



**World Health
Organization**

**Department of Immunization,
Vaccines and Biologicals (IVB)**

SAGE

April 2018

**Strategic Advisory Group of Experts
on Immunization
17 - 18 April 2018**

**Centre International de Conférences
(CICG)
Geneva, Switzerland**

SAGE April 2018

This booklet contains key background documents for the
meeting of the
Strategic Advisory Group of Experts (SAGE) on Immunization
17 - 18 April 2018

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

<http://www.who.int/immunization/sage/meetings/2018/april>

Table of Contents – April 2018 SAGE meeting

| Document | Page |
|---|------|
| Agenda | 1 |
| List of SAGE Members | 5 |
| SAGE Terms of References | 6 |
| Current SAGE Working Groups | 16 |
| Provisional list of participants | 23 |
| Session 1: New leadership and new priorities at WHO (No background documents provided for this session) | |
| Session 2: Report from IVB Director | |
| 1. Meeting of the Strategic Advisory Group of Experts on immunization, October 2018 – conclusions and Recommendations. | 43 |
| 2. SAGE tracking record of recommendations and action points. | 63 |
| 3. Draft Report on Meeting Of The Eastern Mediterranean Regional Technical Advisory Group (RTAG) On Immunization, Muscat, Oman, 14 December 2017 | 92 |
| 4. Report of the Regional Immunization Technical Advisory Group Meeting; Johannesburg, South Africa, 5-7 December 2017 | 109 |
| Session 3: Report from Gavi, the Vaccine Alliance (No background documents provided for this session) | |
| Session 4: Malaria (Jointly SAGE/MPAC) | |
| 1. Executive Summary of Malaria Session | 128 |
| 2. Malaria vaccine implementation programme (MVIP) – a progress update | 130 |
| 3. Framework for policy decision on the RTS,S/AS01 malaria vaccine based on MVIP data – Rationale and process | 141 |
| Session 5: Polio the last mile | |
| 1. Executive Summary of Polio Session | 144 |
| 2. Conclusions and recommendations from the 15th meeting of the polio SAGE Working Group | 146 |
| Session 6: Updating policy recommendations on the use of the first licensed dengue vaccine | |
| 2. Background Paper on Dengue Vaccines | 165 |
| | |
| Session 7: Reports from other Advisory Committees on Immunization | |
| Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC) (No background documents provided for this session) | |
| Expert Committee on Biological Standardization (ECBS) | |
| 1. Biological Standardization: Sixty-eighth report of the Expert Committee on Biological Standardization, Geneva, 17–20 October 2017 | 227 |
| Global Advisory Committee on Vaccine Safety | |
| 2. WER, Global Advisory Committee on Vaccine Safety, 6–7 December 2017 | 229 |
| Session 8: Measles and Rubella | |
| 1. Exploration of future immunization policies for measles and rubella: The need for continued investment and the potential benefits of eradication | 245 |
| 2. Report for the SAGE Working Group on Measles and Rubella | 259 |
| Session 9: Vaccine value propositions and preferred product characteristics | |
| 1. Executive Summary of Vaccine value propositions and preferred product characteristics Session | 282 |
| 2. Estimating the full public health value of vaccination | 284 |
| 3. WHO full public health value proposition (FPHVP) for vaccines draft table of contents | 293 |

Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization

DRAFT Agenda

17 - 18 April 2018

Centre International de Conférences Genève (CICG), Geneva, Switzerland

Tuesday, 17 April 2018

| Time | Session | Purpose of session, target outcomes and questions for SAGE | Duration |
|--------------|--|---|-------------------|
| 09:30 | Welcome – introduction of participants A. CRAVIOTO. Chair of SAGE. | | 20 min. |
| 09:50 | New leadership and new priorities at WHO - Session 1 P. N. SIMELELA. WHO. 20 min. Discussion: 10 min. | FOR INFORMATION | 30 min |
| 10:20 | Report from Director, IVB and Regional Updates - Session 2 Global report including key updates and challenges from regions. M. FRIEDE. WHO. 30 min. | FOR INFORMATION | 1 h 30 min |
| 10:50 | Coffee/tea break | Break | 30 min. |
| 11:20 | Cont. Report from Director, IVB and Regional Updates - Session 2 Discussion: 1 h | | |
| 12:20 | Report from Gavi, the Vaccine Alliance - Session 3 Report from Gavi, the Vaccine Alliance. S. BERKLEY. Gavi, the Vaccine Alliance. 15 min. Discussion: 25 min. | FOR INFORMATION | 40 min. |
| 13:00 | Lunch | Break | 1h 15 min. |
| 14:15 | Malaria Vaccine Implementation Programme (MVIP) - Session 4 Overview of the MVIP F. WERE. MVIP Programme Advisory Group member. 15 min. | FOR INFORMATION Reminder of rationale for SAGE/MPAC Oct 2015 recommendation for pilot implementation; Update on progress of the MVIP; Inform about Programme oversight and advisory | 2 h |

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|---|--|--|
| Current status, pilot country readiness and timelines. G. BONSU, EPI manager in Ghana. 15 min. | | bodies; Outline expected timelines to vaccine introduction. |
| Discussion: 45 min. | | |
| Framework for policy decision. M HAMEL. WHO. 15 min. | | Present IVIR-AC feedback on framework; Review of proposed inputs and output measures for modelling. Discuss timelines for framework development. |
| Discussion: 30 min. | | |
| 16:15 | Coffee/tea break | Break |
| | | 30 min. |
| 16:45 | Polio the last mile - Session 5 | 2 h |
| Overview of the Global Polio Eradication Initiative. M ZAFFRAN. WHO. 25 min. | | FOR INFORMATION Current status of the polio eradication program; Update on process of polio eradication certification; |
| Polio Post-Certification Strategy. M ZAFFRAN. WHO. 15 min. | | FOR DECISION To seek recommendation/endorsement on – proposed Post Certification Strategy; and on revisions to protocol on VDPV outbreak response; |
| Report from SAGE Polio Working Group. P. FIGUEROA. SAGE Polio Working Group Member. 20 min. | | |
| Discussion: 1h | | |
| 18:45 | End of Day | |
| 19:00 | Cocktail | |

Wednesday, 18 April 2018

| Time | Session | Purpose of session, target outcomes and questions for SAGE | Duration |
|--|--|---|-----------------|
| 09:15 | Updating policy recommendations on the use of the first licensed dengue vaccine – Session 6 | FOR INFORMATION Rationale for SAGE 2016 recommendations, long-term safety data, attributable risk and absolute risk reduction, benefit risk assessments, ethical considerations | 2 h |
| Global dengue burden and future projections. TBD. 10 min. | | | |
| Rationale for SAGE April 2016 recommendations. P. SMITH. SAGE Dengue Working Group Member. 10 min. | | FOR DECISION Updating policy recommendations on the use of the dengue vaccine | |
| Long-term safety data stratified by serostatus. P. SMITH. SAGE Dengue Working Group Member. 20 min. | | | |
| Discussion: 15 min. | | | |

| | | | |
|--|--|------------------------|--------------------|
| <p>Modelling population level vaccine impact and coverage rates. N. FERGUSON. Imperial College, London. 20 min.</p> <p>Discussion: 15 min.</p> <p>Draft recommendations. T. NOLAN. SAGE Dengue Working Group Chair. 10 min.</p> <p>Discussion: 30 min.</p> | | | |
| 11:15 | Coffee/tea break | Break | 30 min. |
| 11:45 | <p>Reports from other Advisory Committees on Immunization – Session 7</p> <p>FOR INFORMATION</p> <p>Immunization and Vaccines Related Advisory Committee (IVIR-AC). R. BREITMAN IVIR-AC representative. 10 min.</p> <p>Discussion: 10 min.</p> <p>Expert Committee on Biological Standardization (ECBS). K. CICHUTEK. Chair of ECBS. 10 min.</p> <p>Discussion: 10 min.</p> <p>Global Advisory Committee on Vaccine Safety (GACVS). R. PLESS. Chair of GACVS. 10 min.</p> <p>Discussion: 10 min.</p> | | |
| 12:45 | Lunch | Break | 1 h 15 min. |
| 14:00 | <p>Measles and Rubella – Session 8</p> <p>Session Introduction. N. TURNER. SAGE Measles and Rubella Working Group Chair. 5 min.</p> <p>Global update A. DABBAGH. WHO. 10 min.</p> <p>Discussion: 15 min.</p> <ul style="list-style-type: none"> - Global and regional update - Status of mid-term review recommendations - Global Measles and Rubella surveillance update | | |
| | | FOR INFORMATION | 2 h |

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|---|--|---|----------------|
| The Measles and Rubella Investment Case. K. THOMPSON. Kid Risk Inc. 15 min. Discussion: 20 min. Country classifications for endemic countries. S. REEF. SAGE Measles and Rubella Working Group Member. 25 min. Discussion: 30 min. | | <ul style="list-style-type: none">- Presentation of an integrated global model and prospective immunization scenario impacts on morbidity and mortality- A roadmap for endemic countries towards closing immunity gaps and achieving elimination- Presentation of the Pros and Cons of methods for assessing age-specific population immunity | 30 min. |
| 16:00 | Coffee/tea break | Break | |
| 16:30 | Full Public Health Value Propositions for Vaccines (FPHVPs)- Session 9 | | 1 h 30 min. |
| | Session Introduction A. CRAVIOTO. SAGE. 5 min. Concept and status of FPHVP D. KASLOW. Chair of Product Development for Vaccines Advisory Committee (PDVAC). 20 min. Resource allocation issues related to FPHVPs M. JIT. IVIR-AC Member. 15 min. Discussion: 50 min. | FOR INFORMATION <ul style="list-style-type: none">- The rationale for development of FPHVP for vaccines: priority setting, investment and policy decisions and generating political will- Proposed components in the early vs. late stage FPHVP: objectives and gap analysis- How should FPHVP be used? Stakeholder mapping and customization- Types of economic analysis for FPHVP depending on the budget holder's objectives | |
| 18:00 | Closing | | |
| 18:15 | End of meeting | | |



Meeting of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization
17-18 April 2018 Geneva, Switzerland

SAGE members

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Strategic Advisory Group of Experts (SAGE)

Terms of reference

Functions

SAGE is the principal advisory group to WHO for vaccines and immunization. It is charged with advising WHO on overall global vaccination policies and strategies, ranging from vaccines and technology, research and development, to delivery of vaccination and its linkages with other health interventions. SAGE's remit extends to the control of all vaccine-preventable diseases as part of an integrated, people centred platform of disease prevention that spans the human life-course and in the context of health systems strengthening.

SAGE advises the WHO Director-General specifically on the:

1. adequacy of progress towards the achievement of the goals of control of vaccine-preventable diseases worldwide such as those laid out in the Decade of Vaccines Global Vaccine Action Plan 2011-2020.
2. major issues and challenges to be addressed with respect to achieving the disease control goals, including issues and challenges to achieving and sustaining high and equitable vaccination coverage;
3. immunization programme response to current public health priorities;
4. major general policies, goals and targets including those related to vaccine research and development;
5. adequacy of WHO's strategic plan and priority activities consistent with its mandate and considering the comparative advantages and the respective roles of partner organizations;
6. engagement of WHO in partnerships that will enhance achievement of global immunization goals.

Membership

SAGE comprises 15 independent experts, who shall serve in their personal capacity and represent a broad range of affiliations and a broad range of disciplines encompassing many aspects of immunization and vaccines. Members should refrain from promoting the policies and views and products of the institution for which they work.

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

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

1. professional affiliation (e.g., academia, medical profession, clinical practice, research institutes, and governmental bodies including national immunization programmes, public health departments and regulatory authorities);
2. major areas of expertise (e.g., vaccine research, vaccine and immunization safety, optimization of immunization schedules, vaccine delivery, disease control strategies, impact monitoring); and
3. the strategic focus areas of the WHO's vaccine and immunization work including vaccines norms and standards, vaccine regulation, vaccine programme management, delivery and surveillance and monitoring, and vaccine research & development.

SAGE members, including the Chairperson and the Vice-Chairperson, are appointed by the WHO Director-General. Members are selected upon the proposal of an independent selection panel including representatives of key partner organizations. A public call for nominations is issued. After determination of eligibility, nominations are submitted to the selection panel. Members will be selected on the basis of their qualifications and ability to contribute to the accomplishment of SAGE's objectives. Renewals of term are also submitted to the selection panel.

Consideration will be given to ensuring appropriate geographic representation and gender balance. Chairs of regional technical immunization advisory groups are not eligible to serve on SAGE but are invited to attend SAGE meetings. WHO staff and United Nations staff members are not eligible to serve on SAGE.

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

Prior to being considered for SAGE membership, nominees shall be required to complete a WHO Declaration of Interests form as per the attached form (Annex 1).

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

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

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

1. failure to attend two consecutive SAGE meetings;
2. change in affiliation resulting in a conflict of interest or involvement in activities resulting in a conflict of interest incompatible with serving on SAGE; and
3. a lack of professionalism involving, for example, a breach of confidentiality.

Meetings and operational procedures

SAGE meetings occur biannually, in April and October, and are scheduled 3 years ahead. The frequency of meetings may, however, be adjusted as necessary. The WHO Secretariat will work with SAGE members and key global stakeholders to develop SAGE priorities and workplans as well as specific meeting agendas.

SAGE members are asked to update their declared interests before each meeting. SAGE members with potentially conflicting interests will not participate in deliberations on the specific topic(s) for which they would have a conflict of interest. SAGE member's relevant interests will be made publically available four weeks in advance of the meeting for public comments. Background documents, presentations, final agenda and final list of participants are posted after the meeting are posted on the SAGE public website after the meeting.

Decisions or recommendations by SAGE will, as a rule, be taken by consensus.

The WHO Regional Offices, Chairs of regional technical immunization advisory groups and Chairs of relevant WHO technical advisory committees will be invited to participate in SAGE meetings and contribute to the discussions. The major global immunization stakeholders such as UNICEF, the Secretariat of Gavi, the Vaccine Alliance, and representatives of civil society organizations will also be invited to attend and contribute to SAGE meetings.

WHO may also invite other observers to SAGE meetings, including representatives from non-governmental organizations, international professional organizations, technical agencies, partner organizations, Chairs and members of national technical advisory groups on immunization as well as associations of manufacturers of vaccines and immunization technologies and representatives from the manufacturing companies.

Additional experts may be invited to meetings, as appropriate, to further contribute to specific agenda items. Observers and invited experts will not participate in the decision making process but will be allowed to contribute to the discussions as directed by the Chairperson.

SAGE reports to the WHO Director-General. The SAGE Chairperson will debrief the Director-General (or designee) following each SAGE meeting. The conclusions and recommendations of SAGE meetings shall be published in the Weekly Epidemiological Record and posted on the website within two months of each SAGE meeting. These conclusions and recommendations will be translated into all the WHO headquarters official languages. A brief summary report of the meeting shall also be posted on the SAGE website the day after the SAGE meeting.

Roles and responsibilities of SAGE members

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

SAGE has no executive or regulatory function. Its role is solely to provide advice and recommendations to the Director-General of WHO. This includes providing advice and recommendations on urgent public health issues as needed.

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

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

SAGE members are expected to endeavour to attend all biannual meetings. Further active participation will be expected from all SAGE members throughout the year, including participation in SAGE Working Groups, video and telephone conferences as well as frequent interactions via e-mail. Review of documents may also be solicited. SAGE members may be requested to participate as observers in other important WHO or partners meetings. As a result SAGE members are expected to commit to invest a substantial amount of their time to SAGE.

The secretariat of SAGE is ensured by the Immunization Policy Unit of the Department of Immunization, Vaccines and Biologicals. The function of Executive Secretary is ensured by the Senior Health Advisor who directs this Unit.

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SAGE will be kept informed by WHO and partner agencies on progress concerning implementation of strategies and the attainment of objectives at country and regional level. SAGE will also be informed of conclusions and recommendations from WHO relevant technical advisory groups including regional technical advisory groups.

SAGE Working Groups are established as resources intended to increase the effectiveness of SAGE deliberations by reviewing and providing evidence-based information and options for recommendations together with implications of the various options to be discussed by SAGE during one of its biannual meetings. These Working Groups are normally established on a time-limited basis to help address specific questions identified by SAGE when the issue is particularly complicated or time-consuming and could not be addressed by an existing standing WHO advisory committee. The need and charge for a Working Group is discussed and agreed during SAGE meetings. The purpose, structure and functioning of the Working Groups is described in detail in Annex 3 (Purpose, structure and functioning of the Strategic Advisory Group of Experts on Immunization (SAGE) Working Groups).

For its proceedings, SAGE shall follow an evidence-based review process as outlined in the SAGE guidance document on evidence-based vaccine-related recommendations

(http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf?ua=1).

More detailed information on SAGE operating procedures is available on the SAGE website

(http://www.who.int/immunization/sage/working_mechanisms/en/).

DECLARATION OF INTERESTS FOR WHO EXPERTS

WHO's work on global health issues requires the assistance of external experts who **may have interests related to their expertise**. To ensure the highest integrity and public confidence in its activities, WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential conflict of interest related to the subject of the activity in which they will be involved.

All experts serving in an advisory role must disclose any circumstances that could represent a **potential conflict of interest** (i.e., any interest that may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). You must disclose on this Declaration of Interest (DOI) form any financial, professional or other interest relevant to the subject of the work or meeting in which you have been asked to participate in or contribute towards and any interest that could be affected by the outcome of the meeting or work. You must also declare relevant interests of your immediate family members (see definition below) and, if you are aware of it, relevant interests of other parties with whom you have substantial common interests and which may be perceived as unduly influencing your judgement (e.g. employer, close professional associates, administrative unit or department).

Please complete this form and submit it to WHO Secretariat if possible at least 5 weeks before the meeting or work. You must also promptly inform the Secretariat if there is any change in this information prior to, or during the course of, the meeting or work. All experts must complete this form before participation in a WHO activity can be confirmed. Please note that not fully completing and disclosing all relevant information on this form may, depending on the circumstances, lead WHO to decide not to appoint you to WHO advisory bodies / functions in the future.

Answering "Yes" to a question on this form does not automatically disqualify you or limit your participation in a WHO activity. Your answers will be reviewed by the Secretariat to determine whether you have a conflict of interest relevant to the subject at hand. One of the outcomes listed in the next paragraph can occur depending on the circumstances (e.g. nature and magnitude of the interest, timeframe and duration of the interest).

The Secretariat may conclude that no potential conflict exists or that the interest is irrelevant or insignificant. If, however, a declared interest is determined to be potentially or clearly significant, one or more of the following three measures for managing the conflict of interest may be applied. The Secretariat (i) allows full participation, with public disclosure of your interest; (ii) mandates partial exclusion (i.e., you will be excluded from that portion of the meeting or work related to the declared interest and from the corresponding decision making process); or (iii) mandates total exclusion (i.e., you will not be able to participate in any part of the meeting or work).

All potentially significant interests will be **disclosed** to the other participants at the start of the activity and you will be asked if there have been any changes. Whereas this form is confidential, a summary of declarations and actions taken to manage any declared interests will be **published** on the SAGE public website). Furthermore, if the objectivity of the work or meeting in which you are involved is subsequently questioned, the contents of your DOI form may be made available by the Secretariat to persons outside WHO if the Director-General considers such disclosure to be in the best interest of the Organization, after consulting with you. Completing this DOI form means that you agree to these conditions.

If you are unable or unwilling to disclose the details of an interest that may pose a real or perceived conflict, you must disclose that a conflict of interest may exist and the Secretariat may decide that you be totally recused from the meeting work or process concerned, after consulting with you.

| |
|---------------------------------|
| Name: Institution: Email: |
|---------------------------------|

Date and title of meeting or work, including description of subject matter to be considered (if a number of substances or processes are to be evaluated, a list should be attached by the organizer of the activity):

Please answer each of the questions below. If the answer to any of the questions is "yes", briefly describe the circumstances on the last page of the form.

The term "you" refers to yourself and your immediate family members (i.e., spouse (or partner with whom you have a similar close personal relationship) and your children). "Commercial entity" includes any commercial business, an industry association, research institution or other enterprise whose funding is significantly derived from commercial sources with an interest related to the subject of the meeting or work. "Organization" includes a governmental, international or non-profit organization. "Meeting" includes a series or cycle of meetings.

EMPLOYMENT AND CONSULTING

Within the past 4 years, have you received remuneration in excess of US\$ 5,000 from a commercial entity or other organization with an interest related to the subject of the meeting, work or process?

- 1a Employment Yes ☐ No ☐
- 1b Consulting, including service as a technical or other advisor Yes ☐ No ☐

RESEARCH SUPPORT

Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of the meeting, work or process?

- 2a Research support, including grants, collaborations, sponsorships, and other funding Yes ☐ No ☐
- 2b Non-monetary support valued at more than US \$1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.) Yes ☐ No ☐
- 2c Support (including honoraria) for being on a speakers panel, giving speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting, work or process? Yes ☐ No ☐

INVESTMENT INTERESTS

Do you have current investments (valued at more than US\$5,000 overall) in a commercial entity with an interest related to the subject of the meeting, work or process? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.

- 3a Stocks, bonds, stock options, other securities (e.g., short sales) Yes ☐ No ☐
- 3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company) Yes ☐ No ☐

INTELLECTUAL PROPERTY

Do you have any intellectual property rights that might be enhanced or diminished by the outcome of the meeting, work or process?

- 4a Patents, trademarks, copyrights or other intellectual property (including pending applications) Yes ☐ No ☐
- 4b Proprietary know-how in a substance, technology or process Yes ☐ No ☐

PUBLIC STATEMENTS AND POSITIONS (during the past 4 years)

- 5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting, work or process, for a commercial entity or other organization? Yes ☐ No ☐
- 5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting, work or process? Yes ☐ No ☐

ADDITIONAL INFORMATION

- 6a If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting, work or process enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage? if so, please elaborate? Yes ☐ No ☐
- 6b To your knowledge, would the outcome of the meeting, work or process benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)? Yes ☐ No ☐
- 6c Excluding WHO, has any person or entity paid or contributed towards your travel costs in connection with this WHO meeting, work or process? Yes ☐ No ☐
- 6d Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this WHO meeting, work or process? Yes ☐ No ☐
- 6e Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence? Yes ☐ No ☐

TOBACCO OR TOBACCO PRODUCTS (answer without regard to relevance to the subject of the meeting or work)

Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity? Yes ☐ No ☐

EXPLANATION OF "YES" RESPONSES: If the answer to any of the above questions is "yes", check above and briefly describe the circumstances on this page. If you do not describe the nature of an interest or if you do not provide the amount or value involved where relevant, the conflict will be assumed to be significant.

| Nos. 1 - 4: Type of interest, question number and category (e.g., Intellectual Property 4.a copyrights) <u>and</u> basic descriptive details. | Name of company, organization, or institution | Belongs to you, a family member, employer, research unit or other? | Amount of income or value of interest (if not disclosed, is assumed to be significant) | Current interest (or year ceased) |
|--|---|--|--|-----------------------------------|
| | | | | |
| Nos. 5-8: Describe the subject, specific circumstances, parties involved, time frame and other relevant details | | | | |

CONSENT TO DISCLOSURE. By completing and signing this form, you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product.

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information, I will promptly notify the responsible staff of WHO and complete a new declaration of interest form that describes the changes. This includes any change that occurs before or during the meeting or work itself and through the period up to the publication of the final results or completion of the activity concerned.

Date: _____

Signature _____



CONFIDENTIALITY UNDERTAKING

1. Commercial, academic and other research institutions and individual scientists often submit or present for discussion by committees or groups of WHO on research, products and processes (hereafter referred to as "Information") which the institutions and individuals consider proprietary. To help ensure the appropriate use by WHO of such Information whilst protecting the institutions' or individual's proprietary rights, WHO undertakes to release such Information only to persons who have signed this agreement.
2. Information submitted by such institutions or individuals through WHO to committees or groups for review, discussion or comment, whether at meetings, on internet-based collaborative workspaces, during telephone conferences or otherwise, shall be regarded by the Undersigned as confidential, unless clearly stated otherwise, by the institution, individual concerned and/or the WHO Secretariat.
3. The Undersigned undertakes to treat such confidential Information as proprietary information and agrees not to make copies of it, nor to disclose or use the same in whole or in part.
4. If requested to do so, the Undersigned agrees to return to WHO any and all Information identified as confidential.
5. The Undersigned shall not be bound by confidentiality if he/she is able to demonstrate that the Information:
 - (a) was known to him/her prior to any disclosure to him/her by the institution or individual or WHO;
 - (b) was in the public domain at the time of disclosure by the institution or individual;
 - (c) becomes part of the public domain through no fault of the Undersigned; or
 - (d) becomes available to the Undersigned from a third party not in breach of any legal obligations of confidentiality to the institution, individual or WHO.
6. This Confidentiality Undertaking is valid during the entire time the Undersigned participates in the work of the committee or group, in whatever capacity, and for a period of ten (10) years thereafter.

Signed:

Signature.....

Name.....
(print or type)

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

Purpose and decision to establish a SAGE Working Group

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

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

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

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

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

Working Group composition and selection of membership

Each Working Group should include two or more SAGE members (one of whom functions as Chair), and additional subject matter experts serving in their own individual capacity and with a view to meet the identified needed expertise for the group. SAGE members and other experts who have identified conflicts of interest cannot serve on the Working Group charged with responsibility in the identified areas of conflict. WHO staff (one of whom functions as the Working Group technical lead serve as secretariat to the Working Group. In some instances other UN or non UN agencies can be co-opted as part of the secretariat. For the selection of experts to serve on a Working Group, a public call for nomination for Working Group members will be posted on the SAGE website together with the relevant TORs of the Working Group and indication of the desirable expertise. SAGE members, regional offices, diplomatic missions, WHO staff and key partner organizations will also be approached to propose potential nominations. Nominees will be requested to provide both a Curriculum Vitae and a completed Declaration of Interests form prior to being considered for membership on the Working Group.

