	3 (3.3)
4–9	23	5 (21.7)
10+	23	18 (78.3)
Age (yrs)		
Reference: 1–5	88	3 (3.4)
6–10	15	7 (46.7)
11–15	35	16 (45.7)

Conclusion: This study confirms that the current DPT immunization schedule for children under 5 years of age in Dar es Salaam and Bagamoyo affords an anti-TT antibody level far above the minimum protective level of 0.1 IU/ml and a high avidity index in the majority. However, about half of the children aged 6–15 years are not protected from tetanus. A regular TT booster dose for 6–15-year-old children on school entry is recommended.

Aboud and Lyamuya. 2002

Study type: Cross sectional study conducted in September 1999

Setting: Blood bank, Muhimbili Medical Center, Dar es Sallam, Tanzania

Methodology: Using and antigen competition ELISA Technique, serum tetanus anti-toxin level sin two hundred male blood donors were determined. Two hundred apparently healthy male blood donors were examinsed at the time of donation from MMC Blood bank.

Results: The median age of blood donors was 31 years (range 18-70 years). Forty three (21.5%) blood donors did not report a vaccination history. Among those who reported vaccination histories, 60 (30%) had been vaccinated with DPT3 during childhood, whereas 97 (48.5%) had only vaccination of 1-3 TT doses as prophylaxis following injury/wood infection. None had received both DPT and TT vaccination.

Table 3: Geometric mean tetanus anti toxin levels (IU/ml) according to various characteristics among male blood donors with reported vaccination (n=157)

Characteristic		No.	Protected (%)	Anti-toxin (IU/ml)
Age (years)	18-27	59	49 (83.1)	0.38
	28-37	64	55(85.9)	0.36
	38-47	19	17(89.5)	0.30
	48+	15	7(46.7)	0.08
Vaccination status				
	DPT	60	40(66.7)	0.33
	TT	97	88(90.7)	0.72
TT dose (s)	1	35	28(80.0)	0.15
	2	46	44(95.7)	0.53
	3	16	16(100)	1.95
HIV status	Positive	10	7 (70.0)	0.26
	Negative	147	121(82.3)	0.41
Time after vaccination (years)				
	<10	123	109(88.6)	0.48
	≥10	34	19(55.9)	0.16

Findings showed that blood donors with TT vaccination had significantly higher mean tetanus anti toxin levels than those with DPT vaccination did. Mean tetanus anti-toxin levels were significantly lower, ten years after last vaccination. 72 (36%) male donors were susceptible to tetanus and the susceptibility was highest from 48 years.

Conclusion: A regular TT booster dose at ten yearly intervals is recommended to ensure adequate and long lasting immunity in male adults.

c) *Does co-administration of Td with other vaccines affect its immune response? (i.e. MR during campaign, HPV?)*

Effect of prior immunity on vaccination: Published studies suggest that prior tetanus-diphtheria vaccination can either enhance or suppress the immune response to pneumococcal or meningococcal conjugate vaccines, a phenomenon termed carried-induced epitopic suppression. A reduced immune response to meningococcal C-TT conjugate vaccine was observed in children when DT or Td was administered a month before the conjugate vaccine, although antibody levels were still above the protective threshold. Administering Tdap 3–4 weeks prior to PCV13 also significantly reduced the antibody response to 6 of the 13 pneumococcal serotypes in adults, although antibody levels remained above the protective threshold (WHO 2017b).

iii. Vaccine characteristics

a) *Presentation, storage volume and cold chain requirements*

- Presentation, storage volume and cold chain requirements for Td vaccine

b) *Logistical and cold chain requirements:*

- Additional logistical and cold chain requirements if Td is given to children above 5 years, adolescents and adults?

Table 4: Vaccine characteristics and Costs

Name and Manufacturer	Pharmaceutical Form	Doses	Cold chain requirements	Age	Cost per dose 2017
Adsorbed DT vaccine PT Bio Farma, Persero (Indonesia)	Liquid ready to use. Each dose (0.5ml) contains 20 Lf purified diphtheria toxoid, 7.5 Lf purified tetanus toxoid. Excipients: Aluminium phosphate 1.5 mg, Thiomersal 0.05 mg	10 dose vials	+2 to+8 C Do not freeze Expiry date 2 years Multi dose vials can be used in subsequent sessions for up to max. 4 weeks	Children <7 years	$0.1061 (2006)
Diftet/ Intervax National Center of infectious and Parasitic Diseases (Bulgaria)	Liquid ready to use Each dose (0.5 ml) contains 30 Lf/ml Diphtheria Toxoid, 20 Lf/ml Tetanus Toxoid, Aluminium hydroxide 2.5 mg/ml, Thiomersal 0.1 mg/ml	I does ampoule 10 dose and 20 dose vial	+2 to+8 C Do not freeze Expiry date 2 years Multi dose vials can be used in subsequent sessions for up to max. 4 weeks	Children <7 years	$0.1590
Diphtheria and Tetanus Vaccine Adsorbed (Pediatric) Serum Institute of India	Liquid, ready to use Each dose (0.5 ml) </= 25 Lf Diphtheria toxoid, </= 5 Lf Tetanus toxoid, Aluminium phosphate <1.25 mg and Thiomersal 0.005%.	1 dose Ampoule 10 dose vial 20 dose vial	+2 to+8 C Do not freeze. Open vial can be used up to 28 days after opening. expires 36 months Cartoon of 50 ampules, cold chain space 12.18 cm3 per dose 10 and 20 dose packaging cold chain space per dose 2.611 cm3	Children less than 7 years	$0.1150
DT VAX Sanofi Pasteur France	Liquid ready to use Each 0.5 ml dose contains > 30 I.U diphtheria toxoid, >40 IU tetanus toxoid. Aluminium hydroxide, Thiomersal and buffer solution containing sodium chloride, disodium phosphate dehydrate, mono potassium phosphate and water for injections	1 dose and 10 dose dose vials	+2 to+8 C Do not freeze. Manufacturer cannot assume responsibility for product over 24 hours after the 1st extraction process unless the vial is stored at normal refrigerator temp.	Children less than 7 years	
Diphtheria Tetanus reduced antigen for adults and adolescents	Liquid ready to use Each 0.5 ml dose contains </= 5 Lf (>/=2	, 10 dose vial	+2 to+8 C Do not freeze.	Children older	$0.1150