The selection panel, comprised of the SAGE Chair (or Vice-Chair), the Working Group Chair, the SAGE Executive Secretary and lead WHO technical staff will select Working Group members from the pool of nominees. In addition to meeting the required expertise and avoidance of nominating individuals with conflicts of interest, attention will be given to ensure proper diversity including geographic and gender representation. In general, Chairs of regional technical immunization advisory groups are not eligible to serve on SAGE Working Groups. Should experts be appointed as Chair of a regional technical immunization advisory group after their nomination as member of a Working Group and for SAGE members while still serving on the group after they rotate out of SAGE, they may continue to serve on the Working Group.

For Working Groups which terms of reference require proceedings over a number of years, if a SAGE member rotates out of SAGE while the Working Group is still active, then he/she remains on the Working Group but a new SAGE member should be enrolled to serve on the group. A new SAGE member should be appointed as Working Group Chair when the previous Chair rotates out of SAGE. For Working Groups having proceedings spanning over a number of years, the same rotation process as applied to SAGE membership should be applied i.e. two 3-year terms. The renewal is being determined by a selection panel comprised of the SAGE Chair (or Vice-Chair), the Working Group Chair, lead WHO technical staff and the SAGE Executive Secretary and is based on the contribution of the member to the group. If members resign for personal reasons, are no longer eligible to serve on the group due to arising conflicts of interest, or are unable to meaningfully contribute to the proceedings of the group, they can be replaced with first considering an appointment from the list of initial candidates to join the group. The decision will be made as for the selection of candidates (see above). If no one from this list is suitable then another expert could be solicited and co-opted without resourcing to an open call for nomination.

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

On rare occasions joint reviews of evidence by SAGE and another area WHO advisory committee (focusing on another area than immunization but with expertise and relevance to the topic being considered) may have to be organized. As a result a SAGE Working Group may be formed in conjunction with this other solicited advisory committee. In this instance members of the solicited

advisory committee might also be co-opted on the Working Group and a Working Group co-Chair may be appointed from among members of this other advisory committee. In this case, the selection of Working Group members will equally involve the Chair and secretariat of the solicited advisory committee.

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

Working Group Process

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

All proposed recommendation and comprehensive evidence in support of recommendations including GRADE tables and evidence to decision tables should be presented to SAGE.

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

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

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

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

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

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

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

Management of Conflict of Interest

The value and impact of SAGE recommendations and WHO policy recommendations are critically dependent upon public trust in the integrity of the process. Reported interests are assessed and managed according to SAGE procedures. A summary of the declared interests is publicly posted on the SAGE website in conjunction with the Working Group's TORs and composition (http://www.who.int/immunization/sage/working_mechanisms/en/). Members are expected to proactively inform WHO on any change in relevant interests. These will then be thoroughly assessed by the Working Group Chair, the SAGE Executive secretary as well as the Chair of SAGE. In case of a constituted conflict of interest, the selection panel will meet (see above) to determine a replacement. Should the declared change not result in a conflict of interest, the Working Group member will be able to remain on the Working Group. In both cases, the posted summary will be updated accordingly.



CURRENT SAGE WORKING GROUPS

Disclaimer: this list includes the current working groups and their active members. These working groups are listed in the order in which they were established. For the complete history of current and previous working groups and their membership from inception, please visit the SAGE website

(http://www.who.int/immunization/sage/working_mechanisms/en/).

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

Terms of Reference

1. Prepare SAGE for the development of comprehensive policy guidance on the use of IPV in the post-eradication era in low and middle income settings, including by:
 - Reviewing long-term Polio Risks & Risk Management Strategies: reviewing the long-term risks associated with live polioviruses after wild polio transmission globally, and reviewing the range of strategies for mitigating those risks in low-income settings (e.g. coordinated OPV cessation, mOPV stockpiles and response mechanism).
 - Assessing Current & Future IPV Products: reviewing the existing range of IPV products, in terms of supply capacity, production cost, price, presentations, etc. and their appropriateness and suitability for low-income settings, particularly sub-Saharan Africa; and studying the IPV 'pipeline' and its implications for post-eradication IPV use in terms of potential new products (e.g. Sabin-IPV, adjuvanted-IPV, fractional dose IPV), production costs, and prices.
 - Establishing Potential IPV Policies & Implications: establishing the range of IPV vaccination schedule options that could be utilized in a post-eradication world, given the difference in polio immunization objectives and polio risks compared with a polio-endemic world; and identifying and characterizing the programmatic implications, economics and opportunity costs of those policy options, for both IPV stand-alone and combination formulations, in low-income settings and particularly sub-Saharan Africa;
 - Identifying and prioritizing knowledge gaps that should be addressed to facilitate SAGE decision-making on the role(s) and options for IPV use in the post-eradication era in low-income settings.
2. Propose key recommendations to SAGE for updating the 2003 position paper on IPV and consolidating it with other relevant documents (including the 2006 supplement to the IPV position paper) into one vaccine position paper on routine polio immunization covering both IPV and OPV and giving consideration to the ongoing polio eradication efforts.
3. Advise SAGE on technical guidance to WHO and the GPEI for the development and finalization of the overall polio eradication 'endgame strategy' to reduce long-term risks associated with OPV and to accelerate wild poliovirus eradication, including:
 - Policy and programmatic options for the use of different OPV formulations and IPV delivery options, and
 - Strategy and priorities in the related areas of outbreak response, surveillance, containment, risk assessment (esp. Vaccine Derived Polio Viruses - VDPVs), research and product development, and vaccine supply.

Composition

SAGE Members

- Yagob Al-Mazrou: Health Services Council, Saudi Arabia. (Chair of the Working Group from September 2015)
- Ilesh Jani: National Institute for Health, Mozambique. (Member of the Working Group from October 2016)
- Youngmee Jee: Korean Centre for Disease Control and Prevention, Republic of Korea. (Member of the Working Group from October 2016)

Experts

- Zulfiqar Bhutta: The Aga Khan University, Pakistan. (Member of the Working Group from Nov 2012 and SAGE member until April 2015)
- Peter Figueroa: University of the West Indies, Jamaica. (Chair of the Working Group until August 2015 and SAGE member until April 2015)
- Walter Dowdle: Task Force for Child Health, United States of America.
- Nick Grassly: Imperial College, United Kingdom.
- Jacob John: Christian Medical College, India.
- Elizabeth Miller: Public Health England, United Kingdom. (Chair of the Working Group until February 2014 and SAGE member until November 2013)
- Jeffery Mphahlele: South African Medical Research Council, South Africa. (Member of the Working Group from October 2016)
- Walter Orenstein: Emory University, United States of America.
- Kimberley Thompson: Harvard University, United States of America.
- Khalequzzaman Zaman: International Centre for Diarrhoeal Disease Research, Bangladesh. (Member of the Working Group from October 2016)

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

Terms of Reference

- Review progress towards global measles control targets and regional measles and rubella elimination goals and highlight key obstacles.
- Prepare for regular updates and review by SAGE on progress and challenges in achieving existing measles and rubella control targets and propose necessary updating of current WHO recommendations on vaccines (including outbreak response immunization) and surveillance strategies.
- Identify gaps in essential evidence and programme barriers to achieving measles and rubella/CRS elimination targets and present SAGE with proposed areas for operational or basic science research. The working group will liaise with other relevant technical advisory committees (e.g. Immunization and vaccines related implementation research advisory committee (IVIR-AC), and the Immunization Practice Advisory Committee (IPAC)) to address relevant quantitative issues as well as those related to immunization practices.
- Explore the potential use of new technologies that could help improve coverage and thereby expedite elimination of measles/rubella.
- Advise SAGE, no later than 2020, whether a formal global goal for measles eradication and/or rubella eradication should be set with timeframes for its achievement.

Composition

SAGE Members

- Nikki Turner: University of Auckland, New Zealand. (Chair of the Working Group from October 2016)
- Ilesh Jani: National Institute for Health, Mozambique. (Member of the Working Group from October 2015)
- Jaleela Sayed Jawad, Ministry of Health, Kingdom of Bahrain (Member of the Working Group since January 2017, SAGE Member since 2015).
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Experts

- Narendra Arora: International Clinical Epidemiology Network, India. (Chair of the Working Group until September 2016 and SAGE member until April 2016)
- Natasha Crowcroft: Public Health Ontario, Canada (Member of the Working Group since November 2011).
- David Durrheim: Hunter New England Area Health Service, Australia (Member of the Working Group since November 2011, SAGE Member 2009 - 2012).
- Mark Jit: London School of Hygiene and Tropical Medicine, UK (Member of the Working Group since January 2017)
- Susan Reef: Centers for Disease Control and Prevention, United States of America (Member of the Working Group since November 2011).
- Helen Rees: University of Witwatersrand, South Africa. (former SAGE Chair 2010 - 2013)
- William Moss: Johns Hopkins University, United States of America.
- Walter Orenstein: Emory University School of Medicine, USA (Member of the Working Group since January 2017)

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

Terms of Reference

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

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

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

Updated: March 2018

Composition

SAGE Members

- Noni MacDonald: Dalhousie University, IWK Health Centre, Canada. (Chair of the Working Group of June 2017 to replace Narendra Arora)
- Yagob Al-Mazrou: Health Services Council, Saudi Arabia.

Experts

- Oleru Huda Abason: Parliament of Uganda, Uganda. (Member of the Working Group from May 2016)
- Mahmoud Mustafa Amani: The Carter Center, Sudan.
- Jon Kim Andrus: Sabin Vaccine Institute, United States of America. (Member of the Working Group from May 2016)
- Narendra Arora: International Clinical Epidemiology Network, India. (Chair of the Working Group until May 2017 and SAGE member until April 2016)
- Susan Elden: Department for International Development, United Kingdom. (Member of the Working Group from May 2016)
- Marie-Yvette Madrid: Independent Consultant, Switzerland.
- Rebecca Martin: Centers for Disease Control and Prevention, United States of America.
- Helen Rees: University of Witwatersrand, South Africa. (former SAGE Chair 2010 - 2013)
- David Salisbury: Centre on Global Health Security, United Kingdom. (former SAGE Chair 2005 - 2010)
- Budihardja Singgih: Australia Indonesia Partnership for Health Systems Strengthening, Indonesia. (Member of the Working Group from May 2016)
- Qinqian Zhao: Xiamen University, China. (Member of the Working Group from May 2016)

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

Terms of Reference

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

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

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

Composition

SAGE Members

- Fred Were: University of Nairobi, Kenya. (Co-Chair of the Working Group from April 2016)
- Charles Wiysonge: Stellenbosch University, South Africa
- Kate O'Brien: Johns Hopkins University, United States of America.

Experts

- Nick Andrews: Public Health England, United Kingdom.
- George Bonsu: Ministry of Health, Ghana.
- David Durrheim: Hunter New England Area Health Service, Australia. (SAGE member until April 2012)
- Ann Kelly: University of Exeter, United Kingdom.
- Jesse Goodman: Georgetown University, United States of America (resigned from Working Group in January)

Updated: March 2018

2017).

- Jean-Paul Jemmy: Médecins Sans Frontières, Belgium.
- Keymanthri Moodley: Stellenbosch University, South Africa.
- Cesar Velasco Muñoz: Hospital Clínico Lozano Blesa, Spain.
- Diop Ndack: University Cheikh Anta Diop, Senegal.
- Chris Ockenhouse: PATH, United States of America.
- Helen Rees: University of Witwatersrand, South Africa. (Co-Chair of the Working Group and former SAGE Chair 2010 - 2013)
- Oyewale Tomori: Redeemer's University, Nigeria. (Co-Chair of the Working Group until March 2016 and SAGE member until April 2015)

Ex-Officio members

- Chris Morgan: Chair of WHO Immunization Practices Advisory Committee (IPAC).
- K. Cichutek: Chair of WHO Expert Committee on Biological Standardization (ECBS).
- Robert Breiman: Chair of WHO Immunization and Vaccines Related Implementation Research Advisory committee (IVIR-AC).
- Robert Pless: Chair of WHO Global Advisory Committee on Vaccine Safety (GACVS). (Ex-Officio member of the Working Group from December 2015)

5. SAGE Working Group on Typhoid Vaccines (established March 2016)

Terms of reference

The Working Group will be requested to review the scientific evidence and relevant programmatic considerations to formulate updated recommendations on the use of typhoid vaccines, with a focus on typhoid conjugate vaccines (TCVs). The proposed recommendations will be submitted for consideration by SAGE for revision of the global policy on typhoid vaccine use, and for subsequent updating of the WHO Position Paper on typhoid vaccines (2010). Publication of an updated position paper on typhoid vaccines is tentatively scheduled for 2018.

Specifically, the Working Group will review evidence on:

1. The epidemiology and burden of disease caused by *S. Typhi* and implications for control, including risk factors, diagnostics and other issues related to typhoid surveillance and better understanding of the disease epidemiology;
2. Trends in antimicrobial resistance and implications for the control of typhoid fever;
3. The safety, immunogenicity profile, effectiveness, duration of protection and indications for booster doses of TCVs in the context of existing typhoid vaccines;
4. The optimum schedule and age of administration as well as delivery strategies for typhoid vaccines; including administration of TCVs to children under 2 years of age;
5. The economic burden of typhoid fever and cost-effectiveness of vaccination (including vaccination in the context of other control strategies); and
6. Considerations for the use of typhoid vaccines in endemic as well as epidemic or emergency settings.

Composition

SAGE Members

- Ilesh Jani: National Institute for Health, Mozambique. (Chair of the Working Group)
- Kari Johansen: European Centre for Disease Prevention and Control, Sweden.

Experts

- Narendra Arora: International Clinical Epidemiology Network, India. (SAGE member until April 2016)
- Zulfiqar Bhutta: The Aga Khan University, Pakistan. (SAGE member until April 2015)
- John A. Crump: University of Otago, New Zealand.
- Myron Levine: University of Maryland, United States of America.
- Dafrossa Lyimo: Ministry of Health, United Republic of Tanzania.
- Florian Marks: International Vaccine Institute, Republic of Korea.
- Mark Miller: National Institutes of Health, United States of America.
- Christopher Parry: London School of Hygiene and Tropical Medicine, United Kingdom.
- Richard Strugnell: University of Melbourne, Australia.
- Dipika Sur: retired (former National Institute of Cholera and Enteric Diseases, India).

6. SAGE Working Group on rabies vaccines and rabies immunoglobulins (established July 2016)

Terms of reference

The Working Group is requested to review the scientific evidence and relevant programmatic considerations, to formulate proposed recommendations on the use of rabies vaccines and immunoglobulins.

Updated: March 2018

Specifically the Working Group will be asked to review the following elements:

1. Assess evidence and country practices in the use of human rabies vaccine and rabies immunoglobulins (RIG), including that of targeted vaccination of high risk communities in rural settings;
2. Review the new evidence on the need for pre-exposure prophylaxis (PREP) booster doses and the cost-effectiveness of the interventions;
3. Assess the most recent evidence on the potential shortening of post-exposure prophylaxis (PEP) schedules and new regimens;
4. Review the evidence and revisit the current WHO position for RIG and monoclonal antibody use with the view to improve access to care and increase public health impact;
5. Assess the implementation and evidence of the current recommendation on intradermal use of cell culture-derived vaccines (CCV);
6. Economic burden of rabies and cost-effectiveness of vaccination as well as modelling data should be assessed to inform rabies vaccination strategies (including vaccination in the context of other control strategies);
7. Consideration should be given to new vaccines in different phases of clinical trials or in the process of obtaining WHO prequalification and/or national market authorization by mid/end 2016.

Composition

SAGE Members

- Kate O'Brien: Johns Hopkins University, United States of America. (Chair of the Working Group)
- Terry Nolan: University of Melbourne, Australia.

Experts

- Ahmed Be-Nazir: National Institute of Preventative and Social Medicine, Bangladesh.
- Arnaud Tarantola: Institut Pasteur, Cambodia.
- Deborah Briggs: Kansas State University, United States of America.
- Gade Sampath: Institute of Preventative Medicine, India.
- Henry Wilde: Chulalongkorn University, Thailand.
- Lucille Blumberg: National Institute for Communicable Diseases, South Africa.
- Luzia Queiroz: University of Sao Paulo State, Brazil.
- Mary Warrell: University of Oxford, United Kingdom.
- Mathurin Cyrille Tejiokem: Centre Pasteur, Cameroon.
- Naseem Salahuddin: The Indus Hospital, Pakistan.

7. SAGE Working Group on pneumococcal conjugate vaccine (established December 2016)

Terms of Reference

1. Review and summarize the measured and modelled evidence on PCV immunogenicity and impact (direct and indirect) on carriage, disease, and mortality with respect to the following questions/issues:
 - a. Effectiveness and/or impact of different schedules and strategies for PCV use in industrialized and developing countries;
 - b. Preference of 2p+1 or 3p+0 schedule for current or future impact
 - c. Choice of PCV products;
 - d. Catch-up vaccination of infants and/or older age groups during PCV introduction;
 - e. Maximize herd protection;
 - f. Optimize duration of protection.
2. Propose to SAGE recommendations on optimal PCV use related to the above listed questions and issues in order to revisit the 2012 WHO PCV position paper.
3. Identify and prioritize knowledge gaps and critical questions to prepare a concrete scope of work with a proposed timeline for future PCV working group activities. The following questions/issues will likely be included:
 - a. Serotype replacement in the era of extended valency conjugate vaccines;
 - b. Options for optimal PCV use in the future, including in settings of near-elimination levels of vaccine serotype disease;
 - c. PCV use in adults, including the elderly;
 - d. Incremental benefit of the polysaccharide vaccine in adults in era of PCV use.
4. Provide SAGE with summaries and analyses needed to support its discussion and recommendation process.

Composition

SAGE Members

- Andrew J. Pollard: University of Oxford, United Kingdom (Chair of the Working Group)
- Kate O'Brien: Johns Hopkins Bloomberg School of Public Health, United States of America

Experts

- Narendra Arora: The INCLIN Trust International, New Delhi

Updated: March 2018

- Stefan Flasche: London School of Hygiene & Tropical Medicine, United Kingdom
- Kyung-Hyo Kim: Ewha Womans University School of Medicine, Republic of Korea
- David Goldblatt: University College London, United Kingdom
- Elisabeth Lieke Sanders¹: National Institute for Public Health and the Environment, The Netherlands
- Dafrossa Lyimo: Ministry of Health, Tanzania
- Elizabeth Miller: Public Health England, United Kingdom
- Edward Kim Mulholland: Murdoch Childrens Research Institute, Australia
- Tamara Pilishvili: Centers for Disease Control and Prevention, United States of America
- Betuel Sigauque: Manhica Health Research Centre, Mozambique
- Cristiana Toscano: Federal University of Goiás, Brazil

8. SAGE Working Group on Quality and Use of Global Immunization and Surveillance Data (established August 2017)

Terms of Reference

The Working Group will be requested to review the current global immunization and surveillance data collection, its use and impact as well as limitations and needs and propose recommendations to improve quality, access to, and use of immunization data for enhancing immunization programme performance at national and subnational levels. These recommendations will then be presented for review by SAGE.

1. Take stock of data availability and determine if there are unmet immunization monitoring and evaluation data needs at global level, and guide reporting processes;
2. Review existing and new draft standards and guidance on immunization monitoring and vaccine-preventable disease (VPD) surveillance data to identify gaps, revisions, and areas that require updates;
3. Review and assess the current 'state' of immunization and VPD-surveillance data quality at country and global level;
4. Review evidence on:
 - 1) factors that may cause and/or limit access to quality and use of immunization and VPD-surveillance data for decision-making at different levels;
 - 2) the effectiveness (including where possible, cost-effectiveness) of interventions for improving access to, improving quality of, or promoting the use of data at national and subnational levels;
5. Review the status of information systems that collect immunization and VPD-surveillance data, the availability of modern information technologies, and their current and potential future role in supporting the collection, management, analysis and use of immunization and surveillance data;
6. Identify knowledge gaps and create a prioritized research agenda.

It is anticipated that the Working Group will complete its reporting to SAGE by April 2019.

Composition

SAGE Members

- Jaleela Jawad: Ministry of Health, Bahrain (Chair of the Working Group)
- Noni MacDonald: Dalhousie University, IWK Health Centre, Canada

Experts

- George Bonsu: Ghana Health Service, Ghana
- Michael Edelstein: Public Health England, United Kingdom
- Hashim Ali Elzein Elmousaad: Independent Consultant, Pakistan
- Pradeep Haldar: Ministry of Health and Family Welfare, India
- Claudio Lanata: Instituto de Investigacion Nutricional, Peru
- Ana Morice: Independent Consultant, Costa Rica
- Mimi Mynak: Jigme Dorji Wangchuk National Referral Hospital, Ministry of Health, Bhutan
- Edward Nicol: South African Medical Research Council; Stellenbosch University, South Africa
- Su Qiru: Chinese CDC, China
- Nargis Rahimi: Shifo Foundation, Sweden
- Heather Scobie: Centers for Disease Control and Prevention, United States of America

9. SAGE Working Group on Influenza (established December 2017)

Terms of Reference

The Working Group will be requested to review the scientific evidence and relevant programmatic considerations to assess whether there is sufficient evidence to inform a revision of the global policy on the use of influenza vaccines, and for subsequent updating of the WHO position paper on influenza vaccines.

Updated: March 2018

Specifically the Working Group will be asked to review the following elements:

1. the evidence on the effect of prior immunization on the efficacy and effectiveness of seasonal influenza vaccines, and whether a change in policy would result in improved public health outcomes
2. the evidence on the effectiveness of adjuvanted seasonal influenza vaccines in pediatric populations
3. the evidence on the effectiveness of improved formulations for influenza vaccines for older adults and other risk groups
4. the evidence on the effectiveness of live attenuated influenza vaccines.

Composition

SAGE members

- Rakesh Aggarwal: Institute of Medical Sciences, Lucknow, India
- Andrew J. Pollard: University of Oxford, United Kingdom (Chair of the Working Group)

Experts

- Jon Abramson: Wake Forest Baptist Health, USA;
- Joseph Bresee: Centers for Disease Control and Prevention, USA;
- Cheryl Cohen: National Institute of Communicable Diseases, South Africa;
- Rebecca J. Cox: University of Bergen, Norway;
- Luzhao Feng: Chinese Center for Disease Control and Prevention, China;
- Kawsar Talaat: Johns Hopkins Bloomberg School of Public Health, USA;
- Hanna Nohynek: National Institute for Health and Welfare, Finland;
- Richard Pebody: Public Health England, United Kingdom;
- Sheena Sullivan: WHO Collaborating Centre for Reference and Research on Influenza, Australia;
- Bryna Warshawsky: Public Health Ontario; Ontario Agency for Health Protection and Promotion, Canada;
- Maria Zambon: Public Health England, United Kingdom.

10. Reconvened SAGE Working Group on Dengue Vaccines and Vaccination (established December 2017)

Terms of Reference

The reconvened Dengue Working Group is asked to review new data on the long-term follow-up of dengue vaccine recipients. This includes data generated by further laboratory testing and analysis related to the long-term safety and efficacy of CYD-TDV Phase 3 trial participants. In particular, the group is asked to review the differential performance of the CYD-TDV vaccine (also known as Dengvaxia®) in subjects seronegative versus seropositive at the time of vaccination. The group is asked to advise on a revision of WHO's current vaccine recommendations as published in July 2016. The review at SAGE is tentatively scheduled for April 2018. This will lead to the publication of an amended WHO position paper on the use of a dengue vaccine, which will replace the interim recommendation issued by WHO on 22 Dec 2017 (WHO interim position on the use of Dengvaxia®)

The Working Group will specifically be asked to review data relating to:

- the long-term safety, efficacy, immunogenicity profile and benefit/risk assessment of Dengvaxia stratified by serostatus
- the schedule, age of administration, and potential vaccination strategies for targeting vaccination to individuals seropositive to dengue at the time of vaccination
- the disease impact of dengue immunization programs identification of key data gaps and additional critical issues that need to be considered in drafting amended recommendations to SAGE

Composition

The working group is composed of its previous members, and additional ad hoc experts in accordance to the terms of reference

SAGE members

- Terry Nolan, (Co-Chair of the Working Group), Melbourne School of Population and Global Health, Australia
- Kate O'Brien (Member of the Working Group), Johns Hopkins International Vaccine Access Center (IVAC), Baltimore, USA

Experts

- Jeremy Farrar, (Co-Chair of the Working Group), Wellcome Trust, UK
- Piyani Tharmaphornpilas, Ministry of Public Health, Thailand
- Alan Barrett, University of Texas Medical Branch, USA
- Elizabeth Ferdinand, University of the West Indies, Barbados
- Maria Guzman, Pedro Kouri Tropical Medicine Institute, Cuba
- Maria Novaes, Universidade de São Paulo, Brazil
- Lee Ching Ng, National Environment Agency, Singapore
- Peter Smith, London School of Hygiene and Tropical Medicine, UK
- Ad hoc experts
- Stefan Flasche, London School of Hygiene and Tropical Medicine, UK
- In-Kyu Yoon, International Vaccine Institute, South Korea

Updated: March 2018

**Strategic Advisory Group of Experts (SAGE) on Immunization
17 - 18 April 2018
Centre International de Conférences, (CICG), Geneva, Switzerland**

Provisional list of participants as of 28 March 2018

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Contents

729 Meeting of the Strategic Advisory Group of Experts on immunization, October 2017 – conclusions and recommendations

Sommaire

729 Réunion du Groupe stratégique consultatif d'experts sur la vaccination, octobre 2017 - conclusions et recommandations

Meeting of the Strategic Advisory Group of Experts on immunization, October 2017 – conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on Immunization¹ met on 17–19 October 2017. This report summarizes the discussions, conclusions and recommendations.²

Report from the WHO Department of Immunization, Vaccines and Biologicals

The report focused on the theme “Closing the immunization gap: evidence and the use of data to close the gap”. It included an update on disease impact data, with particular focus on the achievements from use of measles-containing vaccines (MCV), capsular group A meningococcal conjugate vaccine, *Haemophilus influenzae* type b (Hib) vaccines and pneumococcal conjugate vaccines (PCV). An estimated 20 million measles deaths have been averted by use of MCV between 2000 and 2016, nevertheless more than 100 000 measles deaths still occur annually. Since the introduction of the group A meningococcal vaccine in the African meningitis belt in 2011, around 300 million persons have been vaccinated through mass campaigns and routine immunization, with an estimated 300 000 meningitis cases and 30 000 deaths averted. Hib vaccines have averted 1.2 million deaths since 2000, and notably since the SAGE recommendation on inclusion of conjugate Hib vaccines into all routine infant immunization programmes in 2006. PCV uptake has accelerated, and recent esti-

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, octobre 2017 – conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination¹ s'est réuni du 17 au 19 octobre 2017. Le présent rapport résume ses discussions, ses conclusions et ses recommandations.²

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

Ce rapport est axé sur le thème: Combler les lacunes vaccinales: éléments et exploitation de ces éléments à cette fin. Il inclut une mise à jour des données d'impact des maladies, consacrée principalement aux résultats de l'utilisation de vaccins à valence rougeole (MCV), du vaccin conjugué contre le méningocoque du groupe capsulaire A, des vaccins contre *Haemophilus influenzae* type b (Hib) et de vaccins antipneumococciques conjugués (VPC). On estime que 20 millions de décès par rougeole ont été évités entre 2000 et 2016 grâce à l'emploi du MCV, néanmoins >100 000 décès imputables à la rougeole interviennent encore chaque année. Depuis l'introduction du vaccin antiméningococcique A dans la région africaine de la ceinture de la méningite en 2011, environ 300 millions de personnes ont été vaccinées dans le cadre de campagnes de vaccination de masse et de la vaccination systématique et 30 000 décès ont été empêchés. Les vaccins anti-Hib ont permis d'éviter 1,2 million de décès depuis 2000, et notamment depuis la recommandation du SAGE invitant à inclure des vaccins anti-Hib conjugués dans tous les programmes de vaccination systématique des nourrissons en 2006. La mise

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¹ See www.who.int/immunization/sage/en/index.html, accessed October 2017.

² Presentations and background materials used for the SAGE meeting together with the list of SAGE members and summarized declarations of interests are available at www.who.int/immunization/sage/meetings/2017/october/en/, accessed October 2017.

¹ Voir <http://www.who.int/immunization/policy/sage/fr/>, consulté en octobre 2017.

² Les présentations et les documents de référence utilisés pour la réunion du SAGE, ainsi que la liste des membres de ce groupe et les résumés de leurs déclarations d'intérêts, sont disponibles à l'adresse: www.who.int/immunization/sage/meetings/2017/october/en/, consulté en octobre 2017.

mates suggest that around 100 000 deaths are prevented annually. PCV has now been introduced into national immunization programmes in a majority of countries, though global coverage has not yet reached 50%. The report highlighted the potential impact of PCV on reduction of antimicrobial resistance in circulating *Streptococcus pneumoniae* strains.

The report included discussion of vaccination coverage data, focussing on subnational data from 2016. WHO and UNICEF have issued subnational data for the first time. Subnational data were reported by 140 countries, of which 94 reported data from second administrative (district) level. It was noted that data quality needs to be further improved and validated; a SAGE Working Group on Quality and Use of Global Immunization and Surveillance Data has been set up to assist with this task.³ Although children in many countries still do not receive all of the recommended vaccines, coverage is increasing. Hepatitis B and Hib vaccination coverage rates have almost reached that of vaccines such as diphtheria, tetanus and pertussis vaccines, which have been in routine use for many years. The absolute number of vaccinated children has steadily increased in recent years, although vaccination coverage has not increased at the same rate as population growth. Nearly 20 million children still remain under-immunized, including an estimated 13 million who were never vaccinated and 7 million who started vaccination but dropped out before receiving a third dose of diphtheria-tetanus-pertussis vaccine (DTP3).

Fragile countries, and those in conflict, account for the majority of the under/unvaccinated children, while countries with stable environments are progressing towards the Global Vaccine Action Plan (GVAP) goal of 90% DTP3 coverage. Vaccination coverage rates do not differ by sex, but subnational urban-rural and rich-poor disparities are reported in many countries.⁴ The Global Routine Immunization Strategies and Practices (GRISP) has highlighted the areas that require attention and investment to respond to the challenges of vaccination under-performance, and guidance documents and initiatives have been developed to support improvement plans.⁵ WHO has issued guidance on improving access to vaccination in humanitarian emergency situations, introducing the Humanitarian Mechanism for vaccine procurement at the lowest cost.⁶

en œuvre des VPC s'est accélérée et des estimations récentes laissent à penser qu'autour de 100 000 décès sont prévenus grâce à ces vaccins chaque année. Des VPC ont maintenant été introduits dans les programmes nationaux de vaccination d'une majorité de pays, même si la couverture mondiale n'a pas encore atteint 50%. Le présent rapport met en lumière l'effet potentiel de réduction par les VPC de la résistance aux antimicrobiens des souches circulantes de *Streptococcus pneumoniae*.

Ce rapport contient aussi une discussion de données de couverture vaccinale portant principalement sur des données infranationales de 2016. L'OMS et l'UNICEF ont publié des données infranationales pour la première fois. Ces données infranationales avaient été rapportées par 140 pays, parmi lesquels 94 avaient fourni des données émanant du deuxième niveau administratif (district). Il a été noté que la qualité des données devait être encore améliorée et validée; un groupe de travail du SAGE sur la qualité et l'utilisation des données mondiales de vaccination et de surveillance a été constitué pour aider dans cette tâche.³ Bien que dans de nombreux pays, les enfants ne reçoivent pas encore tous les vaccins recommandés, la couverture est en augmentation. Les taux de couverture vaccinale contre l'hépatite B et contre Hib ont presque atteint ceux de vaccins comme les vaccins antidiphtériques, antitétaniques et anticoquelucheux, qui font l'objet d'une administration systématique depuis de nombreuses années. Le nombre absolu d'enfants vaccinés s'est accru fortement au cours des dernières années, même si la couverture vaccinale n'a pas augmenté au même rythme que la croissance démographique. Près de 20 millions d'enfants restent encore sous-vaccinés, parmi lesquels 13 millions n'ont jamais été vaccinés et 7 millions ont commencé à l'être, sans pour autant recevoir la troisième dose de vaccin antidiphtérique-antitétanique-anticoquelucheux (DTC3).

Les pays fragiles ou soumis à des conflits réunissent la majorité des enfants sous- ou non vaccinés, tandis que les pays bénéficiant d'environnements stables progressent vers l'objectif du Plan mondial d'action pour les vaccins (GVAP), consistant à atteindre une couverture par le DTC3 de 90%. Les taux de couverture vaccinale ne diffèrent pas en fonction du sexe, mais des disparités entre populations urbaines/rurales ou riches/pauvres au niveau infranational sont rapportées par de nombreux pays.⁴ Les stratégies et pratiques mondiales de vaccination systématique (SPMVS) ont mis en lumière les domaines nécessitant plus particulièrement de l'attention et des investissements pour répondre aux problèmes de sous-performance de la vaccination et des documents d'orientation et des initiatives ont été mises au point pour appuyer les plans d'amélioration.⁵ L'OMS a publié des orientations pour améliorer l'accès à la vaccination dans les situations d'urgence humanitaire, en introduisant l'Humanitarian Mechanism for vaccine procurement at the lowest cost.⁶

³ WHO SAGE Working Group Quality and Use of Global Immunization and Surveillance Data. Available at www.who.int/immunization/policy/sage/sage_wg_quality_use_global_imm_data/en/, accessed October 2017.

⁴ State of inequality: childhood immunization. World Health Organization, Geneva, 2016. Available at www.who.int/gho/health_equality/report_2016_immunization/en/, accessed October 2017.

⁵ Global Routine Immunization Strategies and Practices (GRISP). World Health Organization, Geneva, 2016. Available at http://apps.who.int/iris/bitstream/10665/204500/1/9789241510103_eng.pdf, accessed October 2017.

⁶ Vaccination in humanitarian emergencies. World Health Organization, Geneva, 2017. Available at www.who.int/immunization/programmes_systems/policies_strategies/vaccination_humanitarian_emergencies/en/, accessed October 2017.

³ WHO SAGE Working Group Quality and Use of Global Immunization and Surveillance Data. Disponible à l'adresse: www.who.int/immunization/policy/sage/sage_wg_quality_use_global_imm_data/en/, consulté en octobre 2017.

⁴ State of inequality: childhood immunization. Organisation mondiale de la Santé, Genève, 2016. Disponible à l'adresse: www.who.int/gho/health_equality/report_2016_immunization/en/, consulté en octobre 2017.

⁵ Stratégies et pratiques mondiales de vaccination systématique (GRISP). Organisation mondiale de la Santé, Genève, 2016. Disponible à l'adresse: http://apps.who.int/iris/bitstream/10665/206454/1/9789242510102_fre.pdf, consulté en octobre 2017.

⁶ Global Routine Immunization Strategies and Practices (GRISP). Organisation mondiale de la Santé, Genève, 2016. Disponible à l'adresse: www.who.int/immunization/programmes_systems/policies_strategies/GRISP/en/, consulté en octobre 2017.

The WHO African Region (AFR) reported on the midterm evaluation of the regional strategic plan. Action areas include: (i) leverage of the Addis Declaration on Immunization commitments for better coordination of all stakeholders while promoting stronger country ownership; (ii) focus on large countries where the maximum gains could be achieved in terms of coverage and equity; (iii) investment in system strengthening and community engagement; (iv) expanding the scope of immunization to a life-course approach starting with the implementation of the 2nd year of life platform; (v) harnessing immunization best practice and peer learning; (vi) ensuring adequate immunization financing with special attention to middle-income countries (MICs) which are not GAVI-eligible; and (vii) preparing for smooth polio transition and phasing out of GAVI support.

The WHO Region of the Americas (AMR), having validated the elimination of MNT in Haiti, announced Regional MNT elimination. AMR also reported on the 29th Pan American Sanitary Conference in September 2017, during which 3 main topics were discussed: the midterm review of the Regional Vaccine Action Plan; the plan of action for the sustainability of measles, rubella and congenital rubella syndrome (CRS) elimination; and the challenges of inactivated polio vaccine (IPV) supply and the use of fractional dose IPV.

The WHO European Region (EUR) reported progress on measles and rubella elimination, hepatitis B control, and establishment of national immunization technical advisory groups (NITAGs) which are now established in 45/53 Member States. However the fragility of the immunization gains was also emphasized, as evidenced by a surge in measles cases in the past 12 months. The majority of the under-vaccinated in the Region live in 12 MICs, not eligible for GAVI support, and where routine vaccination coverage is declining. A MIC Ministerial 'Statement of Intent' will be endorsed in early 2018, providing a foundation for a new MIC road map. There is also grave concern regarding the situation in Ukraine, which accounts for >50% of the unvaccinated or under-vaccinated children in the Region and has reported a progressive decline in coverage over the last 5 years. In 2016 it was estimated that DTP3 vaccination coverage fell to 19%, and polio vaccination coverage to 53% in Ukraine.

The WHO South-East Asia Region (SEAR) announced in 2016 that the Region had eliminated maternal and neonatal tetanus (MNT) through improved access of vulnerable high-risk populations to routine immunization and targeted supplementary immunization activities.

The WHO Western Pacific Region (WPR) reported progress in achieving regional immunization goals: (i) sustaining polio-free status; (ii) elimination of measles, rubella and MNT; (iii) accelerating control of hepatitis B and

La Région africaine de l'OMS (AFR) a présenté un rapport sur l'évaluation à mi-parcours du plan stratégique national. Il faudrait notamment agir selon les axes suivants: (i) tirer parti de la déclaration d'Addis-Abeba concernant les engagements en matière de vaccination pour mieux coordonner l'ensemble des parties prenantes, tout en favorisant une meilleure appropriation par les pays; (ii) se focaliser sur les grands pays où l'on pourrait obtenir les gains les plus importants en termes de couverture et d'équité; (iii) investir dans le renforcement des systèmes et l'engagement des communautés; (iv) élargir le champ d'application de la vaccination en adoptant une approche sur la durée de vie qui débute avec la plate-forme de vaccination à deuxième année de vie; (v) maîtriser les meilleures pratiques et l'apprentissage entre pairs; (vi) assurer un financement suffisant de la vaccination, en accordant une attention particulière aux pays à revenu intermédiaire, qui ne peuvent solliciter l'aide de l'Alliance GAVI; et (vii) se préparer à une transition sans heurt pour la vaccination contre la poliomyélite et à une disparition progressive de l'aide de GAVI.

La Région OMS des Amériques (AMR), ayant validé l'élimination du tétanos maternel et néonatal (TMN) en Haïti, a aussi annoncé l'élimination de cette maladie à l'échelle régionale. Lors de la 29^e Conférence sanitaire panaméricaine, en septembre 2017, elle a présenté son rapport, dans lequel 3 sujets principaux étaient abordés: l'examen à mi-parcours du Plan d'action régional pour les vaccins; le plan d'action pour la pérennité de l'élimination de la rougeole, de la rubéole et du syndrome rubéoleux congénital (SRC); et les difficultés d'approvisionnement en vaccin antipoliomyélitique inactivé (VPI) et d'utilisation des doses fractionnées de ce vaccin.

La Région européenne de l'OMS (EUR) a rapporté des progrès dans l'élimination de la rougeole et de la rubéole, la lutte contre l'hépatite B et la mise en place de groupes consultatifs techniques nationaux sur la vaccination (GCTNV), qui sont maintenant établis dans 45 États membres sur 53. Néanmoins, la fragilité des gains en matière de vaccination a aussi été soulignée et se trouve attestée par la recrudescence des cas de rougeole observés au cours des 12 derniers mois. La majorité des individus sous-vaccinés de la région vivent dans les 12 pays à revenu intermédiaire, ne pouvant bénéficier du soutien de l'alliance GAVI, et dans lesquels la couverture par la vaccination systématique est en baisse. Une déclaration d'intention ministérielle pour ces pays sera approuvée début 2018, pour fournir un socle à leur nouvelle feuille de route. La situation de l'Ukraine, qui totalise >50% des enfants non vaccinés et sous-vaccinés de la région et a signalé une diminution progressive de la couverture vaccinale au cours des 5 dernières années, est également gravement préoccupante. Dans ce pays, en 2016, il a été estimé que la couverture vaccinale par le DTC3 avait chuté à 19% et celle par le vaccin antipoliomyélitique à 53%.

La Région OMS de l'Asie du Sud-Est (SEAR) a annoncé en 2016 qu'elle avait éliminé le tétanos maternel et néonatal (TMN) en améliorant l'accès des populations vulnérables à haut risque à la vaccination systématique et en menant des activités de vaccination supplémentaires ciblées.

La Région OMS du Pacifique occidental (WPR) a rapporté des progrès dans la réalisation des objectifs régionaux en matière de vaccination: (i) maintien du statut d'exemption de la poliomyélite; (ii) élimination de la rougeole, de la rubéole et du TMN;

Japanese encephalitis; (iv) improvement of routine vaccination coverage; (v) introduction of new vaccines, and (vi) implementing GVP-recommended strategies and activities in the Region. In 2013–2017, several Member States were affected by resurgence or large-scale outbreaks of measles, polio due to circulating vaccine-derived polio virus (cVDPV), rubella, diphtheria, and pertussis. Detailed epidemiologic analysis of these outbreaks has helped Member States and WHO to identify high-risk areas and groups, and immunity gaps in different populations.

Report from GAVI, the Vaccine Alliance

GAVI acknowledged the importance of SAGE in providing policy and technical guidance to inform GAVI's programme design and to guide potential future investments. SAGE members are involved in the decision-making processes of GAVI – including in the Programme and Policy Committee (PPC) and the 2018 Vaccine Investment Strategy (VIS).

In June 2017, the GAVI Board approved the continued support of IPV through 2020, after which the IPV support will be decided according to the VIS. GAVI will collaborate with country-level polio transition planning and provide time-limited support to cover gaps in key immunization strengthening activities.

The recommendations from SAGE on the use and impact of the typhoid conjugate vaccine will enable the GAVI Board, at its meeting in November 2017, to specify its support for vaccine implementation. GAVI also invests in implementation research based on the evidence gaps identified by SAGE.

The 2030 Agenda for Sustainable Development is a comprehensive blueprint for overall development. It includes ambitious health goals and bold immunization targets. Broad immunization indicators are needed if the respective health goals are to be achieved.

Several priorities were highlighted as part of the GAVI agenda moving forward, including: mitigating the main risks for countries transitioning from GAVI support and post-transition engagement; scaling up investments to transform and improve data use and accountability; and the future VIS in which vaccine candidates will be evaluated and prioritized to enable potential investment decisions in 2018.

Reports from advisory committees on immunization

Global Advisory Committee on Vaccine Safety (GACVS)

GACVS met in June 2017 and reported to SAGE on 2 specific topics: the safety of RTS,S malaria vaccine in pilot implementations, and the safety of Bacille Calmette-Guérin (BCG) vaccine. GACVS also reviewed human papillomavirus (HPV) vaccines and discussed a template for reviewing the safety profile of new vaccines.

(iii) accélération de la lutte contre l'hépatite B et l'encéphalite japonaise; (iv) amélioration de la couverture par la vaccination systématique; (v) introduction de nouveaux vaccins; et (vi) mise en œuvre des stratégies et des activités recommandées par le GVP dans la région. Sur la période 2013-2017, plusieurs États Membres ont été touchés par des résurgences ou des flambées épidémiques à grande échelle de rougeole, de poliomyélite causée par des poliovirus dérivés d'une souche vaccinale circulants (PVDVc), de rubéole, de diphtérie ou de coqueluche. L'analyse épidémiologique détaillée de ces flambées a aidé les États Membres et l'OMS à identifier les zones et les groupes à haut risque et les lacunes immunitaires dans différentes populations.

Rapport de GAVI, l'Alliance du Vaccin

GAVI a reconnu le rôle important du SAGE dans l'apport d'orientations politiques et techniques pour étayer la conception de ses programmes et guider ses futurs investissements. Les membres du SAGE participent aux décisions prises par GAVI – notamment au niveau du Comité des programmes et des politiques (PPC) et de la stratégie d'investissement en faveur de la vaccination 2018 (VIS).

En juin 2017, le conseil d'administration de GAVI a approuvé la poursuite du soutien accordé à la délivrance du VPI jusqu'en 2020, conformément à la VIS. L'Alliance collaborera à la planification au niveau des pays de la transition entre les vaccins antipoliomyélitiques et fournira un appui limité dans sa durée pour combler les insuffisances dans les principales activités de renforcement de la vaccination.

Les recommandations du SAGE concernant l'utilisation et l'impact du vaccin antityphoïdique conjugué permettront au conseil d'administration de GAVI, lors de sa réunion en novembre 2017, de préciser quelle aide l'Alliance apportera pour la mise en œuvre de ce vaccin. Celle-ci investit aussi dans des recherches sur la mise en œuvre en fonction des lacunes en matière de données identifiées par le SAGE.

L'Agenda 2030 pour le développement durable est un schéma directeur complet pour le développement global. Il prévoit des objectifs sanitaires ambitieux et de cibles audacieuses pour la vaccination. Si l'on veut atteindre ces différents objectifs sanitaires, il faut disposer d'indicateurs larges pour la vaccination.

À mesure que GAVI progresse dans son agenda, plusieurs priorités ressortent, notamment l'atténuation des principaux risques pour les pays en situation transitoire entre l'aide de GAVI et un engagement individuel post-transition; le passage à l'échelle supérieure des investissements pour transformer et améliorer l'utilisation des données et leur fiabilité; et la VIS future, qui devrait évaluer les vaccins candidats et les classer par priorités pour permettre la prise éventuelle de décisions d'investissement en 2018.

Rapports des comités consultatifs sur la vaccination

Comité consultatif mondial de la sécurité vaccinale (GACVS)

Le GACVS s'est réuni en juin 2017 et a fait rapport au SAGE sur 2 sujets spécifiques: l'innocuité du vaccin antipaludique RTS,S dans les mises en œuvre pilotes et celle du vaccin préparé à partir du bacille de Calmette-Guérin (BCG). Le GACVS a aussi passé en revue les vaccins contre le papillomavirus humain (HPV) et discuté d'un canevas pour l'examen du profil d'innocuité des nouveaux vaccins.

SAGE supported the strengthening of routine pharmacovigilance in countries ahead of the RTS,S vaccine pilot introduction in 3 countries in Africa, as well as identification of Adverse Events of Special Interest assessable by active and enhanced passive surveillance. Baseline data on the use of the vaccine in the routine programme and addressing theoretical safety concerns are essential. GACVS has assisted SAGE with the revision of safety and reactogenicity data on BCG vaccines. While the safety profile of the BCG vaccine is well established, its reactogenicity is influenced by multiple factors, which are difficult to quantify, and it needs to be used with caution in human immunodeficiency virus (HIV)-infected and immunocompromised children.

Safety signals and spurious allegations related to HPV vaccines continue to be investigated. There continues to be ever-increasing availability of high-quality studies that reconfirm the safety of the HPV vaccines.

SAGE welcomed a template to review the safety profile of new vaccines, which will ensure standardization and facilitate vaccine safety assessments.

Product Development for Vaccines Advisory Committee (PDVAC)

Since its inception in 2014 PDVAC has engaged with stakeholders across an increasing range of pathogens, platforms and activities. PDVAC was convened for its 4th annual meeting in June 2017. Progress in the development of vaccines and monoclonal antibodies across 10 pathogen areas was discussed.⁷ The status of vaccine development for 4 additional pathogens, including cytomegalovirus (CMV) and gonococcus was reviewed. Advances and challenges with respect to product development using 6 platform technologies and cross-cutting topics that have implications for several priority pathogens were considered.

WHO preferred product characteristics (PPCs) have been published for respiratory syncytial virus (RSV), Group B Streptococcus (GBS) and improved seasonal influenza vaccines, and are in development for Group A Streptococcus (GAS), tuberculosis (TB), Enterotoxigenic *Escherichia coli* (ETEC), Shigella and herpes simplex virus (HSV) vaccines.⁸ Technical roadmaps have been published for RSV and GBS vaccines, and product development consultations to discuss accelerated pathways for ETEC, Shigella, TB, HIV and GAS vaccines have been convened or are planned. The need for early assessment of the projected public health value of potential new vaccines, in order to encourage their development, was underscored. This includes consideration of the potential to reduce or control the emergence and

Le SAGE a appuyé le renforcement de la pharmacovigilance systématique au niveau national, en amont de l'introduction pilote du vaccin RTS, S dans 3 pays d'Afrique, ainsi que l'identification des événements indésirables présentant un intérêt particulier, susceptibles d'être évalués par une surveillance active ou une surveillance passive améliorée. Il est indispensable de disposer de données de référence sur l'utilisation du vaccin dans le cadre du programme de vaccination systématique et de répondre aux préoccupations théoriques concernant son innocuité. Le GACVS a aidé le SAGE à réviser les données d'innocuité et de réactogénicité pour les vaccins BCG. Si le profil d'innocuité de ces derniers vaccins est bien établi, leur réactogénicité est influencée par de multiples facteurs, difficiles à quantifier, et ils doivent donc être utilisés avec précaution chez les enfants infectés par le virus de l'immunodéficience humaine (VIH) et immunodéprimés.

Les signaux relatifs à l'innocuité et les allégations fallacieuses concernant les vaccins anti-HPV continuent de faire l'objet d'investigations. Le nombre grandissant d'études de grande qualité à disposition confirme l'innocuité de ces vaccins.

Le SAGE a accueilli très favorablement le canevas d'examen du profil d'innocuité des nouveaux vaccins, qui permettra de garantir la standardisation et facilitera les évaluations de l'innocuité vaccinale.

Développement de produits pour le Comité consultatif des vaccins (PDVAC)

Depuis sa mise en place en 2014, le PDVAC a pris des engagements, avec des parties prenantes, concernant une gamme grandissante d'agents pathogènes, de plateformes et d'activités. Il a été convoqué pour 4^e réunion annuelle en juin 2017. Les progrès dans la mise au point de vaccins et d'anticorps monoclonaux contre 10 agents pathogènes ont été évoqués.⁷ L'état de développement des vaccins contre 4 agents pathogènes supplémentaires, dont le cytomégalovirus (CMV) et l'agent gonococcus, a été examiné. Les progrès et les difficultés dans la mise au point des produits à l'aide de 6 plates-formes technologiques ont été examinés et des questions transversales ayant des implications pour plusieurs agents pathogènes prioritaires ont été analysées.

Les caractéristiques préférées par l'OMS pour les produits (PPC) ont été publiées dans le cas des vaccins contre le virus respiratoire syncytial (RSV) et les streptocoques du groupe B (SGB) et des vaccins contre la grippe saisonnière améliorés; elles sont en cours de mise au point pour les vaccins contre les streptocoques du groupe A (SGA), la tuberculose, *Escherichia coli* entero-toxinogène (ETEC), les bactéries du genre Shigella et le virus de l'Herpès simplex (VHS).⁸ Des feuilles de route techniques ont été émises pour les vaccins contre le RSV et les SGB et des consultations sur le développement des produits ont été convoquées ou planifiées en vue d'examiner des voies accélérées de mise sur le marché pour les vaccins contre ETEC, Shigella, la tuberculose, le VIH et les SGA. La nécessité d'une évaluation précoce de la valeur projetée pour la santé publique des nouveaux vaccins potentiels, dans la perspective

⁷ WHO Product Development for Vaccines Advisory Committee (PDVAC) meeting – 2017. www.who.int/immunization/research/meetings_workshops/pdvac_2017/en/, accessed October 2017.

⁸ WHO Preferred Product Characteristics (PPCs). World Health Organization, Geneva, 2014. Available at www.who.int/immunization/research/ppc-tpp/preferred_product_characteristics/en/, accessed October 2017.