Name and Manufacturer	Pharmaceutical Form	Doses	Cold chain requirements	Age	Cost per dose 2017
Serum Institute India	IU) diphtheria toxoid, >/= 5 Lf (>/= 40 IU) Tetanus toxoid, adsorbed Aluminium phosphate, Thiomersal 0.005%		Store in a dry dark place. Expiry 36 months Vials may continue to be used for up to 28 dials after 1st vial opening	than 7 years	
IMOVAX dT Adult (reduced antigen content) Sanofi Pasteur, France	Liquid ready to use Each 0.5 ml dose contains >/= 2 I.U diphtheria toxoid purified, inactivated with formaldehyde and adsorbed, >/= 20 I.U tetanus toxoid, purified, inactivated with formaldehyde and adsorbed. Other ingredients are Aluminium hydroxide, Thiomersal, and buffer solution containing sodium chloride, disodium phosphate dehydrate, mono potassium phosphate and water for injection	10 dose	+2 to+8 C Do not freeze Expiry at 36 months Cold chain space per dose 2.46 cm3.	Children older than 10 years	
Tetanus diphtheria reduced antigen content PT Bio Farma (Indonesia)	Liquid ready to use 0.5 ml dose contains 2 Lf (</= 30 IU) Purified Diphtheria toxoid, 7.5 Lf (</= 40 IU) Purified Tetanus toxoid, 1.5 mg Aluminium phosphate, 0.05 Thimerosal	10 dose vial	+2 to+8 C Do not freeze Expiry 36 months Expiry at 36 months Open vial can be used up to 4 weeks from opening of first vial Cold chain space per dose 2.23 cm3.	Children 7 years and older	$0.1150
Diphtheria Tetanus (reduced antigen content) BE Td Biological E Limited (India)	Liquid ready to use Each 0.5 ml dose contains Diphtheria Toxoid 2 Lf (>/= 2 IU), Tetanus toxoid 8.8 Lf (>/= 20 IU), Adsorbed Aluminium Phosphate >/=1.5 mg, Thiomersal 0.01%.	1 dose and 10 dose vials	+2 to+8 C Do not freeze, protect from light Expiry 36 months Open vial can be used up to 4 weeks from opening of first vial Cold chain space per dose 2.93 cm3.	Children 7 years and older	$0.0990

Name and Manufacturer	Pharmaceutical Form	Doses	Cold chain requirements	Age	Cost per dose 2017
Tetadif/ Intervax Tetanus diphtheria (reduced antigen content) National Center of Infectious and Parasitic Diseases (Bulgaria)	Liquid ready to use Each 0.5 ml dose contains Diphtheria Toxoid 2 Lf (>/= 2 IU), Tetanus toxoid 8.8 Lf (>/= 20 IU), Adsorbed Aluminium Phosphate >/=1.5 mg, Thiomersal 0.01%.	1 dose 10 doses and 20 dose vials	+2 to+8 C Do not freeze, protect from light Expiry 36 months Open vial can be used up to 4 weeks from opening of first vial Cold chain space per dose 10 dose vial 3.78 cm3.	Children 7 years and older	$0.1510

Vaccine data from WHO website https://extranet.who.int/gavi/PQ_Web/
Price data Td (10 dose vials) from UNICEF website https://www.unicef.org/supply/files
Comparative TT price from UNICEF website https://www.unicef.org/supply/files

Comparative costs of TT Vaccine

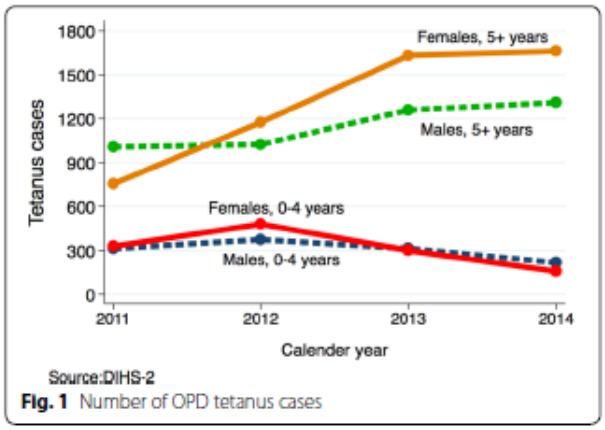
Presentation	Supplier	2017 price
10 dose vials	Intervax	$0.1150
	PT Bio Farma	$0.1150
	Biological E limited	$0.0792