⁷ WHO Product Development for Vaccines Advisory Committee (PDVAC) meeting. Disponible à l'adresse: www.who.int/immunization/research/meetings_workshops/pdvac_2017/en/, consulté en octobre 2017.

⁸ WHO Preferred Product Characteristics (PPCs). Organisation mondiale de la Santé, Genève, 2014. Disponible à l'adresse: www.who.int/immunization/research/ppc-tpp/preferred_product_characteristics/en/, consulté en octobre 2017.

transmission of antimicrobial resistance, particularly in the context of infections for which first-line antibiotic treatments are no longer effective, such as gonorrhoea and shigellosis.

A number of heterologous prime-boost regimens are advancing towards licensure, e.g. for HIV vaccine candidates, some of which may include novel antigen delivery platforms such as RNA. Monoclonal antibody products to prevent infection are in development against an increasing number of pathogens, including HIV, RSV, *Staphylococcus aureus* and rabies virus; some of these, e.g. against HIV and RSV, are in late stage clinical development, with the aim of preventing disease in neonates. PDVAC recommended evaluation of barriers to development, licensure and availability of monoclonal antibodies, specifically for use in low and middle income countries (LMICs).

Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC)

In September 2017 IVIR-AC discussed the following: an update of the global evidence on the age distribution of rotavirus (RV) disease and waning of efficacy of RV vaccines in children aged <5 years; a global research agenda for HPV vaccines used in reduced schedules; the methods for a cholera burden of disease model; rabies and typhoid vaccine impact model comparisons; malaria vaccine delivery costs; the development of a value proposition framework for new vaccines; and the use of data from the Child Health and Mortality Prevention Surveillance (CHAMPS) network, which is designed to ascertain why, where and how children aged <5 years are dying.

As vaccine impact studies are driven by local epidemiology, vaccine effectiveness and immunization costs, IVIR-AC welcomed projects such as CHAMPS that generate epidemiological data on child health in different geographical locations, the HPV project on the impact of reduced schedules on vaccine effectiveness, and the 4-dose malaria vaccine study for detailed vaccine delivery costing.

Global Vaccine Action Plan (GVAP): progress report

SAGE reviewed the draft assessment report and recommendations by the Decade of Vaccines (DoV) Working Group and noted that in 2016, while some progress was made towards the goals set out in the GVAP,⁹ multiple issues at many levels threaten progress, and have the

d'encourager leur développement, a été soulignée. Une telle évaluation prend notamment en compte leur capacité potentielle à réduire ou à endiguer l'émergence et la transmission d'une résistance aux antimicrobiens, notamment pour les infections contre lesquelles les traitements antibiotiques de première intention ne sont plus efficaces, telles que les gonorrhées et les shigelloses.

Un certain nombre de schémas thérapeutique hétérologues, reposant sur l'induction d'une réponse primaire, suivie d'un rappel, progressent vers l'homologation, notamment des vaccins candidats contre le VIH, dont certains incluent de nouvelles plates-formes de délivrance d'antigènes comme des ARN. Des produits à base d'anticorps monoclonaux, destinés à prévenir les infections, sont en cours de mise au point contre un nombre grandissant d'agents pathogènes, y compris le VIH, le RSV, le *Staphylococcus aureus* et le virus rabique; certains de ces produits, par exemple contre le VIH et le RSC, sont parvenus à un stade avancé du développement clinique et visent à prévenir la maladie chez les nouveau-nés. Le PDVAC a recommandé l'évaluation des obstacles à la mise au point, à l'homologation et la mise à disposition des anticorps monoclonaux, et notamment de ceux destinés aux pays à revenu faible ou intermédiaire.

Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC)

En septembre 2017, l'IVIR-AC a discuté des points suivants: mise à jour des données mondiales sur la distribution en fonction de l'âge des maladies à rotavirus (RV) et diminution de l'efficacité des vaccins anti-RV chez les enfants de <5 ans; agenda mondial de la recherche sur les vaccins anti-HPV utilisés dans le cadre d'un calendrier vaccinal réduit; méthodes pour modéliser la charge de morbidité due au choléra; comparaisons de modèles d'impact pour les vaccins antirabique et antityphoïdique; coûts de délivrance du vaccin antipaludique; élaboration d'un cadre de proposition de valeur pour les nouveaux vaccins; et exploitation des données fournies par le Réseau de surveillance de la santé et de prévention de la mortalité infantile (Child Health and Mortality Prevention Surveillance, CHAMPS), destiné à déterminer pourquoi, quand et comment certains enfants de <5 ans sont décédés.

Comme les études d'impact des vaccins sont influencées par l'épidémiologie locale, l'efficacité vaccinale et les coûts de vaccination, l'IVIR-AC a accueilli très positivement des projets tels que CHAMPS qui génèrent des données épidémiologiques sur la santé de l'enfant dans différentes localisations géographiques, le projet PVH sur les répercussions des calendriers réduits sur l'efficacité des vaccins et l'étude de la vaccination antipaludique en 4 doses en vue d'une évaluation détaillée du coût de sa délivrance.

Plan d'action mondial pour les vaccins (GVAP): rapport de situation

Le SAGE a examiné les projets de rapport d'évaluation et de recommandations proposés par le Groupe de travail sur la Décennie des Vaccins (DoV) et a noté qu'en 2016, malgré certaines avancées vers les objectifs fixés par le GVAP,⁹ de multiples problèmes, intervenant à de nombreux niveaux,

⁹ See www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/, accessed October 2017.

⁹ Voir www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/, consulté en octobre 2017.

potential to reverse hard-won gains; these include global economic uncertainty, conflicts and natural disasters, displacement and migration, and infectious disease outbreaks. Moreover, SAGE noted concerning signs of complacency and inadequate political commitment to immunization, as well as limited global appreciation of its power to achieve wider health and development objectives. Additional risks identified include growing levels of vaccine hesitancy, the worrying rise in vaccine stock-outs disrupting access to vaccines, and the continued under-performance of certain countries (the “outlier countries”) relative to others within their region.¹⁰

In order to address the situation and to accelerate progress towards attaining the GVAP goals, SAGE issued 12 recommendations:

1. *Broadening the dialogue:* The entire immunization community should ensure that immunization is fully aligned and integrated with global health and development agendas – including global health security and the International Health Regulations, health systems strengthening and universal health coverage, and the battle against antimicrobial resistance – and that dialogue is strengthened with additional constituencies such as the business and financial sectors.

Subsidiary recommendation:

- 1b. *Joint External Evaluations:* An assessment should be made of immunization-related inputs into national Joint External Evaluations for the International Health Regulations, in order to review the references made to immunization in the evaluations and resulting national action plans.
2. *Funding transitions:* Until polio eradication is achieved, financial and technical support provided through the Global Polio Eradication Initiative, GAVI and WHO support should be maintained in at least the 16 polio priority countries in order to ensure the success of eradication efforts and to mitigate the risks to infectious disease surveillance, routine immunization and global health security more generally.
3. *Polio and communicable disease surveillance:* Poliomyelitis laboratory and epidemiological surveillance capacities should be maintained in countries across all WHO Regions throughout and beyond the polio endgame and certification process, and built upon to strengthen communicable disease surveillance systems, especially for measles and rubella, and other vaccine-preventable diseases.
4. *Outlier countries:* Comprehensive multidimensional assessments should be undertaken in countries experiencing the greatest difficulties in achieving GVAP goals and used to develop bespoke

menaçaient les progrès réalisés et étaient susceptibles d'annuler les gains durement obtenus; il s'agissait entre autre des incertitudes pesant sur l'économie mondiale, des conflits et des catastrophes naturelles, des déplacements de populations et des migrations et des flambées de maladies infectieuses. En outre, le SAGE a enregistré des signes inquiétants d'autosatisfaction et d'engagement politique insuffisant à l'égard de la vaccination, ainsi qu'une reconnaissance limitée à l'échelle mondiale de sa capacité à atteindre des objectifs plus larges en matière de santé et de développement. Parmi les risques supplémentaires identifiés, figurent une augmentation des niveaux de réticence à l'égard de la vaccination, la multiplication inquiétante des ruptures de stock de vaccins perturbant l'accès à la vaccination et la performance durablement insuffisante de certains pays (les «pays atypiques») par rapport à d'autres situés dans la même région.¹⁰

Pour faire face à cette situation et accélérer les progrès vers la réalisation des objectifs du GVAP, le SAGE a émis 12 recommandations.

1. *Élargir le dialogue.* L'ensemble de la communauté de la vaccination doit veiller à ce que la vaccination soit totalement mise en harmonie avec les programmes mondiaux en faveur de la santé et du développement, et y soit incorporée – parmi lesquels la sécurité sanitaire mondiale et le Règlement sanitaire international, le renforcement des systèmes de santé et la couverture sanitaire universelle, ainsi que la lutte contre la résistance aux antimicrobiens – et à ce que le dialogue soit renforcé avec davantage de partenaires, tels que le monde des affaires et le secteur de la finance.

Recommandation subsidiaire

- 1b. *Évaluations externes conjointes.* Une analyse des évaluations externes conjointes réalisées au niveau national conformément au Règlement sanitaire international doit être effectuée afin d'examiner les données relatives à la vaccination et les plans d'action nationaux qui en découlent.
2. *Phases de transition concernant les financements.* Jusqu'à ce que l'éradication de la poliomyélite soit obtenue, le soutien financier et technique apporté par l'Initiative mondiale pour l'éradication de la poliomyélite, l'Alliance GAVI et l'OMS doit être maintenu au moins dans les 16 pays prioritaires afin de garantir le succès des efforts d'éradication et de limiter les risques pour la surveillance des maladies infectieuses, la vaccination systématique et, plus généralement, la sécurité sanitaire mondiale.
3. *Surveillance de la poliomyélite et des maladies transmissibles.* Les capacités en matière de surveillance épidémiologique et de laboratoire spécifiques à la poliomyélite doivent être conservées dans les pays de toutes les régions tout au long de la phase finale de la lutte contre la poliomyélite et du processus de certification, et au-delà, et elles doivent être utilisées pour renforcer les systèmes de surveillance des maladies transmissibles, notamment de la rougeole et de la rubéole, et des autres maladies à prévention vaccinale.
4. *Pays «atypiques».* Des évaluations multidimensionnelles exhaustives doivent être entreprises dans les pays qui rencontrent les plus grandes difficultés à atteindre les objectifs du GVAP, et utilisées pour élaborer des plans

¹⁰ 2017 SAGE Assessment Report of the Global Vaccine Action Plan. Available at http://www.who.int/entity/immunization/web_2017_sage_gvap_assessment_report_en.pdf?ua=1, accessed November 2017.

¹⁰ Rapport d'évaluation 2017 du plan d'action mondial pour les vaccins. Disponible à l'adresse: http://www.who.int/entity/immunization/global_vaccine_action_plan/web_2017_sage_gvap_assessment_report_fr.pdf?ua=1, consulté en novembre 2017.

and costed remediation plans addressing systemic weaknesses, integrating existing improvement plans and including a strong focus on monitoring and evaluation frameworks to support effective implementation.

5. *Maternal and neonatal tetanus:* Concerted efforts should be made to achieve global elimination by 2020 and sustain it thereafter, particularly by exploiting the opportunity to expand coverage to underserved populations through use of compact pre-filled auto-disable devices.
6. *Displaced, mobile and neglected populations:* Existing knowledge on reaching displaced and mobile populations – including individuals escaping conflict zones or natural disasters, economic migrants, seasonal migrants, those moving to urban centres, and traditional nomadic communities – and other neglected populations should be synthesized to identify good practice, innovative new approaches and gaps in knowledge.
7. *Acceptance and demand:* Each country should develop a strategy to increase acceptance and demand for vaccination, which should include ongoing community engagement and trust-building, active hesitancy prevention, regular national assessment of vaccine concerns, and crisis response planning.
8. *Civil Society Organizations:* Countries should aim to broaden and deepen their engagement with CSOs, expanding the range of CSOs with which they interact and extending their input into areas such as programme planning.

Subsidiary recommendation:

- 8b. *Legal frameworks:* A comprehensive global audit should be undertaken to document the ways in which legislation and regulation have been used to promote or undermine immunization at a national level, to identify how legal and regulatory instruments can be best applied in different contexts and for different purposes to strengthen immunization systems.
9. *Technical capacity-building:* Through a multidimensional approach, the technical capacity of countries' immunization programmes should be systematically assessed and strengthened, by leveraging regional and national expertise and opportunities as well as global tools and resources.
10. *Vaccine access:* Multidimensional analyses should be undertaken to identify procurement and other programmatic issues affecting timely provision of vaccination, including to the most neglected and remote populations, and used to develop more effective procurement, stock management and distribution plans.
11. *Vaccine supply:* Current and anticipated vaccine supply and demand for routinely used vaccines should continue to be mapped and constraints identified, integrating and expanding other relevant ongoing work and focusing on vaccines most at risk of supply shortages.

correctifs sur mesure chiffrés visant à corriger les faiblesses du système et intégrant les plans d'amélioration existants tout en étant fortement axés sur les cadres de suivi et d'évaluation pour en permettre la bonne mise en œuvre.

5. *Tétanos maternel et néonatal.* Des efforts concertés doivent être entrepris pour atteindre l'objectif d'élimination d'ici à 2020 et le maintenir par la suite, notamment en élargissant la couverture aux populations mal desservies grâce à l'utilisation des dispositifs pré-remplis autobloquants compacts.
6. *Populations déplacées, mobiles et négligées.* Les connaissances actuelles sur la manière d'atteindre les populations déplacées et mobiles – notamment les personnes fuyant les zones de conflit ou les catastrophes naturelles, les migrants économiques, les migrants saisonniers, les personnes s'établissant dans les centres urbains et les communautés nomades traditionnelles – et autres populations négligées doivent être synthétisées afin de faire ressortir les bonnes pratiques, les nouvelles approches innovantes et les lacunes dans les connaissances.
7. *Acceptation et demande.* Chaque pays doit élaborer une stratégie pour accroître l'acceptation de la vaccination et la demande, stratégie qui devra comprendre une mobilisation durable des communautés et l'instauration d'un climat de confiance, une prévention active de la réticence à la vaccination, une évaluation nationale régulière des sujets de préoccupation à l'égard des vaccins, ainsi qu'une planification de la riposte en cas de crise.
8. *Organisations de la société civile.* Les pays doivent s'efforcer d'élargir et d'approfondir leur collaboration avec les organisations de la société civile, en étoffant le nombre d'organisations avec lesquelles ils interagissent et en poussant leur contribution à des domaines d'intervention tels que la planification programmatique.

Recommandation subsidiaire

- 8b. *Cadres juridiques.* Un examen complet doit être entrepris à l'échelle mondiale afin de décrire la façon dont la législation et la réglementation ont été utilisées au niveau national, permettant de promouvoir la vaccination ou y portant atteinte, et de déterminer comment les instruments juridiques et réglementaires peuvent être utilisés au mieux selon les contextes et les objectifs pour renforcer les systèmes de vaccination.
9. *Renforcement des capacités techniques.* S'appuyant sur une approche multidimensionnelle, les capacités techniques des programmes de vaccination des pays doivent être systématiquement évaluées et renforcées, en mettant à profit l'expertise et les opportunités aux niveaux régional et national, ainsi que les outils et ressources mondiaux.
10. *Accès aux vaccins.* Des analyses multidimensionnelles doivent être entreprises pour cerner les problèmes d'approvisionnement et les autres aspects programmatiques affectant les délais de vaccination, notamment des populations les plus négligées et éloignées, et ces analyses doivent être utilisées pour élaborer des plans d'achat, de gestion des stocks et de distribution qui soient plus efficaces.
11. *Approvisionnement en vaccins.* L'approvisionnement actuel et prévu en vaccins et la demande pour les vaccins de la vaccination systématique doivent continuer à être cartographiés, et les difficultés, repérées, en intégrant et développant les autres activités y afférent qui sont en cours et en portant une attention particulière aux vaccins présentant le plus de risques de faire l'objet de pénuries d'approvisionnement.

12. *Middle-income countries:* WHO Regional Offices should support middle-income countries in their Regions by leveraging all opportunities to promote the exchange of information, the sharing of lessons learnt and peer-to-peer support.

SAGE was also presented with a selection of indicators for immunization that will be monitored under the Sustainable Development Goals (SDGs) framework, along with an options analysis and the recommendations from the DoV Working Group. SAGE was mindful of the need for ambitious and aspirational indicators which nevertheless allow comparability across time and countries and safeguard country ownership. Hence, SAGE proposed to submit for consideration to the Inter-agency Expert Group for SDGs the following option for indicator 3.b.1 (proportion of the target population covered by all vaccines included in their national programme): coverage estimates for 4 vaccines, i.e. DTP-containing vaccine third dose, MCV second dose, PCV last dose in the country schedule, and HPV vaccine last dose in the country schedule. For SDG indicator 3.8.1, SAGE proposed MCV second dose as an option for consideration in 2018, which would replace the current indicator which is DTP-containing vaccine third dose. SAGE recognized the opportunity to submit a revised definition (i.e. wording) for indicator 3.b.1 as well as revised metadata to quantify the indicator by 2020.

Finally, SAGE was presented with an overview on the proposed process to develop a global immunization strategy for the next decade (2021–2030). SAGE agreed on the importance of having the strategy adopted by the World Health Assembly in May 2020 and urged WHO to work with all relevant partners from the immunization and the wider public health community towards this objective.

Reports from international associations of vaccine manufacturers

Two vaccine manufacturers' associations, the Developing Countries Vaccine Manufacturers Association (DCVMN) and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) were invited to present to SAGE.

Both organizations provided insight into their functioning, structure, constituencies and interactions with SAGE and other WHO immunization advisory committees, and with GAVI and UNICEF.

DCVMN described how it supports immunization activities across LMICs. It elaborated on how DCVMN assures that vaccine needs in relation to supply and research are met. The presentation outlined the large increase in the number and quantity of supplied vaccines over time and the newly developed vaccines such as the conjugated typhoid vaccine. The constraints their manufacturers face, in particular regarding heterogeneous processes in different countries to obtain vaccine licensure or prequalification status, were highlighted.

12. *Pays à revenu intermédiaire.* Les bureaux régionaux de l'OMS doivent accompagner les pays à revenu intermédiaire de leur région en mettant à profit toutes les opportunités de promouvoir l'échange d'informations, la mise en commun des enseignements tirés et le soutien entre pairs.

Il a aussi été présenté au SAGE une sélection d'indicateurs pour la vaccination, qui seront suivis dans le cadre de la réalisation des objectifs de développement durable (ODD), accompagné d'une analyse de ces options et des recommandations du groupe de travail DoV. Le SAGE était conscient qu'il fallait disposer d'indicateurs exigeants et ambitieux, permettant néanmoins des comparaisons au cours du temps et entre les pays et préservant les possibilités d'appropriation des objectifs par ces derniers. En conséquence, il a proposé de soumettre pour examen au Groupe d'experts interagences sur les indicateurs d'ODD l'option suivante pour l'indicateur 3.b.1 (proportion de la population cible couverte par l'ensemble des vaccins inclus dans le programme national): estimations de la couverture pour 4 vaccins, à savoir la troisième dose de vaccin contenant les valences DTC, la deuxième dose de MCV, la dernière dose de VPC du calendrier national et la dernière dose de vaccin anti-HPV de ce même calendrier. Pour l'indicateur d'ODD 3.8.1, le SAGE a proposé la deuxième dose de MCV en tant qu'option à envisager en 2018, en remplacement de l'indicateur actuel, la troisième dose de vaccin contenant les valences DTC. Le SAGE a reconnu qu'il était opportun de soumettre une définition révisée (c'est-à-dire reformulée) pour l'indicateur 3.b.1, ainsi que des métadonnées révisées pour quantifier cet indicateur d'ici 2020.

Enfin, on a soumis au SAGE une présentation générale du processus proposé pour élaborer une stratégie mondiale concernant la vaccination au cours de la prochaine décennie (2021-2030). Le SAGE est convenu de l'importance de disposer d'une stratégie adoptée par l'Assemblée mondiale de la Santé en mai 2020 et a invité instamment l'OMS à œuvrer en faveur de cet objectif, avec l'ensemble des partenaires concernés au sein de la communauté de la vaccination et plus largement de la communauté de la santé publique.

Rapports des associations internationales de fabricants de vaccins

Deux associations de fabricants de vaccins, la Developing Countries Vaccine Manufacturers Association (DCVMN) et l'International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) ont été invitées à faire une présentation au SAGE.

L'une et l'autre de ces organisations ont donné un aperçu de leur fonctionnement, de leur structure, des groupes d'intérêts qu'elles représentent et de leurs interactions avec le SAGE et d'autres comités consultatifs sur la vaccination de l'OMS ainsi qu'avec GAVI et l'UNICEF.

L'association DCVMN a décrit comment elle appuyait les activités de vaccination dans l'ensemble des pays à revenu faible ou intermédiaire. Elle a exposé plus en détail comment elle veillait à la satisfaction des besoins en matière d'approvisionnement en vaccins et de recherche dans le domaine vaccinal. Elle a présenté aussi brièvement l'importante augmentation du nombre et de la quantité de vaccins fournis au cours du temps ainsi que les vaccins récemment mis au point comme le vaccin antityphoïdique conjugué. Elle a insisté sur les contraintes auxquelles sont confrontés les fabricants, en particulier l'hétérogénéité des procédures dans les différents pays pour obtenir l'homologation d'un vaccin ou le statut de préqualification.

IFPMA stressed its engagement in relation to vaccine shortages and supply, and work on using vaccines within a controlled temperature chain. It also highlighted the efforts on facilitating delivery of vaccines through reducing cold chain volume and on innovations in vaccine administration devices. IFPMA called for novel approaches for batch-release and shelf-life processes to reduce vaccine wastage.

SAGE expressed appreciation for the work of both organizations and their contributions to the GVAP, and called for increased collaboration to align vaccine demand and supply. SAGE also stressed the need to foster dialogue between these associations, national regulatory authorities and WHO prequalification, in order to leverage the standardization of registration, batch-release and prequalification processes. SAGE also highlighted the need to promote prospective registration of vaccine clinical trials in clinical trial registries as well as the timely publication of their results.

Polio eradication initiative

SAGE reviewed progress of the Global Polio Eradication Initiative (GPEI) towards its 4 objectives: polio virus detection and interruption of transmission; oral polio vaccine (OPV) withdrawal and IPV introduction; containment and global certification; and transition planning.

There have been 6 reported cases of poliomyelitis due to wild polioviruses (WPV) during the 6 months preceding 17 October 2017, 3 in Afghanistan and 3 in Pakistan, compared with 13 cases during the comparable 6-month period in 2016. The virus circulation is limited to trans-border corridors of transmission. The quality of surveillance and immunization campaigns has improved overall, especially in high-risk populations. Nigeria has not reported any WPV case since August 2016. However, surveillance gaps exist due to inaccessibility in some parts of Borno State where the last WPV1 case was detected. Since the tOPV-bOPV switch in April 2016, vaccine-derived viruses have disappeared in most OPV-using countries. Six post-switch cVDPV2 outbreaks occurred in 4 countries (one each in Pakistan and Syrian Arab Republic, and 2 each in Nigeria and Democratic Republic of Congo). However, as of October 2017, no international spread of cVDPV2 viruses has been documented and no cVDPV cases have been detected in Nigeria or Pakistan. In Syrian Arab Republic, 47 cVDPV2 cases have been found to date in 2017.

SAGE expressed concern over waning mucosal immunity against type 2, and reiterated its recommendation from April 2017 that, in case of future co-circulation of WPV and cVDPV2, countries should administer at least 2 doses of mOPV2 before the next bOPV round. Also, countries should maintain high vaccination coverage ($\geq 90\%$ national and $\geq 80\%$ in every district) to sustain population immunity against types 1 and 3, especially in high-risk countries and sub-national high-risk populations.

L'association IFPMA a souligné son engagement concernant l'approvisionnement en vaccins et les pénuries de ces produits ainsi que son travail pour que les vaccins soient utilisés dans le cadre d'une chaîne à température contrôlée. Elle a aussi mis l'accent sur les efforts pour faciliter la délivrance des vaccins grâce à une réduction du volume de chaîne du froid et à des innovations pour améliorer les dispositifs d'administration. L'IFPMA a appelé à adopter de nouvelles approches concernant la mise en circulation des lots et la durée de conservation des vaccins en vue de ce réduire le gaspillage.

Le SAGE a exprimé sa reconnaissance pour le travail des deux organisations et pour leurs contributions à l'activité du GVAP et a appelé à intensifier la collaboration pour faire coïncider l'offre et la demande de vaccins. Il a aussi souligné la nécessité de favoriser le dialogue entre ces associations, les autorités de réglementation nationales et le dispositif de préqualification par l'OMS, afin de tirer parti de la standardisation de l'enregistrement, de la mise en circulation des lots et des procédures de préqualification. Le SAGE a aussi insisté sur la nécessité de promouvoir l'enregistrement prospectif des essais cliniques de vaccins dans les registres consignnant ces essais et de publier en temps utile leurs résultats.

Initiative pour l'éradication de la poliomyélite

Le SAGE a passé en revue les progrès de l'Initiative mondiale pour l'éradication de la poliomyélite (IMEP) vers ses 4 objectifs: détection des poliovirus et interruption de la transmission; retrait du vaccin antipoliomyélique oral (VPO) et introduction du VPI; confinement et certification à l'échelle mondiale; et planification de la transition.