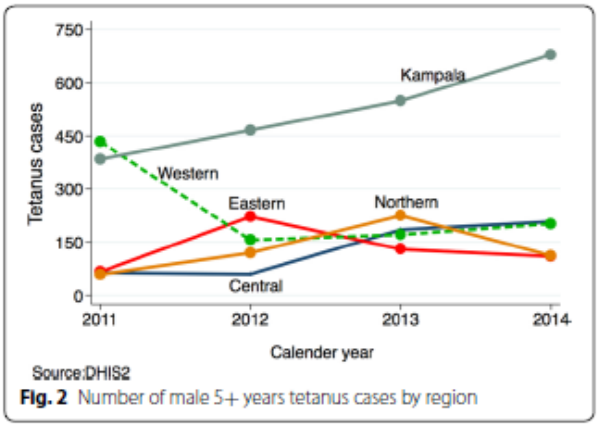
2. The disease

i. Burden of disease

a) *What is the incidence of MNT and tetanus in children above 5 years, adolescents and adults in Uganda? What is the case fatality rate for tetanus in children above 5 years, adolescents and adults in Uganda? What is the geographical difference in incidence of tetanus in Uganda /* Africa

A study published in 2016 (Nanteza et. al. 2016), reviewed medical charts of tetanus cases identified from the inpatients registry at Masafu hospital, Busia district for the period 2009/2010–2013/2014. Data were also abstracted from the inpatients registries, charts and HMIS annual reports, and a key informant interview conducted with the in-charge of the ward that treats tetanus patients. The results are shown in Figure 1.





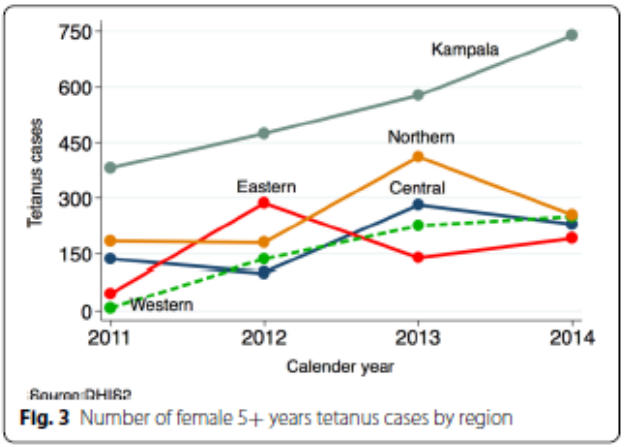
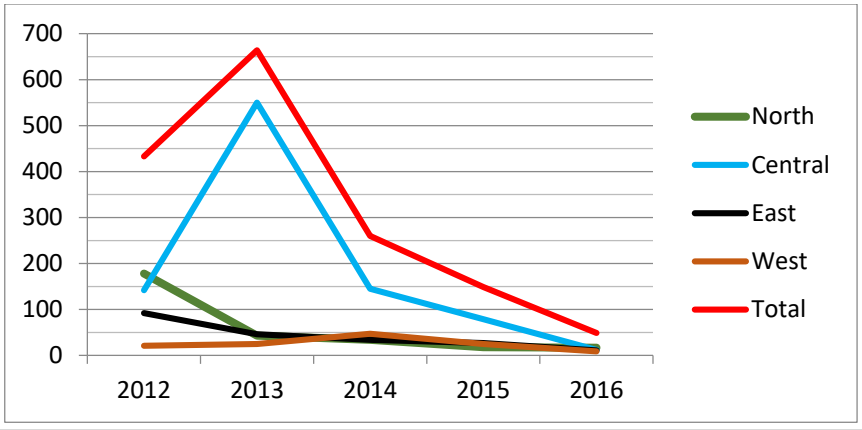


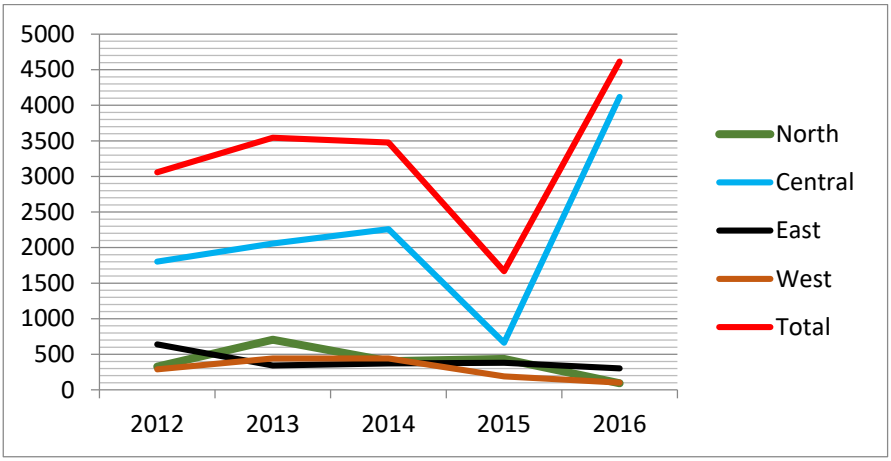
Figure 1: Tetanus cases in Uganda 2011-2014



Source: Graph generated using data from eHMIS Data

Figure 2. Reported Cases of Neonatal Tetanus in Uganda by region 2012-2016,

Uganda achieved MNT elimination status (rate of 1 case per 1000 live births) in 2011(Sluers Hilde, 2011).



Source: Graph generated from eHMIS Data

Figure 3. Reported cases of Tetanus (over 28 days of age) In Uganda by region 2012-2016

Dalal et al. 2016

Objective: a review of the evidence on tetanus vaccination coverage and case notifications in sub-Saharan Africa, supplemented by a literature review of non-neonatal tetanus in Africa over the years 2003–2014.