Au cours des 6 mois précédant le 17 octobre 2017, 6 cas de poliomyélite due à un poliovirus sauvage (PVS) ont été notifiés: 3 en Afghanistan et 3 au Pakistan, contre 13 au cours de la période de 6 mois correspondante en 2016. La circulation des virus se limite aux corridors transfrontaliers de transmission. La qualité de la surveillance et des campagnes de vaccination s'est améliorée globalement, en particulier parmi les populations à haut risque. Le Nigéria n'a pas rapporté de cas de PVS depuis août 2016. Néanmoins, il existe des lacunes dans la surveillance en raison de l'inaccessibilité de certaines parties de l'État de Borno où le dernier cas de PVS1 a été détecté. Depuis le passage du VPOt au VPOb en avril 2016, les virus dérivés d'une souche vaccinale ont disparu de la plupart des pays utilisant le VPO. Six flambées de PVDV2c sont survenues après cette transition dans 4 pays (une au Pakistan et en République arabe syrienne et 2 au Nigéria et en République démocratique du Congo). Cependant, en octobre 2017, aucune propagation internationale de virus PVDV2c n'avait été documentée et aucun cas de PVDVc n'avait été détecté au Nigéria ou au Pakistan. En République arabe syrienne, 47 cas de PVDV2c avaient été enregistrés à ce stade pour l'année 2017.

Le SAGE a exprimé sa préoccupation devant la disparition progressive de l'immunité muqueuse contre le type 2 et a réitéré la recommandation émise en avril 2017: en cas de co-circulation dans l'avenir de PVS et de PVDV2c, les pays devront administrer au moins 2 doses de VPO2m avant la prochaine tournée de VPOb. De même, les pays devront maintenir un fort taux de couverture vaccinale ($>90\%$ au niveau national et $\geq 80\%$ dans chaque district) pour entretenir l'immunité des populations contre les types 1 et 3, en particulier dans les pays et les populations infranationales à haut risque.

The IPV supply situation is expected to improve in 2018; all countries are expected to have access to IPV for routine immunization from the end of Q1 2018. SAGE acknowledged WHO's work with Imperial College, London, to grade risks in Tier 3 and 4 countries based on susceptibility, transmission, exposure, and primary immunodeficiency-associated vaccine-derived poliovirus (iVDPV) prevalence.

To date, 4 countries have decided to move to a fractional IPV (fIPV) 2-dose schedule in their routine immunization programmes (Bangladesh, India, Nepal and Sri Lanka). In addition, the PAHO Technical Advisory Group recommended the implementation of a 2-dose fIPV schedule in 14 countries. The AFR Regional Immunization Technical Advisory Group (RITAG) has encouraged Tier 3 and Tier 4 countries capable of implementing fractional dosing to consider adopting this regimen, taking into account the country's current practices and programme capacity. The 2-dose fIPV schedule (e.g. at 6 and 10 weeks) provides better seroconversion than one full dose of IPV and in the post-cessation era, 2 fIPV doses (the first at or after 14 weeks, and the second at least 4 months after the first dose) will provide sufficient (>90%) seroconversion.

In response to a query on the use of the post-OPV certification schedule (i.e. IPV at 14 weeks and ≥ 4 months later) SAGE agreed that low-risk countries using bOPV may adopt this schedule prior to global OPV cessation. In such cases, countries should continue bOPV in their routine schedule until OPV cessation. SAGE noted that the SAGE Polio Working Group will consider the use of a hexavalent IPV-containing vaccine post-certification.

SAGE recommended that countries which delayed the introduction of IPV or experienced stock-out should provide one full dose or 2 fIPV doses (e.g. at 6 and 14 weeks) to all children who were missed as soon as the vaccine becomes available.

SAGE reinforced the need for protocols for biocontainment in view of the recent incidents of breach of containment in 2 manufacturing facilities.

SAGE noted that WHO has established a team in the Director-General's Office to coordinate an organization-wide effort on transition planning, and has requested that the transition process be better coordinated with other immunization/health security initiatives to mitigate potential risks to these programmes. The GPEI is developing a post-certification strategy (PCS) to define the essential functions that need to be sustained to maintain a polio-free world after the certification of eradication. The PCS will be considered by the SAGE Polio Working Group and presented to SAGE in April 2018 for review prior to submission to the World Health Assembly.

On s'attend en 2018 à une amélioration de la situation pour les approvisionnements en VPI. Tous les pays devraient avoir accès à ce vaccin pour la vaccination systématique à partir de la fin du premier trimestre 2018. Le SAGE a exprimé sa reconnaissance à l'OMS et à l'Imperial College de Londres pour leur travail de gradation des risques dans les pays classés aux niveaux 3 et 4 en fonction des facteurs suivants: susceptibilité, transmission, exposition et prévalence des poliovirus dérivés d'une souche vaccinale associés à une immunodéficience primaire (PVDVi).

À ce jour, 4 pays ont décidé de passer à un calendrier comprenant 2 doses fractionnées de VPI (VPIf) dans le cadre de leur programme de vaccination systématique (Bangladesh, Inde, Népal et Sri Lanka). En outre, le groupe consultatif technique de la Région des Amériques a recommandé la mise en œuvre d'un calendrier en 2 doses de VPIf dans 14 pays. Le groupe consultatif technique régional sur la vaccination de la Région AFR (RITAG) a encouragé les pays des niveaux 3 et 4, en mesure de délivrer des doses fractionnées, à adopter ce schéma thérapeutique, en tenant compte de leurs pratiques actuelles et de leurs capacités programmatiques. Le calendrier en 2 doses de VPIf (administrées, par exemple, à 6 et 10 semaines) fournit une meilleure séroconversion qu'une dose complète de VPI dans la période posttransitionnelle, 2 doses de VPIf (la première à 14 semaines, la seconde espacée de 4 mois au moins par rapport à la première) procurera une séroconversion suffisante (>90%).

En réponse à une demande concernant l'utilisation du calendrier post-certification de l'arrêt du VPO (à savoir, l'administration du VPI à 14 semaines et ≥ 4 mois plus tard), le SAGE a accepté que les pays à faible risque utilisant le VPOb puissent adopter ce calendrier avant l'arrêt à l'échelle mondiale du VPO. Ces pays devront alors continuer à employer le VPOb dans leur calendrier de vaccination systématique jusqu'à l'arrêt du VPO. Le SAGE a noté que son groupe de travail sur la poliomyélite envisagerait l'utilisation d'un vaccin hexavalent contenant le VPI après la certification.

Le SAGE a recommandé que les pays ayant différé l'introduction du VPI ou ayant subi des ruptures de stock délivrent une dose complète ou 2 doses de VPIf (par exemple, à 6 et 14 semaines) à tous les enfants laissés de côté, dès que le vaccin devient disponible.

Le SAGE a réaffirmé la nécessité de protocoles de confinement biologique compte tenu des incidents récents ayant entraîné la rupture du confinement dans 2 installations de fabrication.

Le SAGE a noté que l'OMS avait mis en place une équipe au sein du Bureau du Directeur général, chargée de coordonner un effort à l'échelle de l'Organisation pour planifier la transition et a demandé à ce que le processus de transition soit aussi mieux coordonné avec d'autres initiatives dans les domaines de la sécurité sanitaire/de la vaccination en vue d'atténuer les risques potentiels pour ces programmes. L'IMEP a entrepris l'élaboration d'une stratégie post-certification (SPC) définissant les fonctions essentielles qu'il faut continuer d'assurer pour conserver un monde exempt de poliomyélite après la certification de l'éradication. Cette stratégie post-éradication sera examinée par le Groupe de travail sur la poliomyélite du SAGE et présentée à celui-ci en avril 2018 pour examen avant sa soumission à l'Assemblée mondiale de la Santé.

SAGE reviewed the report from the Polio Working Group on development of readiness criteria for full withdrawal of OPV and requested an updated draft for consideration at the SAGE meeting in April 2018.

Measles and rubella elimination

SAGE reviewed the following categories proposed for classifying countries, based on their level of disease control and likelihood of achieving and sustaining measles and rubella elimination: (1) endemic (the existence of continuous transmission of measles and/or rubella virus, that persists for ≥ 12 months in any defined geographical area, and no previous verification of elimination); (2) eliminated/interrupted but not verified (absence of endemic transmission for ≥ 12 but < 36 months); (3) eliminated and verified (no endemic transmission for > 36 months in the presence of a high quality surveillance system); (4) re-established endemic transmission post verification (ongoing chains of transmission for ≥ 12 months following previous verification of elimination). SAGE considered that the 4 proposed country categories are appropriate and provide a standardized approach to country categorization, and encouraged their use by the Regional Verification Commissions. SAGE noted that countries in the endemic category include countries at different levels of control and that further subcategories should be explored to inform corrective actions.

Measles and rubella control and elimination activities, most notably surveillance, rely heavily on GPEI resources. As resources from GPEI are declining, SAGE recommended that additional investments be identified in order to maintain and strengthen surveillance and immunization activities which are needed to prevent resurgence and to achieve further reductions of measles and rubella.

SAGE reviewed the modelling and serosurvey findings, based on data on age-specific population mixing patterns, in order to derive age-stratified target immunity levels needed to achieve and sustain measles elimination. SAGE stressed that achieving at least 95% immunity across all age groups, geographical regions and population subgroups through coverage of at least 95% of each birth cohort with 2 doses of MCV should remain the primary strategy for measles elimination, and recommended that countries strengthen their routine programme to achieve and maintain 95% vaccination coverage for MCV1 and MCV2. Countries should attempt to identify specific age-group and subpopulation groups with immunity gaps, i.e. those below 95% immunity, and offer catch-up vaccination accordingly. There is no perfect measure of immunity but a combination of coverage data, outbreak demographics and serosurveillance data can assist. The SAGE Measles and Rubella Working Group is developing guidance on estimation of age-specific immunity gaps. Because of high contact rates after school entry, SAGE noted that immunity gaps in school-age children are important.

Le SAGE a examiné le rapport du Groupe de travail sur la polio-myéélite concernant la mise au point de critères pour apprécier l'état de préparation en vue du retrait complet du VPO et a sollicité une version provisoire actualisée destinée à être examinée lors de la réunion du SAGE d'avril 2018.

Élimination de la rougeole et de la rubéole

Le SAGE a examiné les catégories proposées suivantes pour classer les pays en fonction des niveaux d'endiguement des maladies et de probabilité que ces pays réalisent et maintiennent l'élimination de la rougeole et de la rubéole: (1) pays d'endémie (présence d'une transmission continue du virus de la rougeole et/ou de la rubéole qui persiste ≥ 12 mois dans une zone géographique définie quelconque, sans vérification antérieure de l'élimination); (2) pays où la/les maladies ont été éliminées/interrompues sans que cela soit vérifié (absence de transmission endémique pendant ≥ 12 mois, mais < 36 mois); (3) pays où la ou les maladies ont été éliminées et où cette élimination a été vérifiée (absence de transmission endémique pendant > 36 mois, en présence d'un système de surveillance de haute qualité); (4) pays où la transmission endémique a repris après la vérification (chaînes de transmission actives pendant ≥ 12 mois après une vérification antérieure de l'élimination). Le SAGE a considéré que les 4 catégories de pays proposées convenaient et permettaient une standardisation de cette catégorisation. Il a encouragé leur utilisation par les commissions de vérification régionales. Il a noté que les nations classées dans la catégorie Pays d'endémie pouvaient présenter différents niveaux d'endiguement de la maladie et qu'il fallait envisager également des sous-catégories pour étayer correctement les actions correctives.

Les activités de lutte contre la rougeole et la rubéole et d'élimination de ces maladies, et tout particulièrement la surveillance, font fortement appel aux ressources de l'IMEP. Comme ces ressources sont en baisse, le SAGE a recommandé d'identifier les investissements supplémentaires nécessaires au maintien et au renforcement des activités de surveillance et de vaccination indispensables pour prévenir les résurgences et faire régresser encore la rougeole et la rubéole.

Le SAGE a examiné les résultats de la modélisation et des enquêtes sérologiques sur la base de données relatives aux schémas de brassage de populations en fonction de l'âge, afin de déterminer les niveaux d'immunité à viser, stratifiés selon l'âge, pour obtenir et maintenir l'élimination de la rougeole. Le SAGE a souligné qu'atteindre une immunité d'au moins 95% sur l'ensemble des tranches d'âge, des régions géographiques et des sous-groupes de population, grâce à une couverture d'au moins 95% de chaque cohorte de naissance avec 2 doses de MCV, devrait rester la principale stratégie pour l'élimination de la rougeole, et a recommandé que les pays renforcent leur programme de vaccination systématique afin d'atteindre et de maintenir un taux de couverture vaccinale de 95% pour la première et la deuxième doses de MCV. Les pays devront s'efforcer d'identifier les tranches d'âge et les sous-groupes de population particuliers présentant des lacunes immunitaires, c'est-à-dire dont le taux d'immunisation est inférieur à 95%, et proposer des activités de vaccination de rattrapage en conséquence. Il n'existe pas de mesure parfaite de l'immunité, mais une combinaison de données de couverture, de données démographiques concernant les flambées et de données de surveillance peuvent aider à la détermination de ce paramètre. Le

SAGE recommended that countries should put in place school entry checks for vaccination and consider optimal approaches for filling the immunity gaps. These include follow-up MCV vaccination campaigns that also target school-age children, either at the national or at a more targeted subnational level. In countries where the scheduled routine MCV2 age is after school entry, countries should consider lowering the age of MCV2 administration, provided that this does not have a negative impact on coverage levels.

SAGE reviewed the evidence on the humoral and cellular immune responses, duration of immunity, vaccine effectiveness and safety of administering MCV before 6 months of age. Given the paucity of published studies, SAGE concluded that there is insufficient evidence to recommend vaccination of infants aged less than 6 months. Regarding research gaps, SAGE noted that there is a need to address the substantial information gap on transmission drivers, disease burden and role of factors such as blunting and maternal immunity in infants aged <6 months, and the impact of vaccination <6 months of age on subsequent MCV doses. Head-to-head comparisons of measles vaccine strains are also needed to enable recommendations to be developed relating to relative effectiveness.

SAGE finally reviewed studies of measles seroprevalence and measles vaccine immunogenicity among HIV-infected adults and adolescents, and concluded that the available evidence does not support the need for an additional dose of measles vaccine following immune reconstitution with highly active antiretroviral therapy (HAART). Targeted vaccination efforts in measles-susceptible adults, whether or not HIV infected, may be needed to achieve Regional measles elimination goals.

Typhoid vaccines

SAGE noted the continuing high burden of typhoid fever and the alarming increase in antimicrobial resistance of *Salmonella* Typhi (S. Typhi) in LMICs. Global estimates of typhoid fever burden range between 11 and 21 million cases and approximately 145 000 to 161 000 deaths annually. New data have improved the understanding of the burden and risk factors for typhoid fever in sub-Saharan Africa, in addition to the previously documented high burden of disease in South and South-East Asia. In high-incidence settings, a large proportion of severe typhoid fever cases occur in children aged <2 years.

Currently, there is evidence for one injectable typhoid conjugate vaccine (TCV) of longer and higher levels of immunogenicity compared with the injectable Vi polysaccharide (ViPS) vaccine. Immunogenicity data up to

groupe de travail du SAGE sur la rougeole et la rubéole a entrepris de mettre au point des orientations pour l'estimation des lacunes immunitaires en fonction de l'âge. En raison des taux de contact élevés des enfants après leur entrée à l'école, le SAGE a fait observer que les lacunes immunitaires chez les enfants d'âge scolaire étaient importantes. Il a recommandé aux pays de mettre en place à l'entrée dans le système scolaire des contrôles des vaccinations et de rechercher les meilleures solutions pour combler ces lacunes. Il pourrait s'agir de campagnes de vaccination de suivi par le MCV visant aussi les enfants d'âge scolaire, au niveau national ou à un niveau infranational plus ciblé. Dans les pays où la 2^e dose systématique de MCV est prévue après l'entrée à l'école, il faudrait envisager d'abaisser l'âge d'administration de cette deuxième dose, sous réserve que cette intervention n'ait pas d'impact négatif sur les taux de couverture.

Le SAGE a examiné les éléments concernant les réponses immunitaires humorales et cellulaires, la durée de l'immunité, l'efficacité du vaccin et l'innocuité de l'administration du MCV avant l'âge de 6 mois. Compte tenu de la rareté des études publiées, le SAGE a conclu que les éléments disponibles étaient insuffisants pour recommander cette vaccination chez des nourrissons aussi jeunes. S'agissant des lacunes en matière de recherche, le SAGE a noté qu'il était nécessaire de combler le manque substantiel d'informations sur les moteurs de la transmission, la charge de morbidité et le rôle de facteurs tels que l'affaiblissement et l'immunité d'origine maternelle chez les nourrissons de <6 mois et l'impact de la vaccination avant 6 mois sur les doses de MCV ultérieures. Il est aussi nécessaire de comparer les souches vaccinales rougeoleuses les unes avec les autres pour émettre des recommandations à propos de leurs efficacités relatives.

Enfin, le SAGE a examiné des études sur la séroprévalence de la rougeole et l'immunogénicité de la vaccination antirougeoleuse chez les adultes et les adolescents infectés par le VIH et a conclu que les éléments disponibles ne confirmaient pas la nécessité d'une dose supplémentaire de vaccin antirougeoleux après la restauration immunitaire par un traitement antirétroviral hautement actif (HAART). Des efforts de vaccination ciblant les adultes sensibles à la rougeole, qu'ils soient ou non infectés par le VIH, sont parfois requis pour atteindre les objectifs régionaux en termes d'élimination de la rougeole.

Vaccins antityphoïdiques

Le SAGE a pris note de l'ampleur permanente de la charge de fièvre typhoïde et de l'augmentation alarmante de la résistance aux antimicrobiens de *Salmonella* Typhi (S. Typhi) dans les pays à revenu faible ou intermédiaire. Les estimations de la charge mondiale de morbidité due à la fièvre typhoïde se situent entre 11 et 21 millions de cas et celles de la mortalité entre approximativement 145 000 et 161 000 décès par an. De nouvelles données ont amélioré la connaissance de la charge de morbidité et des facteurs de risque pour la fièvre typhoïde en Afrique subsaharienne, en plus de la forte charge de morbidité déjà attestée en Asie du Sud et du Sud-Est. Dans les contextes de forte incidence, une proportion importante des cas de fièvre typhoïde sévère touche des enfants de <2 ans.

Actuellement, on dispose, pour un vaccin antityphoïdique conjugué injectable (VTC), de preuves attestant d'une immunogénicité plus durable et plus forte que celle du vaccin polysaccharidique Vi injectable (ViPS). Les données d'immunogénicité

5 years are available. TCV is licensed for use from 6 months of age, while ViPS and Ty21a are licensed for use from 2 years and 5 years of age, respectively. Co-administration data with MCV (measles only and measles-mumps-rubella vaccines) showed no interference with the immune response or increased reactogenicity.

SAGE re-emphasized the importance of programmatic use of typhoid vaccines for controlling endemic disease. Following review of the available data, SAGE recommended the introduction of TCV for infants and children over 6 months of age as a single dose in typhoid-endemic countries. Routine programmatic administration of TCV is likely to be most feasible at existing vaccine visits at 9 months of age or in the second year of life. Introduction of TCV should first be prioritized for countries with the highest burden of disease or a high burden of antibiotic resistant *S. Typhi*.

Reviewing epidemiological and modelling data, SAGE recommended catch-up vaccination when feasible, with priority for catch up in the youngest age groups (up to 15 years of age), noting that the burden of disease and programmatic feasibility are greater in this age range than in adults. Based on mathematical modelling, the benefit of routine plus catch-up vaccination is greatest where more cohorts are immunized in the initial campaign, and this strategy also has the potential to maximize indirect protection.

Typhoid vaccination is recommended in response to confirmed outbreaks of typhoid fever. Typhoid vaccination may be considered in humanitarian emergencies depending on risk assessment in the local setting.

Decisions on the preferred vaccination strategy (universal, subnational, or phased, as well as catch up) should be based on an analysis of disease burden, availability and quality of surveillance data, affordability, and operational feasibility. The experiences and impact of different vaccination strategies, as well as integration with water, sanitation and hygiene (WASH) or other interventions, should be monitored and documented in order to support a learning agenda for typhoid control.

SAGE highlighted the need for countries to strengthen the surveillance of typhoid fever, and to monitor the occurrence of antibiotic resistant strains of *S. Typhi* in endemic and epidemic disease, before and after programmatic use of TCV.

Introduction of TCV should include post-licensure monitoring of effectiveness, persistence of protection, and robust monitoring of vaccine safety, including any potential risks in special population groups.

Priority should be given to further research to support TCV policy and decisions on its introduction. In particular, data will be needed on co-administration of TCV

sont disponibles sur une durée allant jusqu'à 5 ans. Le VTC est homologué pour un usage à partir de 6 mois, tandis que le ViPS et le Ty21 sont homologués pour être utilisés à partir de 2 et 5 ans, respectivement. Les données de co-administration avec le MCV (vaccin antirougeoleux seulement et vaccins antirougeoleux-anti-ourliens-antirubéoleux) n'ont fait apparaître aucune interférence avec la réponse immunitaire ou augmentation de la réactogénicité.

Le SAGE a insisté à nouveau sur l'importance de l'utilisation programmatique des vaccins antityphoïdiques pour endiguer la maladie sous forme endémique. Après examen des données disponibles, il a préconisé l'introduction du VTC, sous forme de dose unique, chez les nourrissons et les enfants de >6 mois dans les pays d'endémie pour la typhoïde. L'administration programmatique systématique du VTC est probablement tout à fait praticable à l'occasion des visites vaccinales déjà instaurées à 9 mois ou au cours de la deuxième année de vie. L'introduction du VTC devra s'effectuer en priorité dans les pays supportant la plus forte charge de morbidité ou de bactéries *S. Typhi* résistantes aux antibiotiques.

En examinant les données épidémiologiques et de modélisation, le SAGE a préconisé des activités de vaccination de rattrapage lorsque cela était faisable, en donnant la priorité aux tranches d'âge des plus jeunes (jusqu'à 15 ans) et en prenant note que la charge de morbidité et la faisabilité programmatique sont plus fortes dans cette tranche d'âge que chez les adultes. D'après la modélisation mathématique, les bénéfices d'une vaccination systématique complétée par des activités vaccination de rattrapage sont d'autant plus importants que l'on vaccine un grand nombre de cohortes pendant la campagne initiale, une stratégie pouvant aussi maximiser la protection indirecte.

La vaccination antityphoïdique est recommandée pour répondre à des flambées confirmées de fièvre typhoïde. Cette vaccination peut être envisagée dans les situations d'urgence humanitaire, en fonction de l'évaluation des risques dans le contexte local.

Les décisions concernant la stratégie vaccinale à privilégier (universelle, infranationale, par étapes ou de rattrapage) devront s'appuyer sur une analyse de la charge de morbidité, de la disponibilité et de la qualité des données de surveillance, du caractère abordable ou non des interventions et de leur faisabilité opérationnelle. Les expériences avec les différentes stratégies de vaccination et l'impact de celles-ci, ainsi que leurs possibilités d'intégration avec des interventions concernant l'eau, l'assainissement et l'hygiène (WASH) ou autres, devront être suivis et documentés afin d'appuyer un programme d'apprentissage pour combattre la fièvre typhoïde.

Le SAGE a souligné la nécessité pour les pays de renforcer la surveillance de la fièvre typhoïde et de surveiller l'apparition de souches de *S. Typhi* résistantes aux antibiotiques dans les pays d'endémie et d'épidémie, avant et après l'utilisation programmatique du VTC.

L'introduction du VTC devra s'accompagner d'un suivi post-homologation de l'efficacité de ce vaccin et de la persistance de la protection qu'il confère, et d'une surveillance très sérieuse de son innocuité, et notamment des risques potentiels pour des groupes de population particuliers.

En priorité, les recherches futures devront viser à étayer la politique concernant le VTC et les décisions relatives à son introduction. En particulier, il faudrait disposer de données concer-

with routine childhood vaccines in typhoid-endemic countries, including PCV and yellow fever, meningococcal A conjugate and Japanese encephalitis vaccines. Data on vaccination of pregnant women are also needed; clinical trials of TCV in pregnant women have not been done and would be useful.

Pneumococcal conjugate vaccines

Since the previous review by SAGE of data and recommendations on use of PCV, the availability and use and of evidence on impact of the higher valency PCV products, particularly from LMICs, have increased. Prior to considering a revision of the vaccine recommendations, an updated review was therefore conducted. SAGE reviewed data on the optimal use of PCV with respect to dosing schedules (3p+0 and 2p+1), and products – PCV10 (10-valent) and PCV13 (13-valent) formulations, and use of catch-up vaccination. SAGE also reviewed primary data reporting PCV impact on serotype-specific immunogenicity, impact on nasopharyngeal carriage and invasive pneumococcal disease, and modelled evidence on the incremental impact of catch-up vaccination.

Recommendations on choice of schedule

SAGE concluded from the evidence provided that the 2p+1 and 3p+0 schedules both have a substantial impact on overall vaccine-type disease. SAGE also concluded that 2p+1 has a desirable impact on serotype 1 (ST1) disease; more limited data on 3p+0 also suggest an impact on ST1 disease using this schedule. SAGE therefore recommends administration of PCV in either a 2p+1 or a 3p+0 schedule starting as early as 6 weeks of age. SAGE recommends a minimum interval of 4 weeks and a maximum of 8 weeks in the primary series for the 2p+1 schedule, with a booster dose 9–18 months thereafter.

Recommendations on choice of product

SAGE considered the latest evidence on serotype-specific immunogenicity, and impact on nasopharyngeal carriage and disease endpoints for the 2 available PCV products. SAGE found that both vaccines have substantial impact against pneumonia, vaccine-type invasive disease and carriage. There is at present no evidence of different net impact on overall disease burden between the 2 products. PCV13 may have additional benefit in settings where disease attributable to serotype 19A (ST19A) or serotype 6C (ST6C) is significant. Product switching for individual children is only acceptable if it is not possible to complete the primary series or booster with the original product.

Recommendations on catch-up vaccination

Modelled data indicate that catch-up vaccination in children aged <5 years will accelerate PCV impact on

nant sa co-administration avec des vaccins administrés systématiquement aux enfants dans les pays d'endémie de la typhoïde, et notamment les vaccins VPC, contre la fièvre jaune, antiméningococcique A conjugué et contre l'encéphalite japonaise. Il faudrait aussi obtenir des données sur la vaccination des femmes enceintes; il n'a pas encore été réalisé d'essais cliniques du VTC chez des femmes enceintes et de tels essais seraient utiles.