Results:

Table 5: African countries reporting cases of Tetanus in the study period (2003-2014)

Country	Population[a]	No. of reported tetanus cases			No. of non-neonatal cases per 1 000 000 population[c]
		All	Neonatal	Non-neonatal[b]	
Angola	21 471 617	360	33	327	15.2
Burkina Faso	16 934 838	27	0	27	1.6
Democratic Republic of the Congo	67 513 680	1 359	1 327	32	0.5
Liberia	4 294 078	8	0	8	1.9
Madagascar	22 924 850	556	8	548	23.9
Mali	15 301 650	37	12	25	1.6
Mauritania	3 889 882	4	0	4	1.03
Niger	17 831 269	71	1	70	3.9
Nigeria	173 615 344	556	468	88	0.5
Senegal	14 133 280	78	4	74	5.2
South Sudan	11 296 174	32	25	7	0.6
Uganda[d]	37 578 880	2 928	406	2 522	67.1

Zzwia, 2009

Objective: This study was carried out in St Francis Hospital Buluba (SFHB) after observing that the hospital was registering an abnormally high number of tetanus patients. Its aim was to retrospectively establish the socio-demographic characteristics of the patients and determine the case-fatality rate among tetanus patients admitted between 2005- 2008**.**

Methodology: Records of all patients registered and treated for tetanus up to the time of death or discharge on the Medical and Pediatric wards were evaluated. Case notes of 71 patients were retrieved and analyzed for clinical characteristics.

During the three-year period under study, 163 patients (0.65% of all admissions) were managed for tetanus. Analysis was done for only 154 (94.5%) patients because records of the others lacked basic data.

Results: The majority of the patients were male, with a male to female ratio of 2:1. Most (58%) of the patients came from Mayuge district and the rest (42%) came from other neighboring districts. The number of cases admitted with tetanus increased with time, with 26 in 2005; 27 in 2006; 41 in 2007 and 60 in 2008.

Most (124 or 81%) of the patients were children aged 13 years or less. The mean age of cases was 13.5 years (range 1week - 72 years). Neonatal tetanus was reported in 18 (12%) patients. Death occurred in 72 cases resulting in an overall in-hospital case-fatality of about 47%. Death was highest in the extremes of age, with about 78% in the neonates and about 91% in those aged 45 years and above.

The mean duration of hospitalization for all cases was 17.5 days (range hours – 32 days). For those who died, their mean duration of hospitalization was 1.3 days (range hours- 9 days) and for those who survived it was 7.4 days (range 3-32 days).

Only 6 (20%) among 30 adult patients above 13 years were females. Neonatal tetanus contributed 12% of tetanus cases. Children below 13 years contributed 81% of all the cases with majority aged 5-13 years (54%).

Table 6: Characteristics of the 154 Tetanus cases

Characteristic	Cases (%)	Died (%)
Total	154	72 (46.8)
Sex		
Male	102 (66.2)	44 (43.1)
Female	52 (33.8)	28 (53.8)
Origin		
Within catchment	89 (57.8)	46 (51.7)
Outside catch-ment	65 (42.2)	26 (40.0)
Age		
≤1 month	18 (11.7)	14 (77.8)
1 month < 5 years	23 (14.9)	7 (30.4)
5 - 13 years	83 (53.9)	33 (39.8)
14 – 45 years	19 (12.3)	8 (42.1)

ii. Use and cost of health care

a) *Consequences of tetanus infections in terms of: mortality, disability, length of stay, and cost of treatment in Uganda.*

Data from Nanteza e. al. 2016 study looking at inpatients registry at Masafu hospital, Busia district for the period 2009/2010–2013/2014 provided information on the 19/25 tetanus patients that had information on patients' duration of hospital stay based on dates on admission and Discharge. Hospital stay was longer in the 3 patients discharged healed, median (IQR) 12 (9, 15) days, followed by the six discharged on request 4.5 (2, 8) days, and least for the nine who died 2 (1, 3) days. The patient who escaped from hospital before healing had spent 3 days. The case fatality rate of the tetanus patients at this facility was 47.4 % (9/19) and the self-discharged from the hospital were 36.8 % (7/19). Data from DHIS 2 showed that Death rates per 1000 tended to increase over the three fiscal years 2010/11: 2.3 2011/12: 4.2, and 2012/13: 6.3, but declined in 2013/14: 2.0.
On treatment: Only five patients had charts with detailed case notes that provided presenting complaint, the nature and cause of wounds/injuries, treatment administered and outcome at discharge. However, only three patients received anti-tetanus serum (20,000 IU). All patients were treated with antibiotics (metronidazole), diclofenac, diazepam, chlorpromazine, Nasal Gastric Tube for feeding and isolation in a dark room. Access to critical care services such as dedicated ICU was limited or non-existent.

A study reviewing the Intensive Care Service at St. Mary's Hospital Lacor in Northern Uganda over a 12 month period from July 2005 to July 2006 (Towey and Ojara. 2008) made the following report:

Six neonates were admitted with tetanus of which 5 died. All were managed by sedation mainly with diazepam (diazemuls to preserve venous access as generic diazepam causes loss of venous access from phlebitis in a short time). Of the six children (over one month to 18 years) admitted with tetanus all survived among whom 4 required long term IPPV for about 3 weeks when magnesium failed to control the spasms. Eleven adults were admitted with tetanus and 8 died. No adult patient who was given IPPV when magnesium failed to control the spasms survived. Long term IPPV for tetanus is a major commitment of resources and would only be embarked upon after careful planning of available resources but in our experience children gave good outcomes. At present with our limited resources we rarely start IPPV for tetanus in the older patient. Ten patients had a tracheostomy for some form of upper airway obstruction and 6 for tetanus. Eighteen patients had tracheostomies and 4 died from the underlying condition. Intermittent positive pressure ventilation was carried out on 30 patients with a mortality rate of 53%. 4 of these were child tetanus cases of which all survived, and 4 of these were adult tetanus cases of which all died.