Vaccins antipneumococciques conjugués

Depuis le précédent examen par le SAGE des données et des recommandations concernant l'utilisation du VPC, la disponibilité et l'exploitation d'éléments sur l'impact de vaccins de ce type de plus forte valence, en particulier dans les pays à revenu faible ou intermédiaire, ont progressé. Avant d'envisager une révision des recommandations vaccinales, un examen actualisé a donc été réalisé. Le SAGE a analysé les données relatives à l'optimisation de l'utilisation du VPC à travers le choix du calendrier (3 p + 0 ou 2 p + 1) et des produits (formulations de VPC décavalente ou à 13 valences) et la mise en œuvre d'activités de vaccination de rattrapage. Il a aussi étudié les données primaires reflétant l'impact du VPC sur l'immunogénicité spécifique au sérotype, le portage nasopharyngé et les maladies à pneumocoques invasives, et modélisé les données relatives à l'impact supplémentaire des activités de vaccination de rattrapage.

Recommandations concernant le choix du calendrier

Au vu des éléments fournis, le SAGE a conclu que les calendriers 2p + 1 et 3 p + 0 avaient tous les deux un impact substantiel sur l'ensemble des maladies imputables à des souches contenues dans le vaccin. Il a aussi conclu que le calendrier 2p + 1 avait un impact intéressant sur les maladies dues au sérotype 1 (ST1); les données plus limitées concernant le calendrier 3 p + 0 laissent supposer également un impact de sa mise en œuvre sur les maladies dues au ST1. Le SAGE recommande donc l'administration du VPC sous forme de calendrier 2p+1 ou 3p+0, dès l'âge de 6 semaines. Il préconise un intervalle de 4 semaines au minimum et de 8 semaines au plus dans la série primaire du calendrier 2 p + 1, avec une dose de rappel 9 à 18 mois après.

Recommandations concernant le choix du produit

Le SAGE a étudié les derniers éléments concernant l'immunogénicité spécifique du sérotype et l'impact sur le portage nasopharyngé et les critères de jugement relatifs à la maladie des 2 produits de type VPC disponibles. Il a constaté que ces 2 vaccins avaient un effet substantiel contre la pneumonie, les maladies invasives dues à des souches vaccinales et le portage. Il n'existe actuellement aucune preuve d'une différence nette d'impact entre les 2 produits sur la charge de morbidité globale. Le VPC13 peut présenter un bénéfice supplémentaire dans les contextes où la part des maladies attribuables au sérotype 19A (ST19A) ou au sérotype 6C (ST6Ct) est importante. Chez les enfants, un changement de produit en cours de vaccination n'est acceptable qu'en cas d'impossibilité d'achever la série primaire ou d'administrer la dose de rappel avec le produit de départ.

Recommandations concernant les activités de vaccination de rattrapage

La modélisation des données indique que les activités de vaccination de rattrapage chez les enfants de <5 ans accélèrent

disease burden regardless of transmission intensity. However, the efficiency of catch-up vaccination (cases prevented per doses delivered) varies by age strata, and that variation depends on the transmission intensity of the setting. Catch-up vaccination in children aged <5 years should also be considered in humanitarian emergency settings, for possible control of outbreaks, and for improved disease control where PCV coverage is low. Vaccination in children aged >5 years may be useful in the control of outbreaks that include older children and adults.

Recommendations on surveillance and research

Based on current evidence gaps, SAGE proposed surveillance and research priorities to guide future policy revisions, including: (i) sustained high quality, sentinel and population-based surveillance for pneumococcal disease and carriage, ideally indefinitely but no shorter than 5 years following full PCV introduction, in order to quantify long-term impact and monitor serotype changes; (ii) establishment of serotype-specific immune correlates of protection against invasive pulmonary disease; (iii) assessment of duration of protection; (iv) further assessment of dosing schedules and pneumococcal outbreak epidemiology, particularly epidemics of ST1 disease; (v) PCV impact on antimicrobial resistance and on antibiotic use; and (vi) a systematic analysis comparing 1-dose versus 2-dose catch-up schedules.

Rabies vaccines

Rabies is a vaccine-preventable viral zoonotic disease responsible for an estimated 60 000 human deaths every year. Most cases occur in Africa and Asia, and more than 40% of cases occur in children. Bites by infected dogs are responsible for over 99% of all human rabies cases. Rabies prevention involves 2 main strategies: (i) vaccination of dogs to interrupt virus transmission to humans; and (ii) human vaccination, either pre-exposure prophylaxis (PrEP, using vaccine only) and/or post-exposure prophylaxis (PEP, using vaccine alone or together with rabies immunoglobulin [RIG]). Current inactivated cell-cultured rabies vaccines are extremely well tolerated and have no contra-indications. The immune response and clinical effectiveness of established vaccination regimens approach 100% when appropriately administered. Although measurable antibody titres may wane following vaccination, a booster dose, which is typically administered only in response to a suspected rabies exposure, results in a rapid recall of the immune response. This applies even if no measurable antibody is present and a lengthy period of time has passed since the previous vaccine dose.

Barriers to PEP implementation include long complicated PEP vaccine regimens, as well as the high cost, low demand, uncertain supply, availability, variable quality and short shelf-life of RIG. Current WHO recom-

l'effet du VPC sur la charge de morbidité, quelle que soit l'intensité de la transmission. Néanmoins, l'efficacité de ces activités (nombre de cas prévenus par dose délivrée) varie selon la strate d'âge et cette variation dépend de l'intensité de la transmission dans le contexte considéré. Une vaccination de rattrapage des enfants de <5 ans devra aussi être envisagée dans les situations d'urgence humanitaire pour endiguer les flambées potentielles ou améliorer la lutte contre la maladie lorsque la couverture par le VPC est faible. La vaccination de ces enfants peut être utile pour combattre des flambées qui touchent aussi des enfants plus âgés et des adultes.

Recommandations concernant la surveillance et la recherche

Au vu des lacunes actuelles en matière de données, le SAGE a proposé des priorités pour la surveillance et la recherche afin de guider les futures révisions des politiques, et notamment: (i) une surveillance sentinelle et en population, maintenue à un haut niveau de qualité, des maladies à pneumocoques et du portage de ces germes, dans l'idéal sur une durée indéfinie ou, tout au moins, supérieure ou égale à 5 ans après l'introduction complète du VPC, pour quantifier l'impact à long terme et suivre les évolutions des sérotypes; (ii) la définition de corrélats immunitaires spécifiques d'un sérotype de la protection contre les maladies pulmonaires invasives; (iii) l'évaluation de la durée de la protection; (iv) une évaluation plus poussée des schémas posologiques et de l'épidémiologie des flambées de pneumocoques, en particulier des épidémies de maladies à pneumocoque ST1; (v) l'impact du VPC sur la résistance aux antimicrobiens et sur l'utilisation d'antibiotiques; et (vi) une analyse systématique comparant des schémas de rattrapage utilisant 1 dose et 2 doses.

Vaccins antirabiques

La rage est une maladie zoonotique virale, évitable par la vaccination, dont on estime qu'elle provoque 60 000 décès chaque année. La plupart des cas interviennent en Afrique et en Asie et >40% d'entre eux touchent des enfants. La morsure par un chien enragé est à l'origine de >99% des cas humains de rage. La prévention de cette maladie fait appel à 2 stratégies principales: (i) la vaccination des chiens pour interrompre la transmission du virus aux hommes; et la vaccination des humains, soit sous forme de prophylaxie préexposition (PrEP, utilisant le vaccin seulement) et/ou de prophylaxie postexposition [PEP, utilisant le vaccin seul ou en association avec de l'immunoglobuline antirabique (IGR)]. Les vaccins antirabiques inactivés, préparés sur culture cellulaire, actuels sont extrêmement bien tolérés et ne présentent aucune contre-indication. La réponse immunitaire et l'efficacité clinique obtenues avec les schémas vaccinaux établis sont voisines de 100%, lorsque ces schémas sont administrés de manière appropriée. Même si les titres d'anticorps peuvent diminuer jusqu'à devenir parfois non mesurable après la vaccination, une dose de rappel, qui n'est administrée habituellement qu'en réponse à une exposition présumée à la rage, entraîne un rappel rapide de la réponse immunitaire. Ce rappel intervient même si aucun titre d'anticorps n'est mesurable ou si une période prolongée s'est écoulée depuis la dose vaccinale précédente.

Les obstacles à la mise en œuvre d'une PEP sont notamment la longueur et la complication des schémas vaccinaux pour réaliser cette prophylaxie, ainsi que le coût élevé, la faible demande, la disponibilité et l'approvisionnement incertains, la

recommendations for PrEP and PEP have proven difficult to implement; only about 1% of patients in need receive RIG in rabies-endemic countries.

Although vaccination of dogs is a cornerstone of the strategy to achieve the global goal of zero dog-transmitted human rabies deaths by 2030, immunization of humans remains essential to save lives.

SAGE reviewed new evidence and programmatic experiences available since the 2010 WHO position paper on rabies vaccines and proposed revisions to the recommendations on PrEP, PEP and RIG administration.

SAGE issued recommendations that aim to be more public health directed, and cost, dose, and time sparing, while assuring safety and maintaining efficacy. Although training of health-care providers would be needed, using fractional intradermal (ID) doses of the vaccine is cost-saving, safe and effective in settings where ID vaccination allows for better use of vaccine vials. Shortened schedules for both PEP and PrEP were proposed.

PrEP makes administration of rabies immunoglobulin unnecessary after a dog bite. Accelerated PrEP regimens for all age groups of healthy individuals in the general population are either a 2-site (0.1 mL per site) ID regimen on days 0 and 7, or a 1-site (1 vial per site) intramuscular (IM) regimen on days 0 and 7. Special regimens apply for immunocompromised subjects.

PEP regimens for ID injection are cost- and dose-sparing, even in clinics with low patient throughput. Three PEP regimens have proven effective and are recommended depending on health service and patient needs: (i) the IPC regimen: 2-site (0.1 mL per site) ID on days 0, 3 and 7; (ii) the Essen regimen: 1-site (1 vial per site) IM on days 0, 3, 7 and 14–28, unrestricted for all populations, and (iii) the Zagreb regimen: 2 sites IM on day 0 and 1 site IM on days 7 and 21. Patients with documented immunodeficiency should be evaluated on a case-by-case basis.

There is no contraindication for use of PrEP and PEP, including for children, pregnant women, immunocompromised individuals and those receiving chloroquine or hydroxychloroquine. PrEP is indicated for individuals exposed to rabies by virtue of occupation, place of residence or travel. PrEP can further be considered when (a) there is a very high bite incidence above 5% annually and (b) when the local setting (e.g. remoteness), prevailing reservoir host and/or rabies epidemiology make it a cost-effective intervention for an entire subpopulation.

New evidence from Cambodia and United Republic of Tanzania shows that when thorough wound washing and prompt administration of vaccine are provided to

qualité variable et la courte durée de conservation de l'IGR. Les recommandations actuelles de l'OMS pour la PrEP et la PEP se sont révélées difficiles à mettre en œuvre; environ 1% seulement des personnes qui en auraient besoin reçoivent de l'IGR dans les pays d'endémie de la rage.

Même si la vaccination des chiens est la pierre angulaire de la stratégie pour réaliser l'objectif mondial «Zéro décès humain dû à la rage transmise par les chiens d'ici 2030», la vaccination des humains reste indispensable pour sauver des vies.

Le SAGE a réexaminé les expériences programmatiques et les éléments devenus disponibles depuis la parution en 2010 du document Vaccins antirabiques: note d'information de l'OMS, et proposé des révisions des recommandations relatives à l'administration de la PrEP, de la PEP et de l'IGR.

Le SAGE a publié des recommandations s'efforçant de viser davantage la santé publique et les économies de coûts, de doses et de temps, tout en garantissant la sécurité et en préservant l'efficacité. Même si elle suppose de former les prestataires de soins de santé, l'utilisation de doses vaccinales fractionnées, administrées sous forme intradermique (ID), permet de réduire les coûts et reste sûre et efficace dans les contextes où ce mode d'administration permet une meilleure utilisation des flacons de vaccin. Des calendriers raccourcis ont été proposés pour la PEP et pour la PrEP.

La PrEP rend inutile l'administration d'immunoglobuline antirabique après une morsure de chien. Les schémas accélérés de PrEP administrables à l'ensemble des tranches d'âge d'individus en bonne santé de la population générale sont les suivants: un schéma intradermique en 2 sites (0,1 mL par site), délivré aux jours 0 et 7 et un schéma intramusculaire en 1 site (1 flacon par site), délivré aux jours 0 et 7. Des schémas particuliers s'appliquent aux sujets immunodéprimés.

Les schémas de PEP à injecter par voie intradermique permettent des économies de coûts et de doses, même dans les dispensaires où le flux de patients est faible. Trois schémas de PEP se sont révélés efficaces et sont recommandés en fonction des besoins du service de santé et des patients : (i) le schéma IPC: délivré en 2 sites (0,1 mL par site), par voie ID, aux jours 0, 3 et 7; (ii) le schéma Essen: délivré en 1 site (1 flacon par site), par voie IM, aux jours 0, 3, 7 et 14–28, sans restriction pour l'ensemble des populations, et (iii) le schéma Zagreb: délivré en 2 sites, par voie IM, au jour 0, ou en 1 site, par voie IM, aux jours 7 et 21. Les patients souffrant d'un déficit immunitaire attesté devront être évalués au cas par cas.

Il n'y a aucune contre-indication à l'utilisation de la PrEP et de la PEP, y compris pour les enfants, les femmes enceintes, les individus immunodéprimés et ceux recevant de la chloroquine ou de l'hydroxychloroquine. La PrEP est indiquée pour les individus exposés à la rage en raison de leur métier, de leur lieu de résidence ou de leurs déplacements. Elle peut en outre être envisagée dans les cas (a) où le taux d'incidence des morsures est très élevé et supérieur à 5% par an et (b) où le contexte local (éloignement, par exemple), l'hôte réservoir prévalent et/ou l'épidémiologie de la rage font que cette intervention est d'un bon rapport coût/efficacité pour l'ensemble d'une sous-population.

De nouveaux éléments provenant du Cambodge et de la République-Unie de Tanzanie montrent que, moyennant un lavage soigneux de la plaie et une administration rapide du vaccin,

category III bite victims, 99% survive. Trials and programmatic experience indicate that infiltration of RIG in and around the wound neutralizes rabies virus within hours, whereas RIG administered IM distant to the wound is of limited value. These procedures allow RIG dose-sparing by calculating the maximum dose based on body weight, and injecting only the volume needed to infiltrate the wound(s). Guidance for aseptic use of remaining RIG will need to be developed. Equine RIG (eRIG) is clinically equivalent to human RIG (hRIG) and skin testing prior to its administration is unnecessary and should be discontinued.

SAGE welcomed these updates and accepted the proposed recommendations which should allow a more efficient, prudent and equitable use of human rabies biologicals, particularly in endemic settings.

Bacille Calmette-Guérin vaccine

SAGE was presented with epidemiological data, currently used schedules, as well as safety and efficacy data of BCG vaccine against tuberculosis and leprosy.

In 2015, there were an estimated 10.4 million new TB cases (142 per 100 000 population) worldwide, including 1.2 million new cases in HIV-infected persons; 480 000 of new infections were multidrug resistant and an additional 100 000 were rifampicin resistant. An estimated 1.8 million people died, including 210 000 children. Prevention of TB-related deaths relies mainly on 2 strategies: BCG vaccination of infants, preferably at birth, and treatment of latent TB infection, mainly in HIV-infected persons and young childhood contacts of TB patients.¹¹

Neonatal BCG vaccination protects against the more severe types of disseminated TB, such as miliary TB and tuberculous meningitis, to which infants and young children are particularly susceptible. Evidence from systematic reviews shows that BCG is protective against pulmonary TB for up to 20 years, especially when given to neonates, or to school-age children who are tuberculin skin test or interferon-gamma release assay (IGRA) negative. The protective effect appears to vary by geographic latitude, with the lowest protection being observed in populations living in latitudes close to the equator, though these findings may be confounded.

Although the fight against leprosy has had considerable success, more than 200 000 cases were notified in 2016 and the annual case detection rate is only slowly declining. The WHO SEAR accounts for 75% of the global leprosy burden and reported 161 263 new leprosy cases in 2016, but cases are reported in all Regions. Evidence indicates that BCG given at birth is effective for prevention of leprosy. Several studies suggest BCG vaccines

99% des victimes de morsures de catégorie 3 survivent. Des essais et l'expérience programmatique indiquent que l'infiltration d'IGR à l'intérieur et autour de la plaie neutralise le virus de la rage en l'espace de quelques heures, tandis que l'administration distante, par voie IM, de cette immunoglobuline est d'un intérêt limité. Ces procédures permettent d'économiser des doses d'IGR en calculant la dose maximale d'après le poids corporel et en n'injectant que le volume nécessaire pour infiltrer la ou les plaies. Il faudra mettre au point des orientations pour l'utilisation aseptique de l'IGR restante. L'IGR équine (IGRe) est cliniquement équivalente à l'IGR humaine (IGRh) et la pratique d'un test cutané avant son administration n'est pas utile et ne devrait pas être poursuivie.

Le SAGE a accueilli très positivement ces mises à jour et a accepté les recommandations proposées, qui devraient permettre un usage plus efficace, plus prudent et plus équitable des produits biologiques contre la rage humaine, notamment dans les contextes d'endémie.

Vaccin préparé à partir du bacille de Calmette-Guérin

On a présenté au SAGE des données épidémiologiques, des schémas actuellement utilisés ainsi que des données d'innocuité et d'efficacité pour le vaccin BCG contre la tuberculose et la lèpre.

En 2015, on estimait à 10,4 millions le nombre de nouveaux cas de tuberculose (142 pour 100 000 habitants) dans le monde, dont 1,2 million apparus chez des personnes déjà infectées par le VIH; 480 000 des nouvelles infections étaient multirésistantes et 100 000 autres étaient résistantes à la rifampicine. On estimait aussi la mortalité due à la tuberculose à 1,8 million, dont 210 000 enfants. La prévention de cette mortalité repose principalement sur 2 stratégies: vaccination par le BCG des nourrissons, de préférence à la naissance, et traitement des infections tuberculeuses latentes, principalement chez les personnes infectées par le VIH et chez les jeunes enfants en contact avec des malades tuberculeux.¹¹

La vaccination par le BCG des nouveau-nés apporte une protection contre plusieurs types sévères de tuberculose disséminée, comme la tuberculose miliaire et la tuberculose méningée, auxquels les nourrissons et les jeunes enfants sont particulièrement sensibles. Des éléments tirés de revues systématiques montrent que le BCG protège contre la tuberculose pulmonaire sur une durée allant jusqu'à 20 ans, en particulier lorsqu'il est administré à des nouveau-nés ou à des enfants d'âge scolaire dont le test tuberculinique ou le test de libération d'interférons gammas (IGRA) est négatif. Cet effet protecteur semble varier avec la latitude géographique, la protection la plus faible étant observée parmi des populations vivant à des latitudes proches de l'équateur, bien que les résultats ne soient pas très clairs.

Si la lutte contre la lèpre a remporté des succès considérables, >200 000 cas ont été notifiés en 2016 et le taux de détection annuelle des cas n'a que faiblement baissé. La Région SEAR de l'OMS totalise 75% de la charge mondiale de lèpre et a signalé 161 263 nouveaux cas de cette maladie en 2016; néanmoins toutes les régions OMS notifient des cas. Des éléments indiquent que le BCG administré la naissance est efficace dans la prévention de la lèpre. Plusieurs études laissent à penser que les

¹¹ Global tuberculosis report 2016. World Health Organization, Geneva, 2016. Available at www.who.int/tb/publications/global_report/en/, accessed October 2017.

¹¹ Rapport sur la lutte contre la tuberculose dans le monde 2016. Organisation mondiale de la santé, Genève, 2016. Disponible à l'adresse: www.who.int/tb/publications/global_report/fr/, consulté en octobre 2017.

might also prevent other mycobacterial infections including Buruli ulcer disease.

BCG vaccination is generally safe in immunocompetent children. Lymphadenitis and other severe reactions have been described, and products as well as vaccine lots have occasionally been associated with increased reports of adverse events following immunization. However, vaccination of immunocompromised persons, including HIV-infected infants, is not recommended. While robust evidence is lacking, reduction in HIV mother-to-child transmission rates, earlier diagnosis of neonatal HIV infection and earlier initiation of antiretroviral treatment are expected to reduce the overall risk of acquiring HIV and/or severe immune suppression. This changing epidemiology of HIV infection is likely to reduce the risk of BCG adverse events in HIV-infected children.

SAGE reaffirmed the current recommendation of universal birth dose vaccination with BCG in high incidence TB settings, and expanded this to include high burden leprosy settings regardless of the TB incidence. SAGE concluded that due to paucity of evidence to assess differences in the vaccine efficacy/ effectiveness and safety of vaccination at different ages (birth versus age 6 weeks, 6 months or one year), no policy change regarding the age of vaccination is justified. SAGE further stressed that BCG vaccination together with hepatitis B vaccination should be administered as soon as possible after birth, ideally within 24 hours and that it is safe to do so.

SAGE recommended that countries with a low incidence of TB and leprosy may choose to selectively vaccinate neonates in recognized groups at high risk of developing disease. SAGE reiterated that BCG re-vaccination is of little additional benefit and is therefore not recommended. SAGE further stressed that BCG vaccination is contraindicated for HIV-infected persons and those with congenital cell-mediated or severe combined immunodeficiency, acquired immunodeficiency diseases and for patients or infants born to mothers receiving immunosuppressive therapy. However, SAGE considered that administration of BCG can be recommended if HIV-infected individuals have started anti-retroviral therapy (ART), are clinically well and immunologically stable (CD4% >25% for children aged <5 years or CD4 count ≥200 if aged >5 years), especially for those living in high incidence TB settings. Neonates born to women known to be HIV-infected and whose HIV infection status is unknown but who demonstrate no signs or reported symptoms suggestive of HIV infection should be vaccinated, particularly if the mother is already receiving ART.

In view of the complexity of the issues, SAGE identified several topics for further research and emphasized the need for new vaccines against TB and leprosy for all age groups. ■

vaccins BCG pourraient aussi prévenir d'autres infections mycobactériennes, dont l'ulcère de Buruli.

La vaccination par le BCG est généralement sûre chez les enfants immunocompétents. Des lymphadénites et d'autres réactions graves ont été décrites et des produits ainsi que des lots de vaccins ont été occasionnellement associés à une augmentation des notifications de manifestations postvaccinales indésirables. Cependant, la vaccination des personnes immunodéprimées, et notamment des nourrissons infectés par le VIH, n'est pas recommandée. Malgré le manque de preuves robustes, on s'attend à ce que la réduction des taux de transmission mère-enfant du VIH, le diagnostic plus précoce des infections néonatales par ce virus et la mise en route plus rapide des traitements antirétroviraux réduisent le risque global de contracter le VIH et/ou celui d'immunodépression sévère. Les évolutions dans l'épidémiologie des infections à VIH réduiront probablement le risque de manifestation indésirable due au BCG chez les enfants infectés par ce virus.

Le SAGE a réaffirmé la recommandation actuelle incitant à l'administration universelle d'une dose de BCG à la naissance dans les contextes de forte incidence de la tuberculose et a étendu cette recommandation aux situations de forte charge de morbidité due à la lèpre, indépendamment de l'incidence de la tuberculose. Le SAGE est parvenu à la conclusion qu'en raison du manque de preuves pour évaluer les différences d'efficacité du vaccin pour différents âges d'administration (à la naissance par comparaison avec 6 semaines, 6 mois ou un an), aucune modification de la politique relative à l'âge de vaccination ne se justifiait. Le SAGE a encore souligné que la vaccination par le BCG associée à la vaccination contre l'hépatite B, devait être administrée dès que possible après la naissance, dans l'idéal dans les 24 heures qui suivent, et que cette manière de procéder était sans risque.

Le SAGE a recommandé que les pays présentant une faible incidence de la tuberculose et de la lèpre, puissent choisir de vacciner sélectivement les nouveau-nés appartenant aux groupes reconnus comme à haut risque de contracter la maladie. Il a rappelé que la revaccination par le BCG n'offrait que peu de bénéfices supplémentaires et n'était donc pas recommandée. Il a en outre souligné que la vaccination par le BCG était contre-indiquée chez les personnes infectées par le VIH et chez celles souffrant d'un déficit immunitaire congénital à médiation cellulaire ou combiné sévère, de maladies entraînant une immunodéficience acquise et chez les personnes ou les nourrissons nés de mères recevant un traitement immunosuppresseur. Néanmoins, le SAGE a considéré que l'administration du BCG pouvait être recommandée chez les individus infectés par le VIH ayant débuté un traitement antirétroviral (ART) qui se portent bien cliniquement et sont stables sur le plan immunologique (% CD4 >25% chez les enfants de <5 ans où numération des CD4 ≥200 chez les individus de >5 ans), et en particulier chez ceux vivant dans des contextes de forte incidence de la tuberculose. Les nourrissons nés de femmes que l'on sait infectées par le VIH ou dont le statut pour ce virus n'est pas connu et qui présentent des signes ou des symptômes rapportés suggérant une infection à VIH, devront être vaccinés, en particulier si leur mère reçoit déjà un traitement ART.

Compte tenu de la complexité de ces questions, le SAGE a identifié plusieurs thèmes de recherche à explorer plus avant et a souligné la nécessité de disposer de nouveaux vaccins contre la tuberculose et la lèpre, administrables dans toutes les tranches d'âge. ■

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SAGE TRACKING RECORD OF RECOMMENDATIONS AND ACTION POINTS

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

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

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

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|-------------------------|--|--------------|---------|---|
| General | SAGE stressed that additional disaggregation was needed in the analysis of the progress achieved on the ground, and in identifying bottlenecks for progress, and recommended that reports display disparities observed at sub-national levels. | Apr 2015 | Ongoing | WHO headquarters (HQ) is working closely with regional offices to obtain subnational level data. Surveillance data for measles and rubella as well as for new vaccines is collected at the district level on regular basis and there are efforts to collect sub-national level coverage data. Currently this is happening in the African Region on monthly as well as annual basis; and in the South East Asian Region and the European Region it is done on annual basis. In October 2016, at the Global Monitoring Meeting all regions agreed to collect and submit to HQ district level coverage data (numerator, denominator and coverage from DTP1, DTP3 and MCV1) as part of annual data collection exercise. Out of 194 member states, 125 countries reported subnational coverage, 36 at the 1st subnational level and 89 at the 2nd subnational administrative level (often corresponding to districts). The 20,000 districts for which data were received are home to 88 million children, two-thirds of the surviving infants worldwide. An initial analysis shows large differences in the size of these districts and the coverage they report. A large proportion report coverage over 100%, revealing the challenges to accurately measure coverage at subnational level. Detailed analysis and reported data are available from http://www.who.int/immunization/monitoring_surveillance/data/subnational/en/ |
| General | SAGE recommended that ways to improve curricula for medical personnel should be explored. | Nov 2008 | Ongoing | The Regional Office for Africa (AFRO) has published the pre-service curriculum and efforts are being made to disseminate the findings and ensure that medical and nursing schools change their outdated curriculum. This is a long process but few steps have started in that direction. |
| AEFI reporting | SAGE urged that efforts be pursued to enhance Adverse Events Following Immunization (AEFI) reporting worldwide. | Apr 2016 | Ongoing | With Gavi support, 30 African countries have established work plans. A first analysis of the new Global Vaccine Action Plan (GVAP) indicator for adverse events following immunization (AEFI) monitoring has identified 84 member states that meet the recommended level of at least 10 AEFI cases reported per 100,000 surviving infants per year. A manuscript is currently submitted that describes the AEFI reporting ratio through Joint Reporting Form (JRF). 2016 data are currently analyzed and indicate an increase in the number of member states that fulfill the indicator requirement. In addition, a paper is in press that describes the AEFI ratio indicator during 2000-2015. |
| Data quality | SAGE requested the establishment of a Working Group on Quality and Use of Global Immunization and Surveillance Data. | Apr 2017 | Ongoing | The Working Group was established in August 2017. Thirteen members are part of this working group. The terms of reference were split into 6 and a member was assigned as a lead each. Several teleconferences have been held and nine members participated in the "Data Partners Meeting" organized by EPI/WHO in October 2017. Work is ongoing. |
| Decade of vaccines/GVAP | The SAGE working group should continuously review the need for reformulation of the indicators or mechanisms for collection and reporting of data. | Nov 2012 | Ongoing | The SAGE Decade of Vaccines (DoV) Working Group (WG) continues to review annually progress on the Global Vaccine Action Plan (GVAP) indicators. The SAGE report of progress with the Global Vaccine Action Plan (GVAP) for 2017 was published online and is available at: http://www.who.int/immunization/global_vaccine_action_plan/en/ This report was noted by the Executive Board in Jan 2018. The WG will start its calls in March for the yearly planning and proceed with its regular calls in July and August 2018 when draft secretariat report becomes available. The SAGE DoV WG will meet in person from 28-30 August for the yearly revision of progress in the implementation of GVAP for the year 2017. GVAP will an item on the SAGE Oct 2018 agenda. |

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| Diphtheria | SAGE recommended that surveillance standards, guidelines for the investigation including diagnostics and reporting of diphtheria cases and outbreaks, be updated to improve the quality of data and to facilitate pooled analysis. The guidelines should include standard formats for reporting age with increased granularity and immunization status categorization. | Apr 2017 | Ongoing | Work is ongoing to update the global vaccine-preventable disease (VPD) surveillance standards and will include a new and improved chapter on diphtheria surveillance. It will address the points recommended by SAGE and should be ready by early 2018. |
| Diphtheria | SAGE advised that WHO collaborate closely with partners to establish and manage a global procurement mechanism and a physical or virtual DAT stockpile that would be available to all countries. SAGE further urged that regulatory pathways be established to ensure the rapid deployment of DAT. In the long term, SAGE advised WHO to identify mechanisms to support the development of a monoclonal antibody as an alternative to DAT of equine origin. | Apr 2017 | Ongoing | <p>WHO has established a DAT international working group to coordinate and allocate extremely limited DAT supplies. In the short term the working group will coordinate the procurement of DAT to avoid competition among different procurement agencies and partners. The DAT-WG currently prioritizes the urgent requests from Yemen, Bangladesh, Indonesia, Venezuela and Haiti. Around 20,000 vials have been deployed between WHO, PAHO and MSF supply mechanism. In the mid-long term the DAT-WG is looking for more sustainable solutions to establish a stockpile and a decision making mechanism for allocation like the ICG for vaccines.</p> <p>WHO DAT-WG coordinates the group to look at the following areas of work:</p> <ol style="list-style-type: none"> 1. Procurement strategy 2. Forecasting and Stockpiling 3. Decision making criteria and mechanism for DAT allocation 4. Quality, standardization and WHO prequalification 5. DAT production capacity and new products (mAbs) <p>Members of the coordinating group: MSF, UNICEF, ECDC, CDC, PEI, MHRA, EC, FDA, EMA, PHE, NIBSC</p> |
| Diphtheria | SAGE expressed concern with the shortage of Td vaccine (tetanus toxoid + reduced diphtheria toxoid content) for routine immunization of children and adolescents, catch-up vaccination of adults and tetanus prevention after injury, and recommended that the demand and supply scenarios for Td vaccines should be assessed. | Apr 2017 | Ongoing | <p>An assessment of global demand and supply for Diphtheria and Tetanus containing vaccines has been finalized and is available for SAGE members and wider public. The main objective of the assessment was to understand possible supply implications of global implementation of WHO recommended schedule for D&T containing vaccines. The assessment can also be useful to guide current supply access issues. The assessment was conducted with support from Linkbridge and MMGH consulting group. A temporary Advisory Group of expert was convened to guide this work advising on methodology, assess current and future supply risks and advice on policy implications. A final meeting of the Advisory Group was held on September 13th concluding that:</p> <ul style="list-style-type: none"> • WHO recommends for all countries: 1) a life course of 6 doses of Diphtheria and Tetanus containing vaccines and 2) use of Td in place of TT • 100 / 194 countries do not meet these recommendations, but due to conducive circumstances, they are now likely to implement WHO recommendations • Full implementation of the recommendations would increase global demand for all D&T containing vaccines by ~20% • Sufficient supply is available to cover both current and future demand for wP / non-aP containing vaccines • Supply of aP-containing vaccines is currently sufficient to support demand from countries where the product is in use; access in additional countries may be problematic • Countries with only one locally-registered product are at risk of supply shortages, irrespective of the global supply-demand balance |

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| Ebola vaccines | Noting WHO's unique position to coordinate the development of Ebola vaccines, SAGE stressed the importance of transparent and prompt sharing of information on the trial protocols and data from the phase 3 clinical trials, and the need for a greater role for WHO in facilitating the sharing of information so that results between studies will generate the greatest benefit for policy decision-making. | Apr 2015 | Ongoing | <p>SAGE established an Ebola working group (WG) in Nov 2014 which met regularly via teleconference as well as during a face-to-face meeting on the 9-10 Mar 2015. The WG reviewed the epidemiological data on Ebola Virus Disease (EVD), the preliminary results of the phase 1 trials, the status of the phase 2 and 3 trials, and the preparations for the large scale deployment of vaccines. They also identified the scope of the recommendations and the key questions and data for formulating recommendations. The framework was presented to SAGE at the Apr 2015 meeting. The WG met again on 19-20 Aug 2015 to review the available information and to start framing recommendations, based on the framework approved by SAGE in Apr 2015. The WG input was presented to SAGE at the Oct 2015 meeting.</p> <p>Now, that the final results of the Ring trial have been published in the Lancet in Dec 2016, a WG meeting took place 14-15 Mar 2017 to discuss the results.</p> <p>Regulatory evaluation of the vaccine is currently ongoing.</p> <p>There is information regarding a Russian developed vaccine that was licensed in Russia, but despite WHO requests no detailed data are available. The emerging data and draft recommendations were discussed during the face to face meeting of the WG which took place Mar 2017. The evidence was presented during the April 2017 SAGE meeting.</p> |

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| Hepatitis A | Long-term protection from single or 2-dose schedules should be regularly monitored by countries and reviewed by SAGE. | Apr 2012 | Ongoing | <p>Post-market surveillance continues in Argentina and a detailed report on the recent epidemiological situation was provided to WHO in March 2017. The next active follow-up report will be requested ahead of the April 2018 SAGE meeting.</p> <p>In 2014, in the context of a localized outbreak in a border area, 8 potential breakthrough cases were identified. For 5 of them there is uncertainty about the vaccination status and/or conditions (cold chain) in which vaccination was administered. Seven of these cases are in the 5-9 age group (distributed throughout the period) and one in the 1-4 age group. This resulted in an enhanced vigilance in the country. As exemplified by the outbreak in San Martin, the risk persists in the population. 73% of hepatitis A virus (HAV) acute infection cases reported occurred in individuals over >10 years. All cases reported occurred in unvaccinated individuals.</p> <p>After now 11 years of follow-up, there is currently still no evidence of waning immunity and the outbreak experienced in 2014 was compatible with very high vaccine effectiveness. Hepatitis A cases have remained low in 2014, 2015, and 2016. Although a reduction in hepatitis A rates was experienced in all age groups, there is an increasing proportion of the remaining cases occurring in persons > 14 years of age in the post vaccination period. Most of these represent non-vaccinated adolescents or adults that escaped HAV-infection in previous outbreaks.</p> <p>Both Colombia and Paraguay also introduced a single dose national immunization schedule for 1 year old children. Yearly review of the Argentinian surveillance data will continue as Argentina was the front runner country to introduce a 1 dose schedule with the inactivated vaccine.</p> <p>A third phase immunogenicity study is ongoing in Argentina, to assess long term protective antibodies in children more than 9 years following single dose vaccination. The results of the phase 2 study conducted in 2013 with a median post-vaccination interval of 7.7 years were quite reassuring with a prevalence of protective antibodies of 97.4% (95% CI: 96.3-98.3) still protected. More recent analysis (phase 3) indicates that the prevalence of protective antibodies in children > 9 years following a single dose of hepatitis A vaccine was still 87.6% but a decrease was observed in all centers with decreased GMCs. It is still unclear if different samples or differences in methodology or recall bias in seronegative individuals could actually account for the difference, but this requires continued follow up. For the time being epidemiologic surveillance continues to show very low infection rates in all regions and age groups with sporadic cases occurring mainly in frontier regions and non-vaccinated adolescents.</p> |
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| Hepatitis B | SAGE recommended that the timely delivery of a birth dose of hepatitis B vaccine (that is, within 24 hours of birth) should be used as a performance measure for all immunization programmes. Reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose. | Apr 2009 | Ongoing | <p>WER on status of global introduction and implementation of hepatitis B birth dose has been drafted and cleared; scheduled for publication in Feb 2018.</p> <p>A new indicator for Hepatitis B birth dose has been added to the WHO /UNICEF Joint Reporting Form (JRF) 2017 - this new indicator will allow the distinction between timely (24 hours) and late birth dose administration.</p> <p>In Nov 2016, AFRO held consultation on hepatitis B control and included discussing barriers, actions and support needed towards hepatitis B birth dose introduction. This was part of joint meeting held with viral hepatitis counterparts.</p> <p>A consultation on implementation of a new universal birth dose recommendation was conducted in Dec 2010 with special focus on countries with a high percentage of home births. Outputs include a monograph documenting the systematic review and best practices from the consultation. Immunization Practices Advisory Committee (IPAC) reviewed this work in early 2011 and again in Apr 2012, and endorsed the 2013 publication of 'Practices to Improve Coverage of the Hepatitis B birth dose vaccine.' From this, work is ongoing to develop field guidelines for scaling up Hepatitis B birth dose. The JRF and associated materials have been revised to improve reporting of birth dose with a particular focus in Western Pacific Regional Office (WPRO). The WHO/UNICEF estimate process was piloted in 2012 in WPRO and was applied globally for the first time to the 2013 JRF birth dose data. Analysis of timely birth dose data for 2008 shows no significant changes from 2006 analysis and the major issue is lack of data quality. A study of the cost of scaling up the birth dose by country has been completed, based upon previously published methodology estimating the cost of implementing the Global Immunization Vision and Strategy (GIVS) goals. In 2012, WPRO convened Expanded Program on Immunization (EPI) and Maternal and Child Health (MCH) managers from the five priority countries to jointly propose actions towards improving birth dose uptake.</p> <p>In Jan 2015 the African Regional Office (AFRO), and in Mar 2015 WPRO, held Hepatitis B birth dose consultations to improve birth dose coverage. In Feb 2015, an AFRO workshop on birth dose introduction was conducted in Brazzaville; this workshop included guidance on birth dose monitoring. An assessment of birth dose implementation has taken place in Sao Tome Principe in July 2015 and Nigeria in September 2015 and in the Gambia in Dec 2015. Senegal held a Hepatitis B birth dose training workshop in Dec and introduced birth dose in Jan 2016.</p> <p>Guidance for hepatitis B birth dose introduction was published on June 2016 ('Preventing Perinatal Hepatitis B Virus Transmission: A Guide for Introducing Hepatitis B Birth Dose Vaccination', available from: http://www.who.int/immunization/documents/general/ISBN9789241509831/en/ in English, French and Spanish. An Arabic version is under development). The guidance includes a chapter on reporting and monitoring birth dose vaccination.</p> |

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| Hepatitis B | All regions and associated countries should develop goals for hepatitis B control appropriate to their epidemiologic situations. Serologic surveys of hepatitis B surface antigen (HBsAg) prevalence, representative of the target population, will serve as the primary tool to measure the impact of immunization and achievement of the control goals. | Nov 2008 | Ongoing | <p>In 2017, it was approved to collect an additional variable on hepatitis B birth dose to distinguish birth dose vaccine administered within 24 hours (TIMELY) and any birth dose administered (TOTAL) as part of the WHO/UNICEF Joint Reporting Form (JRF). Previously only timely birth dose was requested.</p> <p>As of August 2017, all regions have had the regional committees (RCs) on immunization endorse hepatitis B control goals, except for the South East Asian Regional Office (SEARO) which as noted below had a 2016 ITAG recommendation to establish a goal. Regional goals slightly differ in target dates, threshold prevalence and specific ages in which to measure prevalence - but are largely similar nonetheless.</p> <p>In Sept 2016, the European Regional Office (EURO) held a consultation to discuss establishing a regional verification mechanism.</p> <p>In June 2016, the SEARO's ITAG recommended to establish a Regional control goal of less than or equal to 1% HBsAg sero prevalence by 2020 among children aged 5 years. In August 2015, an HQ mission took place to discuss HepB control targets.</p> <p>In August 2016, the The African Regional Office (AFRO) Regional Committee discussed adopting a viral hepatitis strategy in line with the Global Health Sector Strategy (GHSS) for viral hepatitis which includes a hepatitis B control target in-line (although more ambitious) with the target endorsed as part of the immunization strategy at the 2014 RC meeting.</p> <p>In April 2016, WHA Endorsed the GHSS for viral hepatitis that includes immunization-related 'elimination targets'; specifically to reduce chronic HBV infection rates (HBsAg prevalence) in children to at least 1% by 2020 and to at least 0.1% by 2030.</p> <p>In 2014, the AFRO RC meeting adopted resolution to reduce Hep B infection to <2% among children under 5 years of age by 2020 and adopted hepatitis B activities as part of the RVAP that was also endorsed at the same RC meeting.</p> <p>The Eastern Mediterranean Region (EMR) has a RC goal of reducing childhood hepatitis B prevalence to <1% among children <5 years by 2015. Its regional office, EMRO is working with Member States to ensure achievement of this goal.</p> <p>The Western Pacific Region (WPR) established a RC goal to reduce hepatitis B infection to <1% among children at least 5 years of age by 2017.</p> <p>The EURO will consider a regional hepatitis B control goal as proposed by ETAGE.</p> <p>The Pan American Health Organization (PAHO) has resolved to eliminate hepatitis B virus transmission and is formulating a regional strategy.</p> <p>Documenting the "Impact of Hepatitis B Immunization: best practices for conducting a serosurvey" (WHO/IVB/11.08) was published in 2011 by the department of Immunization, Vaccines and Biologicals.</p> <p>In 2012, WHO HQ has published a framework for global action to control viral hepatitis (http://www.who.int/csr/disease/hepatitis/Framework/en/index.html).</p> <p>As of March 2018, one Hepatitis B vaccine manufacturer is actively testing its birth-dose vaccine with a view to seeking a label variation for licensed and WHO Pre-qualified use in a Controlled Temperature Chain (CTC). In parallel, the CTC working group under the Immunization Practices Advisory Committee (IPAC) is finalizing a landscape analysis and strategy to further promote the use of hepatitis B birth-dose in a CTC.</p> |
| Hepatitis B | SAGE strongly urges all the pre-qualified vaccine manufacturers of monovalent hepatitis B vaccine to pursue regulatory approval for Controlled Temperature Chain (CTC) as soon as possible, given the available evidence of compatibility with CTC requirements. | Oct 2016 | Ongoing | |
| Hexavalent IPV-based combination vaccines PQ and supply | tracking progress on Hexavalent IPV-based combination vaccines prequalification and supply | Oct 2017 | ongoing | |

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| HIV | SAGE requested regular updates on the progress of HIV-vaccine research. | Apr 2010 | Ongoing | Two HIV vaccine efficacy studies have started in Africa, late 2017. The HVTN702 phase 2b efficacy trial in Southern Africa, builds on analyses of correlates of protection in the RV144 Phase 3 trial in Thailand (which showed 31 % protection against new HIV infection during the 3.5 years after vaccination, 60 % during the first year), is testing an immunization regime based on a canarypox-based vaccine called ALVAC-HIV and a bivalent gp120 protein subunit vaccine. As compared to the RV144 trial this regimen includes a new adjuvant, targets the HIV Clade C and includes the addition of booster doses. The HVTN 705 Phase 2b trial in several African countries will test for a regimen based on 4 mosaic recombinant Ad26 and the gp140 protein trimer in alum. Another important development relates to the testing of several monoclonal antibodies having broadly neutralizing antiretroviral properties. Two multicenter, multi-country studies, one of which in women in South Africa, will test for prevention of HIV infection after several VRC01 monoclonal antibody injections. Building on progress in B cell biology and the structural characterization of the envelope protein, vaccine studies aiming to induce broadly neutralizing are starting . Several other approaches are being tested in translational research . WHO IVR will organize a consultation on HIV vaccine development late february to discuss the status of HIV vaccine research and the need for the global health community to prepare for the outcome of ongoing efficacy trials in highly endemic countries. |
| Immunization schedules | SAGE requested that IVIR-AC assess optimal immunization schedules based on both direct and indirect effects and not only direct effects. | Oct 2015 | Ongoing | As part of any vaccine impact evaluation, IVIR-AC reviews and encourages studies of optimal schedules on both direct and indirect effects. Study projects and meetings have been held and are planned on HPV, Hep B vaccines, rotavirus vaccines among others. |

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| Immunization schedules | SAGE requested a critical appraisal of alternative schedules for pneumococcal conjugate vaccine, rotavirus vaccine and Hib vaccine in 2011. | Nov 2010 | Ongoing | <p>The funding grant from Bill & Melinda Gates Foundation (BMGF) for schedules-related work to inform SAGE discussions on immunization schedules is now over. All delays in regard to this work were due to the Ebola outbreak and the R&D Blueprint on staff responsibilities.</p> <ul style="list-style-type: none"> - Pneumococcal Conjugate Vaccine (PCV): evidence was reviewed by SAGE in November 2011. A new position paper was published in 2012. - Rotavirus: evidence was reviewed by an ad-hoc group of experts in February 2012 and presented to SAGE in April 2012. An updated vaccine position paper was published in February 2013. A new review of evidence is ongoing. - Haemophilus influenzae type b (Hib): The issue was revised during the April SAGE 2013 meeting. A new position paper was issued. - Pertussis: evidence was reviewed by SAGE in 2015. A new position paper was published in August 2015. - Hepatitis B: evidence was reviewed by SAGE in Oct 2016. A new position paper was published in July 2017. - HPV: evidence was reviewed by SAGE in Oct 2016. A new position paper was published in May 2017. - TT vaccine: evidence was reviewed by SAGE in Oct 2016. A new position paper was published in February 2017. - Diphtheria: evidence was reviewed by SAGE in Apr 2017. A new position paper was published in August 2017. <p>A consultation to develop analytic tools to support countries with the selection and/or adjustment of vaccine schedules in different epidemiological and operational scenarios took place in December 2016. The critical evidence elements needed at country level to inform the choice of schedules were outlined. The tools are being further developed with the inputs of policy makers.</p> <p>With support from the BMGF we are updating the review of the evidence (epidemiology, vaccine efficacy and effectiveness, safety, risk benefit, impact) of rotavirus vaccines. A consultation will take place in the October 2017. The data presented and discussed did not indicate that the 2013 SAGE policy recommendation needs to be changed.</p> <p>We are now reviewing the evidence on human papilloma virus vaccines (epidemiology, vaccine efficacy and effectiveness, safety) and assessing the impact of different HPV vaccination strategies as well as examining the conditions under which elimination could be possible.</p> |