Zzwia 2009

A total of 25,118 patients were registered on the pediatrics and medical wards in the period of study (2005-2008). Of these 163 (0.65%) were managed for tetanus. Analysis was done for only 154 (94.5%) patients because the rest had incomplete basic information.

Table 7: treatment administered and outcomes

Medicine Administered	Total (%)	Died (%)
Metronidazole only	33(46.5)	18 (54.5)
Penicillin +/- Metronidazole	38 (53.5)	19 (50.0)
Diazepam	71 (100)	
Chlopromazine	71 (100)	
Anti tetanus serum	24 (33.8)	7 (29.2)

Only 24 (33.3%) of the 71 cases received ATS, mainly because it was not readily available due to its cost. Though mortality rate was lower in patients who received ATS compared to those who did not (29.2% vs57.5%), this cannot fully be attributed to ATS because the study was not designed to evaluate this effect.

This hospital like many others in the region does not have intensive care (ICU) facilities and hence patients are managed on the general medical and pediatric wards.

In Nigeria it was found that the average cost of treating 5 tetanus patients with mean hospitalization in ICU of 10 days was US$ 363.24 (Ahmadsyah et al 1985). This is extremely high compared to the cost of the vaccine.

3. Economic and operational considerations

i. Vaccine related cost and resource use

a) *What is the current cost of Td vaccine per dose compared to TT? What would be the total (direct and indirect) cost of administering Td vaccine compared to TT vaccine to children above 5 years, adolescents and adults in Uganda?*

2016 costing study put TT cost per dose at $0.05. (WHO 2016c) The international Weighted Average Price per dose of TT and Td is the same (UNICEF website)https://www.unicef.org/supply/files).

ii. Vaccine availability

b) *Is there sufficient international reliable potential supply of Td for Uganda*

UNICEF anticipates overall TT/Td forecasted demand to reach 165 million doses a year during 2016-2017, and anticipates an increasing share of Td vaccines. However, Td vaccine country demand forecasts remain somewhat uncertain and are dependent on country TT/Td transition decisions and timing.

UNICEF launched its TT/Td vaccine tender in June 2015 to supply 165 million doses a year over 2016 -2017 to meet country demand for RI and campaign activity. UNICEF awarded long-term arrangements (LTA) in October 2015 to five suppliers.

UNICEF website https://www.unicef.org/supply/files

Figure 4: TT and Td Procurement through UNICEF -Overview and demand 2000-2012, forecasts 2013-2015, showing price trends
Source UNICEF website
https://www.unicef.org/supply/files/5._TT_and_Td_vaccines_tender_overview.pdf

iii. Vaccine affordability

a) What would be the annual fiscal implications to the Ugandan government if tetanus control is started using Td vaccine compared to TT vaccine for children above 5 years, adolescents and adults?

Introduction costs: Infants -$2.8 million, above 5 -$ 2.5million, Adolescents - $ 2.6 million (Healthnet Consult 2017).

b) What would be the annual fiscal implications to the Ugandan government if Td vaccine compared to the TT immunization of pregnant women?
Introduction cost $ 4.2 million (Healthnet Consult 2017).

iv. Economic impact on the immunization programme

a) *What are the available grant opportunities from partners and Uganda government for introduction of Td vaccine into Uganda's routine immunization schedule for children above 5 years, adolescents and adults*?

Td is not listed among vaccines supported by GAVI for Uganda. (Gavi website 2017)

b) *Cost benefit to Uganda/Region of introducing Td vaccine into routine immunization of children above 5 years, adolescents and adults?*

c) *Cost benefit to Uganda/Region of introducing TT vaccine into routine immunization of children above 5 years, adolescents and adults*
The WHO position paper (WHO 2017b) showed that evidence is strong on cost effectiveness in introducing TT vaccine into routine immunization of children above five years, adolescents, and adults. Such results can be applicable to Uganda as well. For pregnant women, the incremental cost effectiveness ratio is $22 per disability adjusted life year (DALY) averted for TT vaccine.

d) *Cost effectiveness of introducing Td vaccine into routine immunization of children above 5 years, adolescents and adults to Uganda/Region*.

e) *Cost effectiveness of introducing TT vaccine into routine immunization of children above 5 years, adolescents and adults to Uganda/Region* Costing studies with EPI data, Systematic literature search

Mcgovern and Canning 2015

Type of study: Modelling study

Objective:

- To determine the relationship between vaccination coverage and the probability of dying between birth and 5 years of age considering the childhood measles, bacillus Calmette-Guérin, diphtheria-pertussis-tetanus, polio, and maternal tetanus vaccinations.

Methods

- We combined all publicly available data sets from the DHS for which we were able to measure child mortality, the vaccination status for all 5 basic vaccines in living children, and household wealth
- In addition, women reported the number of tetanus toxoid injections that they received during their last pregnancy, and we used that as a child health intervention because immunity to tetanus is transferred to the child in utero
- We use modified Poisson regression to estimate the relative risk for the average vaccination rate

Results

- The results imply that vaccination coverage has a substantial association with under-5 mortality at the cluster level, particularly for measles and maternal tetanus vaccination
- For maternal tetanus vaccination, our estimates imply that increasing immunization coverage by 40 percentage points to 100% would result in approximately 240,000 fewer deaths.
- Figures provide some indication that increases in vaccination coverage as a means to reduce child mortality and achieve the targets laid out in the Millennium Development Goals are likely to be highly cost effective, particularly for maternal tetanus immunization.

4. Health Policy and programmatic issues

i. Feasibility

a) Feasibility of the WHO schedule for Td vaccine in children above 5 years, adolescents and adults in Uganda

b) Are there strategies/programmes in place providing preventative services to them? (+5years, adolescents, adults?)

The second year of life provides a platform for vaccination against several diseases including pertussis, measles, and meningococcal A conjugate vaccines. The pre-adolescent and adolescent vaccination platform includes HPV vaccination. Introduction of tetanus toxoid-conjugate vaccines where TT vaccine is used as a carrier protein, including meningococcal group A (MenAfriVac), meningococcal group C (Men-C), Haemophilus influenzae type b (Hib) represent another possible opportunity for a boost in population immunity to tetanus. Increased tetanus sero-protection has been shown in affected age cohorts following Hib/Men-C routine introduction in England, a Men-C catch-up campaign in the Netherlands, and MenAfriVac catch-up campaign in Mali. (WHO 2016a).

ii. Vaccine registration and policy requirements

a) *NDA Requirements in Uganda to license Td vaccine use in children above 5 years, adolescents and adults*.

b) *EPI policy changes will be required to expand the routine immunisation platform to include adolescents and adults*?

Ministry of Health 2012. Uganda Immunisation Policy

According to the Uganda Immunisation Policy 2012, the target age groups for routine immunization by UNEPI includes; children 0-12 months, adolescents, women of childbearing age (15-45 years both pregnant and non-pregnant) and other high-risk groups as determined by the epidemiological pattern of a disease.

IV. Discussion

a) Disease Burden

Members reviewed evidence provided on disease burden and noted that:

- Uganda has a high incidence of tetanus in older individuals, which would be a justification for the booster doses. The high incidence of tetanus particularly in older females (5+ years), who are targeted by the MNT strategy, calls for a deeper investigation. It was also noted that the Ministry of Health has a case based surveillance strategy for neonatal tetanus but none for tetanus in older individuals, which needs to be initiated.
- Case fatality rates are very high ranging from 40 to 70%, even with good intensive care. Fatal cases die within 3 days of admission.
- Treatment costs of tetanus patients are very high, and taking care of those who live beyond 3 days is extremely costly. Because tetanus patients require a lot of attention from the medical team, they create a shortage of staff in the treatment wards, which causes the treatment of those with tetanus to impact the treatment of other patients.

- Uganda seems to show a comparatively high number of cases as country, comparative to the burden in other countries in sub-Saharan Africa.
- Although the absolute number for tetanus cases is not as high compared to other high burden diseases in Uganda, the case fatality rate and the high cost of treatment makes it a serious disease in need of preventive intervention.

b) Vaccine Characteristics: safety, efficacy and effectiveness

- Tetanus containing vaccines are safe, with mild side effects like injection site pain and mild fevers commonly reported and major adverse events are extremely rare. The safety profile of TT and Td is comparable, in children and pregnant women.
- Evidence suggests that diphtheria toxoid increases the immunogenicity of tetanus toxoid as well as other vaccine antigens.
- Td vaccine is safe and effective when co-administered with most other antigens. Exception was noted when Td was administered a month prior to PCV 13 and Men C vaccines which resulted in reduced reactogenicity of the two vaccines although titre levels remained above protective limits.

c) Economic Considerations

- The costs per dose for Tt and Td are similar ranging from $0.07 to $0.09 per dose. Packaging volumes are similar too, with 10 dose vials, indicating that the financial implications of the switch may not be significant. The additional financial costs will be due to addition of three booster doses targeting both sexes.
- Td is highly cost effective in terms of lives saved, particularly for maternal tetanus immunization.
- Td is not listed among the vaccines supported by Gavi. Government of Uganda currently fully funds TT vaccination.

d) Health Policy and Programmatic Issues

- The second year of life provides a platform for vaccination against several diseases including measles, and meningococcal A conjugate vaccines. The pre-adolescent and adolescent vaccination platform includes Child Days and HPV vaccination.
- Programmatic issues of concern to the booster doses include: high drop-out rates for vaccines administered to individuals over a year old, e.g. HPV, low coverage (55 %) of TT among Pregnant women (high coverage of booster doses would eventually eliminate need to vaccinate pregnant women), increased number of doses will present higher work burden to the health workers and require more cold chain space.
- Making it a requirement for full vaccination before school enrollment at the nursery, primary and high school, can help increase coverage among school going children.

V. Proposed recommendation (s) /options

a) Uganda should switch from TT to Td. This will not only strengthen the protection against tetanus, but also provide protection against diphtheria. This also goes with current worldwide trends and Uganda might be left behind if it does not make the switch.

b) Uganda should add 3 booster doses of Td to the routine immunization schedule at 24 months, 4–7 years of age; and 9–15 years of age. This will provide lifelong protection against tetanus as well address the low coverage problem with pregnant women and help maintain MNT elimination.

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VII. Annexes

1. Ministry of Health Letter of Request

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THE REPUBLIC OF UGANDA

Ministry of Health
P.O. Box 7272
Kampala
Uganda

IN ANY CORRESPONDENCE ON THIS SUBJECT PLEASE QUOTE NO: **ADM:215/306/01**

22nd June 2016

Dr. Nelson Sewankambo,
Chairperson for NITAG Uganda,

RE: REQUEST TO NITAG TO ADVICE THE IMMUNIZATION PROGRAM TO PRIORITIZE WHICH NEW VACCINES SHOULD BE INTRODUCED

The goal of immunization program is to ensure that every child and high-risk group is fully vaccinated with high quality and effective vaccines against the target diseases according to recommended strategies through five operational components: vaccine supply and quality, logistics, service delivery, surveillance, advocacy and communication.

SAGE has made several recommendations to countries to introduce new vaccines into their routine immunization program following evidence presented to them to show that they are effective and efficacious. Over the last three years, Uganda has introduced three new vaccines into the routine immunization program and plans to introduce yellow fever vaccine, Measles and Rubella Vaccine including second dose, Men A and Tetanus Diptheria(Td) Vaccine.
However along the way the program has observed some challenges and anticipates more to come as more new vaccines are introduced into the routine immunization program. Among these challenges, includes fulfilling co financing requirements for the recently introduced vaccine affecting the performance of new vaccine introduction

In line with the WHO recommendation, Uganda established the NITAG to provide evidence based advice to the Ministry of Health on immunization.

The purpose of this letter is therefore to request the NITAG to provide guidance on which new vaccine Uganda's immunization program should prioritize in order of importance in the next five years. Your response will highly be appreciated preferably by end of 2016.

Prof. Anthony K. Mbonye
FOR DIRECTOR GENERAL HEALTH SERVICES

Cc: The Permanent Secretary, Ministry of Uganda
Cc: The Director Health Services, Clinical and Community
Cc: Commissioner Health Services, National Disease Control
Cc: The Program Manager, UNEPI

2. Members of Tetanus Diphtheria Working Group

1. Prof. George Kirya(Chair)
2. Dr. Peter Waiswa– Core member, Public Health
3. Dr. Lawrence Kagwa – Core member, Health Systems
4. Hon. Benson Obua Ogwal – Core member, Sociology
5. Dr. Jesca Nsungwa Sabiiti - Liaison member, Child Health
6. Dr. Immaculate Ampeire – Liaison member, EPI
7. Dr. Issa Makumbi– co-opted expert (Epidemiologist/ Health Systems)

3. Evidence search process and results.

Excel Sheet with Recommendation Framework.

Cost Estimates for Introduction of New Vaccines

Cost Estimates for Introduction of New Vaccines

Background

The NITAG requested that we compute costs for introducing new vaccines in Uganda. This paper presents an estimate of costs for introducing the following vaccines:

- Measles Rubella
- Hep at birth
- Men A
- Yellow Fever
- Td.

The cost estimates include the cost of the vaccine (antigen) plus the cost of new vaccine introduction activities that include: training, injections and supplies, social mobilization and advocacy, planning and coordination, program management, supervision, surveillance, cold chain (maintenance & equipment), as well as costs pertaining to vaccine distribution and collection. In other words:

Total Cost = Cost of Vaccine + Cost of NUVI activities.

While it was very straightforward to obtain the cost of the vaccine (from UNEPI), the estimation of NUVI activities for each of the individual new vaccines was not very straightforward given the amount of time and resources required for this. As a result, we relied on a recently concluded costing study for PCV introduction (WHO 2017). This implies that for the new vaccines cost estimates presented here, there is a huge assumption that has been made which is that the introductory activities for each of the new vaccines is somewhat similar to that of PCV introduction activities. This means that the results presented here should be interpreted with caution, as they are mere estimates, which might be under or over estimated. However, these cost estimates can be very helpful in giving a general picture of how one new vaccine's introduction compares with another new vaccine – given that the price of each individual vaccine and the target population are accurate.

UNEPI provided the vaccine costs (price of the antigen) and an 8% was factored in for handling and freight charges. UNEPI also provided the target population guidelines for each new vaccine. We used the UBOS 2014 population census estimates and a 3.0% population growth rate was used to project the target population over a 5-year period. Costs for vaccines were inflated at 2%, which is the usual inflation rate used for vaccine prices. Other costs were inflated based on the projected inflation rates from UBOS.

Cost Estimates

This section presents the cost estimates for introducing each new vaccine in a given year. For instance, how does the cost of introducing MR in 2017/18 compare with introducing it in 2019/20. Therefore, the tables below don't show the cumulative cost of introducing a new vaccine over a 5-year period but rather, the cost of introducing the new vaccine in any one given year of the 5-year period.

Measles Rubella

Table 1 presents the total costs required to introduce MR for two doses – one dose at 9 months and the other at 15-18 months. If MR is introduced in 2017/18 the total cost is about US $3.8 million. If it is introduced in 2020/21 the cost estimate is US $4.6 million due to an anticipated increase in population and inflation.

Table 1: Total cost for introduction of MR in a given year

MR	2016/17 (US$)	2017/18 (US$)	2018/19 (US$)	2019/20 (US$)	2020/21 (US$)
Vaccine Costs	1,680,715	1,765,759	1,855,107	1,948,975	2,047,593
New vaccine introduction costs	1,923,701	2,054,817	2,247,901	2,431,105	2,629,240
Total costs for introducing MR	**3,604,416**	**3,820,576**	**4,103,008**	**4,380,080**	**4,676,834**

Hep at birth

For Hep at birth, the cost estimates for introducing this new vaccine are presented in Table 2.

Table 2: Total cost for introduction of Hep at birth in a given year

Hep Birth	2016/17 (US$)	2017/18 (US$)	2018/19 (US$)	2019/20 (US$)	2020/21 (US$)
Vaccine Costs	285,794	300,255	315,448	331,409	348,179
New vaccine introduction costs	2,031,363	2,169,817	2,373,708	2,567,165	2,776,389
Total costs for introducing Hep	**2,317,157**	**2,470,072**	**2,689,155**	**2,898,574**	**3,124,567**

Men A

For Men A, the cost estimates for introducing this new vaccine are presented in Table 3.

Table 3: Total cost for introduction of Men A in a given year

Men A	2016/17 (US$)	2017/18 (US$)	2018/19 (US$)	2019/20 (US$)	2020/21 (US$)
Vaccine Costs	676,616	710,853	746,822	784,612	824,313
New vaccine introduction costs	1,923,701	2,054,817	2,247,901	2,431,105	2,629,240
Total costs for introducing Men A	**2,600,317**	**2,765,670**	**2,994,724**	**3,215,717**	**3,453,553**

Yellow Fever

The cost estimates for yellow fever introduction are presented in Tables 4-5. Table 4 presents the costs of introducing yellow fever vaccine to surviving infants only while Table 5 presents the cost estimates for introducing the yellow fever vaccine to the whole population (6 months and above).

Table 4: Total cost for introduction of yellow fever to surviving infants in a given year

Yellow fever (Surviving Infants)	2016/17 (US$)	2017/18 (US$)	2018/19 (US$)	2019/20 (US$)	2020/21 (US$)
Vaccine Costs	722,225	758,770	797,164	837,500	879,878
New vaccine introduction costs	1,923,701	2,054,817	2,247,901	2,431,105	2,629,240
Total costs for introducing YF	**2,645,926**	**2,813,587**	**3,045,065**	**3,268,605**	**3,509,118**

Table 5: Total cost for introduction of yellow fever to the whole population

Yellow fever whole population	2016/17 (US$)	2017/18 (US$)	2018/19 (US$)	2019/20 (US$)	2020/21 (US$)
Vaccine Costs	21,602,768	22,695,868	23,844,279	25,050,799	26,318,370
New vaccine introduction costs	2,703,249	2,887,497	3,158,826	3,416,270	3,694,696
Total costs for introducing YF	**24,306,016**	**25,583,365**	**27,003,104**	**28,467,069**	**30,013,065**

Td

The cost estimates for Td introduction are presented in Tables 6-9. Table 6 presents the costs of introducing Td vaccine to surviving infants only, Table 7 to 7 year olds only (both sexes), Table 8 to 10 year olds only (both sexes) and Table 9 to pregnant women.

Table 6: Total cost for introduction of Td to surviving infants

Td (surviving infants only)	2016/17 (US$)	2017/18 (US$)	2018/19 (US$)	2019/20 (US$)	2020/21 (US$)
Vaccine Costs	148,856	156,388	164,301	172,615	181,349
New vaccine introduction costs	1,923,701	2,054,817	2,247,901	2,431,105	2,629,240
Total costs for introducing Td	**2,072,557**	**2,211,204**	**2,412,202**	**2,603,720**	**2,810,589**

Table 7: Total cost for introduction of Td to 7 year olds (both sexes)

Td (7 year olds -- both sexes)	2016/17 (US$)	2017/18 (US$)	2018/19 (US$)	2019/20 (US$)	2020/21 (US$)
Vaccine Costs	143,253	150,502	158,117	166,118	174,524
New vaccine introduction costs	1,851,302	1,977,483	2,163,301	2,339,610	2,530,288
Total costs for introducing Td	**1,994,555**	**2,127,985**	**2,321,418**	**2,505,728**	**2,704,812**

Table 8: Total cost for introduction of Td to 10 year olds (both sexes)

Td (10 year olds -- both sexes)	2016/17 (US$)	2017/18 (US$)	2018/19 (US$)	2019/20 (US$)	2020/21 (US$)
Vaccine Costs	140,545	147,657	155,128	162,978	171,225

New vaccine introduction costs	1,816,305	1,940,101	2,122,406	2,295,382	2,482,456
Total costs for introducing Td	**1,956,851**	**2,087,758**	**2,277,535**	**2,458,360**	**2,653,681**

Table 9: Total cost for introduction of Td to pregnant women

Td (Pregnant women)	2016/17 (US$)	2017/18 (US$)	2018/19 (US$)	2019/20 (US$)	2020/21 (US$)
Vaccine Costs	222,624	233,889	245,723	258,157	271,220
New vaccine introduction costs	2,877,029	3,073,122	3,361,893	3,635,887	3,932,212
Total costs for introducing Td	**3,099,653**	**3,307,010**	**3,607,616**	**3,894,044**	**4,203,432**

Summary of the results

Table 10 presents a summary of the cost estimates for each new vaccine. We note that introducing yellow fever to the whole population attracts the highest costs. This is followed by the introduction of MR, then Td to pregnant women and then yellow fever to surviving infants. Introduction of Men A, Hep at birth and Td to surviving infants attracts almost similar costs. Lastly, the introduction of Td to 7 year olds and 10 year olds attracts the lowest costs of the proposed new vaccines.

Table 10: Total costs for introduction of new vaccines

Antigen	2016/17 (US$)	2017/18 (US$)	2018/19 (US$)	2019/20 (US$)	2020/21 (US$)
Yellow Fever (Whole population)	24,306,016	25,583,365	27,003,104	28,467,069	30,013,065
MR	3,604,416	3,820,576	4,103,008	4,380,080	4,676,834
Td (pregnant women)	3,099,653	3,307,010	3,607,616	3,894,044	4,203,432
Yellow Fever (12 months)	2,645,926	2,813,587	3,045,065	3,268,605	3,509,118
Men A	2,600,317	2,765,670	2,994,724	3,215,717	3,453,553
Hep Birth	2,317,157	2,470,072	2,689,155	2,898,574	3,124,567
Td (surviving infants)	2,072,557	2,211,204	2,412,202	2,603,720	2,810,589
Td (7 year olds_	1,994,555	2,127,985	2,321,418	2,505,728	2,704,812
Td (10 year olds)	1,956,851	2,087,758	2,277,535	2,458,360	2,653,681