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| Implementation | SAGE recommended that WHO promote further progress in the area of implementation more actively, and that a preparatory team continue the dialogue and develop a more targeted agenda. | Apr 2016 | Ongoing | <p>The WHO is currently implementing multiple World Health Assembly (WHA) resolutions that mandate integration of disease-specific programs, using a Health Systems Strengthening (HSS) framework to achieve Universal Immunization coverage as part of Universal health Coverage (UHC). This fits well with the Sage proposal to make integration a 'third pillar' of immunization service provision. Within the Gavi sphere, the Alliance has committed to having HSS underpin the Country Engagement Framework (CEF), under which all Gavi grants will be aligned and managed as a single package of results-focused investments. WHO Health Systems and Innovation (HIS)/Health Sys Governance, Policy & Aid Effectiveness (HGS) has assisted the Gavi Alliance Partners and Gavi Secretariat in developing CEF. The WHO's Regional and Country Office HGS/HSS Focal Points are the organizational drivers for CEF engagement, providing technical Assistance on strategic, financial and operational integration of core immunization functions and systems.</p> |
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| Implementation research | The implementation research agenda should define equity beyond traditional economic money metrics such as social economic status gradients, to include other measures of inequity such as the multidimensional poverty index or impacts on marginalized populations. SAGE suggested that studies to examine the integration of immunization with other health interventions should be included in the implementation research agenda. | Nov 2013 | Closed | This recommendation is part of the new Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) agenda under research to minimize barriers and improve coverage of vaccines currently in use. Since 2014 research topics on the non-specific effects of vaccines, missed opportunities and community vaccine acceptance have been part of the agenda of IVIR-AC. |
| Implementation Research | SAGE outlined some considerations for IVIR-AC to include in their deliberations – assessment of the use of high quality randomized controlled trials where feasible (noting the substantial ethical and methodological challenges involved), with sufficient power to explore sex differences, and a priori defined and standardized immunological endpoints designed to answer the specific question of non-specific effects– and emphasized that future research should draw on a broad investigator pool and from a wide range of geographic locations using a standardized protocol. | Apr 2014 | Closed | During the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) June 2015 meeting, IVIR-AC endorsed the designing of one or more protocols to assess the prospective non-specific effects (NSE) of immunization on mortality. The work of the WHO Secretariat needs to be completed in preparing the protocols for the questions identified and trials outlined during the ad-hoc expert consultation of Feb 2016. These generic protocols would enable harmonized implementation of the trials across multiple settings. While further development of all the proposed trial designs is important, IVIR-AC recognizes that full evaluation necessitates a complete protocol. IVIR-AC will help inform decisions on feasibility and the selection of designs, and formulate questions. At the February 2017 meeting, IVIR-AC reviewed the final proposals for 2 trial designs suggested by the ad-hoc Working Group on NSE. It was presented at the SAGE April 2017 meeting as part of the briefing of IVIR-AC by chair Rob Breiman. |
| Implementation Research | SAGE identified the conditions necessary for pertussis resurgence and the effective strategies for prevention of resurgence as important topics for modelling research. | Apr 2014 | Ongoing | The June 2015 meeting of the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) meeting agreed on the plan for phase 1 of the comparison of pertussis models from Australia, England & Wales and the United States of America, which is meant to be a rapid assessment on the relative contributions of vaccine formulations, waning immunity, vaccine coverage and schedule to the observed pertussis resurgence in these countries. If successful, phase 2 offers further opportunities to test whether existing models are sufficiently robust to changes in factors such as demographics, spatial heterogeneity, immunity and contact matrices across multiple settings. In many countries using aP vaccine in the national immunization programme, aP vaccine is used in the private sector which represents a variable proportion of infant immunizations, so these complexities will need to be reflected when the models are extended to low and middle income settings. Phase 1 has been implemented and preparations are under development for Phase 2 and implementation will depend on funds being made available. Pertussis surveillance and laboratory capacity are still extremely poor in LMICs (particularly in Africa), and beyond the scope of the model comparison exercise to address. The committee noted that data are expected to be forthcoming through ongoing studies and follow-on analysis of maternal influenza trials, and strongly endorses the identification of further opportunities to add pertussis markers (primarily PCR on respiratory specimens) to studies such as Gavi– or the BMGF– supported vaccine impact studies. There were concerns that the opportunistic process by which the 3 models were identified may not have included all relevant parameters or modelling approaches. The feasibility of taking into account other models and parameters identified through a literature review and/or open call should be assessed, focusing on the main results of the different models for phase 1, and if they are interested to include them in phase 2. The work under Phase 1 has recently been completed by the modelers and will be shared with SAGE Chair soon for further follow up. Meanwhile the WHO burden of pertussis disease estimates have been updated by the WHO secretariat in collaboration with Hong Kong University. The global pertussis estimates for age under 5 have been published in Lancet Infect Dis. 2017 Jun 13; pii: S1473-3099(17)30390-0. |
| Influenza | SAGE issued the recommendation to establish a Working Group on influenza vaccines. | Apr 2017 | Ongoing | A SAGE Working Group on Influenza Vaccines has been established in December 2017. http://www.who.int/immunization/policy/sage/sage_wg_influenza_dec2017/en/ |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
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| Integration | WHO should discuss and develop guidelines on how to fully integrate vaccination (GVAP) into the operation of all aspects of the health-care system and to reduce missed opportunities to vaccinate. | Oct 2014 | Ongoing | <p>During the April 2016 SAGE meeting, SAGE members were successfully updated on the ongoing work in AFRO, PAHO and SEARO on using the missed opportunities for vaccination (MOV) strategy to facilitate the integration of immunization with other health services. Following the SAGE session, WHO received multiple requests from countries for technical assistance to implement the MOV strategy in additional countries. Based on MOV assessments conducted in Chad and Malawi in 2015 (draft manuscripts prepared for peer reviewed journal submission) and Kenya in 2016, WHO has published a set of updated guidance documents and field tools in Q3-2017. These include: a planning guide, the assessment methodology (including the MOV protocol, sample questionnaires and generic field tools) and an intervention guidebook (in draft status). In the meantime, WHO has launched an MOV web page with links to all the available materials for easy access to countries.</p> <p>Having strengthened the capacity of AFRO to implement MOV assessments (Chad, Malawi, Burkina Faso (led by partner AMP), Kenya, DRC and Nigeria completed; Jordan, Mozambique and Zimbabwe completed in Q4-2017), collaboration is ongoing with SEARO (MOV assessment completed in Timor Leste; interventions are ongoing) and WPRO (MOV workshop in Q4-2017 in Cambodia, in collaboration with CDC). A network of partners engaged in MOV has been established since March 2016 to provide regular updates via teleconference on the process and outcomes of the recent country MOV assessments, share future plans and framework for implementation, exchange lessons learned, and achieve consensus on a coordination mechanism for all MOV work among all partners. The fourth partner coordination call took place on Oct. 31, 2017.</p> <p>In May 2017, WHO held a training workshop in AFRO for partners and consultants on the MOV strategy with the objectives of training a pool of consultants to support countries in planning and conducting MOV assessments, to further strengthen the regional, subregional and country capacity for MOV work and to serve as a platform to discuss opportunities to address MOV and improve routine immunization coverage. The workshop was attended by 8 partner organizations (CDC, UNICEF, VillageReach, AMP, MSF, JSI, SA-MRC, CHAI), WHO-CO, partner and MOH staff from 8 countries (Cameroon, Ethiopia, Liberia, Mozambique, Nigeria, Uganda, South Sudan, Zimbabwe) and WHO colleagues from HQ, AFRO and IST-Eastern and Southern.</p> <p>The focus for 2018 is to ensure that all countries that have completed the assessments move on to implement interventions. Through monitoring and evaluation, these country intervention action plans will be assessed and reported back to SAGE at a future date.</p> |
| IPV Supply | THE IPV supply situation is expected to improve in 2018; all countries are expected to have access to IPV for routine immunization from the end of Q1 2018. SAGE acknowledged WHO's work with Imperial College, London, to grade risks in Tier 3 and 4 countries based on susceptibility, transmission, exposure, and primary immunodeficiency-associated vaccine-derived poliovirus (iVDPV) prevalence. | Oct 2017 | ongoing | |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|--|---|--------------|---------|--|
| Lower middle-income countries: sustainable adoption and financing for new vaccines | SAGE requested that WHO facilitate the establishment of a partnership among all relevant stakeholders to consider: pooled procurement; tiered pricing; greater transparency of pricing; and exploring the role that UNICEF, the Pan American Health Organization and foundations can have in assisting these countries with procuring and financing vaccines. | Nov 2010 | Ongoing | <p>WHO set up a Middle Income Countries (MIC) Task Force in June 2014 with main immunization stakeholders (WHO, UNICEF, World Bank, Gavi Secretariat, BMGF, AMP, Sabin, Task Force for Global Health), which led to the creation of the "MIC strategy", presented at SAGE in April 2015. The strategy aims at improving sustainability of immunization programmes and access to vaccines in non-Gavi MICs. The MIC strategy is based on four pillars : i) Strengthening evidence-based decision-making; ii) Enhancing political commitment and ensuring financial sustainability of immunization programmes; iii) Enhancing demand for and equitable delivery of immunization services; and iv) Improving access to timely and affordable supply.</p> <p>The timeline for the strategy is up to 2020 to align with the GVAP timeframe and up to 2025 for a longer term horizon. In the longer term, the MIC strategy could provide a platform to ensure sustainability of Gavi's investments in fully self-financing countries.</p> <p>Following SAGE endorsement of the MIC Strategy in Apr 2015, the WHO-led MIC Task Force initiated a country engagement process: in collaboration with key immunization partners WHO started multi-partner dialogues with four countries struggling with raising or maintaining high immunization coverage and/or introducing new vaccines. With each of these countries, the MIC Task Force has identified obstacles to achieving and sustaining the immunization system performance and potential solutions to reaching GVAP targets through plans of action. The MIC Task Force selected four countries for the MIC strategy implementation based on potential for impact (birth cohort, coverage of traditional vaccines, status of new vaccines introduction) and feasibility of engagement. Selected countries were Romania, Swaziland, Jordan and Philippines.</p> <p>Also, some efforts to support all MIC countries in the area of access to timely and affordable supply have been implemented. Notably, the creation of a mechanism for access to supply in humanitarian emergencies in MICs not supported by Gavi: set up of a peer platform and regional workshop to strengthen country procurement capacity; work on price transparency continues successfully with 85% of world (n. of countries) sharing vaccine product, price and procurement information since the beginning of WHO price transparency efforts and the recent launch of the Market Information for Access to Vaccine (MI4A) project. Despite these efforts, progress in implementation of the strategy across its 4 pillars is very slow due to lack of funding. As discussed at the Apr 2015 SAGE meeting, the partners would require about US\$20M per year to fully implement the strategy.</p> <p>In Oct 2016, a meeting of the MIC Task Force was held to review progress and discuss next steps. The TF determined having concluded its mandate through a review of the MIC issue and the development of a partner-shared MIC strategy. It was thus proposed that the TF comes to a close. Anticipating that considerable time may be needed for funding to become available, the TF proposed that partners focus on i) regular normative/guidance work benefitting all countries including non Gavi MICs and ii) access to affordable and timely supply (continuing working on implementation of ongoing activities and potentially new one as possible). Partners committed to continue information sharing and collaborative spirit in these efforts.</p> |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|-----------------------|---|--------------|---------|--|
| Malaria Vaccine | SAGE requested continued review of the planning of the pilot implementations and to receive regular updates on the results. | Oct 2015 | Ongoing | <p>Critical cross-cutting elements of the Malaria vaccine implementation programme (MVIP) are now in place to move the Programme forward: (1) In October 2017, WHO signed a Collaboration Agreement with PATH and GSK to define roles and responsibilities of these partners in the MVIP. GSK has committed to supply, without charge, sufficient quantities of the vaccine to allow sound implementation of the MVIP, up to a maximum of 10 million doses. (2) Agreements between WHO and the 3 MVIP Funders (Gavi, the Global Fund and Unitaid) have been fully executed and funding is now available for phase 1 of the MVIP, through 2020. (3) The hiring of dedicated staff in AFRO and the three pilot countries (Ghana, Kenya and Malawi) is moving forward.</p> <p>All pilot countries have developed and submitted RTS,S/AS01 vaccine introduction plans and initiated preparatory activities, including on communications, logistics and supply planning, adaptation of monitoring tools and strengthening of routine pharmacovigilance.</p> <p>Use of RTS,S/AS01 in the MVIP will require special approval by national regulatory authorities (NRA) of the three countries prior to vaccine introduction. A joint regulatory review by the three NRAs, convened under the African Vaccine Regulatory Forum (AVAREF) took place in February 2018. Timelines for final decision by regulators about the special approval have been agreed upon.</p> <p>The master protocol for the pilot evaluations received approval by the WHO Research Ethics Review Committee in February 2018. Country-based research partners will be contracted to implement country-specific protocols.</p> <p>The two key advisory bodies for the MVIP have been set-up: the MVIP Programme Advisory Group (PAG), the highest-level advisory body to WHO on MVIP-specific aspects, has been convened for the second time in March 2018. The MVIP Data Safety and Monitoring Board (DSMB), responsible for safeguarding the well-being of children vaccinated in the MVIP by providing advice and recommendations to WHO on issues concerning the safety of RTS,S, has met for the first time in February 2018.</p> <p>A comprehensive update on the MVIP will be provided to SAGE during its meeting in April 2018.</p> |
| Maternal immunization | SAGE recommended that WHO endorse the importance and ethical imperative of clinical trials in pregnant women for potentially life-saving interventions such as RSV vaccine (and future vaccines against other targets currently in development, such as group B streptococcal disease). | Apr 2016 | Closed | <p>WHO is promoting vaccine trials be conducted in pregnant women. Updated TRS guidance for vaccines includes a section on trials in pregnant women. WHO Draft Preferred Product Characteristics for Next Generation Influenza Vaccines includes advocacy for clinical trials in pregnant women.</p> <p>Also, IVR has supported two efforts evaluating the ethics of maternal immunization:</p> <p>1) Beeler JA, Lambach P, Fulton TR, Narayanan D, Ortiz JR, Omer SB. A systematic review of ethical issues in vaccine studies involving pregnant women. Hum Vaccin Immunother. 2016 May 31;1-8. [Epub ahead of print] PubMed PMID: 7246403; and</p> <p>2) Verweij M, Lambach P, Ortiz JR, Reis A. Maternal Immunisation: Ethical Issues. In press at Lancet Infectious Diseases.</p> <p>Both publications advocate for the ethical imperative of clinical trials in pregnant women.</p> |
| Maternal Immunization | SAGE encouraged the Regional Office for the Americas to document the successful regional experience of delivering influenza vaccine to pregnant women. | Apr 2015 | Ongoing | <p>Regarding the Pan-American Health Organization's (PAHO) documentation of the successful regional experience of delivering influenza vaccines to pregnant women, PAHO has progressed with its in-depth survey to develop case-studies with key countries that have acquired a lot of experience in maternal immunization (currently ongoing in three countries). Also, PAHO has published its field guide for maternal immunization (in English and Spanish). It is available from http://www.paho.org/hq/index.php?option=com_content&view=article&id=13445%3Amaternal-and-neo-natal-immunization-field-guide-for-latin-america-and-the-caribbean&catid=6774%3Aslide-show&Itemid=40557&lang=en.</p> |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|------------------------|--|--------------|---------|--|
| Maternal Immunization | SAGE concluded that the recommending bodies, including WHO, need to engage in a dialogue with regulators and manufacturers to review current regulatory practices against the evidence on risks and benefits and biological plausibility on product safety. SAGE requested WHO to develop a process and a plan to move this agenda forward in support of an increased alignment of data safety evidence, public health needs and regulatory processes. | Nov 2013 | Ongoing | WHO has completed evaluations of product monograph language regarding safety and use during pregnancy, as well as a survey of health care provider's perceptions of the specific product monograph language regarding use in pregnancy. WHO has reviewed various regulatory approaches to labelling of the pregnancy and lactation sections of product inserts and has produced a document titled, "Labelling information of inactivated influenza vaccines for use in pregnant women." The document was reviewed and endorsed by Expert Committee on Biological Standardization (ECBS) in late 2016. Future vaccines intended for use by pregnant women will undergo phase III trials in pregnant women. Currently available vaccines recommended for use in pregnancy (influenza, tetanus, acellular pertussis) are unlikely to have phase III trials necessary for an indication for use during pregnancy, however, there is regulatory consensus that pregnant women are not contra-indicated from receiving vaccines merely because a product is not indicated for use in that group. |
| Maternal Immunization | SAGE encouraged WHO to promote more implementation research to generate generalizable data on the best ways to integrate maternal immunization into routine antenatal care in low resource settings | Apr 2015 | Ongoing | WHO's Initiative for Vaccine Research (IVR) is in the process of producing many implementation research tools and guidance regarding: 1) assessment of vaccine confidence/hesitancy in pregnant women; 2) maternal influenza immunization program costing tool; 3) guidance document to estimate the influenza economic burden of a country (not pregnancy specific); 4) guidance document to estimate the cost effectiveness of influenza vaccines in a country (not pregnancy specific); 5) field guide for the evaluation of influenza vaccine effectiveness (not pregnancy specific); and 6) implementation guidance document. IVR is collaborating with several research and public health groups to pilot some of these tools in low and middle income countries. |
| Measles | SAGE recommended that the most expeditious clinical development and regulatory pathway to licensure of measles containing vaccines (MCV) micro-array patch (MAP) be determined, and that barriers to the development, licensure, and use of MAPs for measles and rubella vaccine delivery be identified and addressed urgently. | Oct 2016 | Ongoing | a Measles and Rubella/ micro-array patch (MAP) Working Group (WG) was set up and has had two conference calls. A face to face meeting is planned in April in 2018. The outcomes and recommendations from this WG will be shared with SAGE. |
| Measles | SAGE stressed that the accumulation of susceptible persons at both the national and subnational level should continue to be monitored to identify and address immunity gaps. SAGE requested that the Measles and Rubella Working Group refine the recommendations as to when follow-up SIAs should be conducted. | Oct 2016 | Ongoing | The updated measles position paper (published May 2017) stresses the importance of monitoring the accumulation of susceptible persons at both the national and subnational level to identify and address the immunity gaps. The SAGE MR Working Group is looking at refining recommendations as to when follow up supplementary immunization activities (SIAs) should be conducted. Initial modeling results and data analyses were discussed at the SAGE WG meeting in June 2017. The results of this work will be presented to the IVAR-AC and will be presented at the October SAGE in 2018. |
| Measles | SAGE noted that there is a need to address the substantial information gap on the role of factors such blunting and maternal immunity in infants aged <6 months, and the impact of vaccination <6 months of age on subsequent MCV doses. | Oct 2017 | ongoing | This is an information gap and research is needed. The SAGE WG is working to prioritize research areas in order to increase interests of donors to fund and of research institutions to carry out the needed research |
| Measles - Transmission | SAGE noted that there is a need to address the substantial information gap on transmission drivers. | Oct 2017 | ongoing | This work needs to be addressed through improved surveillance and outbreak investigations in country. |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|-----------------------------------|---|--------------|---------|--|
| Meningococcal A conjugate vaccine | SAGE recommended that countries completing mass vaccination campaigns introduce meningococcal A conjugate vaccine into the routine childhood immunization programme within 1–5 years following campaign completion, along with a one-time catch-up campaign for birth cohorts born since the initial mass vaccination and which would not be within the age range targeted by the routine immunization programme. | Oct 2014 | Ongoing | The recommendations from SAGE are reflected in an update to the WHO meningococcal vaccine position paper. The updated guidance has been published in the Weekly Epidemiological Record (WER) on 20 Feb 2015: http://www.who.int/wer/2015/wer9008/en/ . Ten of the 26 meningitis belt countries have received approval from Gavi, the Vaccine Alliance for introduction of the meningococcal A conjugate vaccine into their routine immunization programme, with a single dose at 9, 15 or 18 months of age concomitantly with the administration of the first or second dose of Measles/Rubella vaccine. Among them, 7 countries have launched their introduction at the age of 9 months (Sudan, July 2016; Mali, Feb 2017; Central African Republic, June 2017; Chad, July 2017; Niger, October 2017); at the age of 18 months (Ghana, November 2016) and at the age of 15 months (Burkina Faso, Mar 2017), respectively. The remaining three countries intend to do so in 2018 (The Gambia, Côte d'Ivoire, Nigeria). Another 3 countries (Guinea; Guinea Bissau; Togo) have applied to Gavi through its new country engagement framework for an introduction in 2019. Two additional countries have applied to Gavi to conduct their initial mass vaccination campaigns: Burundi in Q4-2018 with the intention to enhance surveillance waiting for availability of affordable multivalent vaccines to consider introduction into routine; and Eritrea in Q2-2019 with the intention to introduce the vaccine into routine in Q4-2019. Other meningitis belt countries intend to apply for the introduction of the vaccine into their routine programme at the next Gavi application windows in May and September 2018. |
| Migrant Population | Existing knowledge on reaching displaced and mobile populations - including individuals escaping conflict zones or natural disaster, economic migrants, seasonal migrants, those moving to urban centers and traditional nomadic communities - and other neglected populations should be synthesized to identify good practice, innovative approaches and gaps in knowledge. | Oct 2017 | ongoing | How to reach migrant populations? Is this considered in microplans or catch-up? |
| MNTE | UNICEF, UNFPA, and WHO should make all efforts to secure timely supply of the available WHO prequalified TT vaccine in compact single-dose pre-filled auto-disable injection devices to facilitate vaccination of inaccessible populations by community workers. Should the supply of TT vaccine in this latter presentation be less than expected, a clear plan for prioritizing and allocating available doses should be established. | Oct 2016 | Ongoing | The proposal submitted to the Gavi Alliance Policy and Programme Committee (PPC) to request for financial assistance to support the production and availability of this critical pre-filled device aimed at markedly increasing access to the Tetanus Toxoid vaccine to very remote parts of some selected countries where currently access is seriously compromised as a result of insecurity, active conflicts and lack of human resources has been rejected by the PPC through a communication in January 2018. It is very unlikely that this very important initiative will ever be funded under the circumstance. |
| MNTE | UNICEF, UNFPA and WHO should work with countries to generate and sustain political commitment to maintaining elimination of MNT, in order to guard against complacency once a country has been declared to have achieved elimination. | Oct 2016 | Ongoing | All opportunities including the Regional Immunization Technical Advisory Group (RITAG) meetings and Immunization Managers' meetings are being utilized to advocate for efforts by countries to sustain their Maternal and Neonatal Tetanus Elimination (MNTE) status. Update on the status of implementation of the AFR RITAG recommendations were presented at the annual meeting of the AFR RITAG in December 2017. MNTE was one of the topics discussed at the SEAR and WPR TAG meetings in June 2017 as well. Additionally, efforts are being made to finalize the guidelines on sustaining MNTE to ensure that countries are guided through the appropriate steps to take to sustain their achievements. |
| MNTE | UNICEF, UNFPA, and WHO should urgently develop an MNTE investment case and resource mobilization strategy to secure predictable and timely funding support for the remaining 18 countries, if the 2020 elimination timeline is to be met. | Oct 2016 | Ongoing | There is currently a collaborative work by WHO, UNICEF and The United Nations Population Fund (UNFPA) that has led to contracting the University of North Carolina to conduct the work on the investment case for MNTE. Work is progressing in earnest, and the first phase of the work focusing on the attainment of elimination by the 16 remaining priority countries is expected to be completed by the end of Q1 2018. Discussions on the second phase of the investment case work on sustaining MNTE have started. |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|---------------------|--|--------------|---------|--|
| MNTE | Where feasible, the use of serosurveys to validate assessment of risk identified from other data sources should be considered to guide vaccination strategies, especially in high-risk districts. Close attention should be paid to sampling strategies and laboratory methods to ensure that results are valid and interpretable. WHO should provide guidance on: sampling methods; sample collection and testing; and analysis, interpretation and use of serosurvey data for monitoring. WHO should consider establishing reference laboratories and reference serum panels to support standardization and quality assurance of the laboratory methods used in serosurveys. | Oct 2016 | Ongoing | There is a recent effort to integrate tetanus serosurveys with the DHS, and a concept note has been written to that effect. This initiative is to be facilitated by US CDC in collaboration with WHO. |
| MNTE | UNICEF, United Nations Population Fund (UNFPA), and WHO should support countries in securing the necessary resources to implement their national elimination plans, including procurement of Td vaccine and operational costs for SIAs. | Oct 2016 | Ongoing | The first phase of the MNTE investment case that focuses on the remaining countries yet to attain elimination (14 at the moment) is almost completed. This will highlight the areas of resources' need, and will also be used for resource mobilization. UNICEF, UNFPA and WHO have significantly contributed to this. |
| Multiple injections | SAGE noted the need for further research on multiple injections during the same visit and recommended the following research topics and activities: (i) impact of multiple injections in the same visit on vaccine coverage, disease reduction, vaccine programme success and caregiver and provider experience; (ii) development of a standardized monitoring protocol for acceptance and acceptability by caregivers and providers and for prevalence of adverse events; (iii) development of optimal provider and infant caregiver communication approaches; (iv) optimal multiple injection administration techniques, and (v) development of new technologies, such as intradermal patches and new combination vaccines, which would decrease the number of vaccine injections in a single visit. | Apr 2015 | Ongoing | Multiple injection studies have been conducted in collaboration with US CDC in South Africa, Gambia, and Albania, with studies ongoing in the Philippines, Sudan, and Columbia. Studies are primarily designed to evaluate healthcare provider and infant caregiver attitudes and practices regarding administration of multiple injectable vaccines in the same visit, in most cases following the introduction of IPV and PCV. A new time motion study has also been initiated in Uganda. The findings of these studies will feed into the development of future guidance required to address concerns related to multiple injections and pain. For now, to better support countries in this area, new training modules for health workers on addressing pain at the time of vaccination and multiple injections will be imminently published. |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|--|--|--------------|---------|---|
| National immunization programme management | SAGE welcomed the initiative and stressed the importance and urgency of developing guidance that can be tailored to each country's unique structure and needs. SAGE emphasized the importance of looking at functions and competencies from a health-system perspective whereby all the immunization functions are adequately addressed with competent staff, regardless of the country's health system structure. SAGE recommended sharing of experiences between countries and regions on immunization workforce planning. SAGE suggested creating tools to assist countries in different aspects of immunization human resources management including: staff turnover and rotation policies, performance evaluations, and design of training. SAGE recommended that this work be piloted in a range of countries. | Apr 2017 | Ongoing | A joint meeting with the US CDC and other relevant partners (JSI, BMGF, GAVI) was conducted in November 2017, to review the competencies needed at different level of the programme. A final list of competencies needed at national level will be available by Mar, 2019. The US CDC had drafted an article on this topic for a peer-reviewed journal, which should be published by end of Feb, 2019. |
| National Immunization Technical Advisory Groups (NITAGs) | SAGE recommended that tailored guidance, tools, training, mentoring programmes and sharing of information are needed to assist NITAGs. Therefore, SAGE stressed that initiatives such as the Global NITAG Network and the NITAG Resource Centre are essential and that these would require dedicated financial and human resources. SAGE further noted that NITAG evaluations are important beyond the current process indicators and should be continued and supported by countries and partner institutions. NITAG evaluations need to focus on function, quality and integration. | Apr 2017 | Ongoing | The second Global NITAG Network (GNN) meeting was successfully held from the 28th to 29th of June 2017 in Berlin, Germany. The meeting was attended by 38 NITAG country representatives (NITAG Chair, member or secretariat) from a total of 26 countries. During this meeting the GNN was formally established and its strategic document endorsed. The next meeting is scheduled in December 2018 and will be hosted by the Public Health Agency of Canada. The secretariat of GNN is now ensured by WHO HQ and the NITAG Resource Centre is also being managed by WHO. |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|-----------------|---|--------------|---------|---|
| Pain mitigation | SAGE recommends that WHO: 1) includes pain mitigation recommendations with WHO immunization practice guidance materials; 2) disseminates pain/distress mitigation recommendations through the usual dissemination channels, immunization managers, National Immunization Technical Advisory Group (NITAG) and partner organizations; 3) monitors and evaluates the implementation success of pain mitigation measures; 4) works with industry, ECBS and regulatory agencies to advocate that grading of pain experienced during the vaccine injection be included in data for licensing and in the product monograph. | Apr 2015 | Ongoing | Internal discussions have taken place on how to move forward across relevant WHO departments. A brief position paper was drafted based on the SAGE recommendations and published in the Weekly Epidemiological Record on 25 September 2015. This formed the basis for additional proactive communication activities. As example of actions in response to points 1 and 2, WHO ensured that information in WHO guidance on multiple injections and IPV was consistent with the SAGE recommendations on reducing pain, specifically in two documents: Practical considerations for the successful introduction of IPV, and Multiple Injections: Acceptability and Safety, both available on this web page. The WHO position paper on reducing pain was also added on the same web page. In relation to the training aspects for IPV introduction, we updated training modules for health workers, also to reflect the recommendations from the latest WHO position paper. The Immunization in Practice recently published has in module 5 'Managing immunization sessions', recommendations on vaccine sequence (increasing pain- oral before injection, rota before OPV), positioning the recipient, no aspiration etc. IIP has been distributed to countries and the last edition was also translated into several local languages. Work is also ongoing to ensure appropriate incorporation of pain mitigation in WHO guidance documents when they get updated and to ensure that any recommendation posted on the web at odds with SAGE's guidance be adjusted/removed. The pain mitigation guidance has been included in the NITAG resource center. As a further example of use and integration in WHO documents, reference to the pain mitigation position paper has been made in the recently published updated tetanus position paper. PDVAC will consider pain mitigation within their preferred product characteristics to guide target product profiles. Steps have been taken and discussions started to also reflect the measurement of pain at time of injection in the updated Guidelines on clinical evaluation of vaccines were discussed and endorsed by ECBS in October 2016. They allude to pain mitigation. More specific activities still need to be implemented with respect to points 3 and 4. |
| PCV | SAGE proposed surveillance and research priorities to guide future policy revision, including further assessment of dosing schedules and pneumococcal outbreak epidemiology, particularly epidemics of ST1 disease. | Oct 2017 | ongoing | SAGE PCV working group was convened in 2017 and presented results at October 2017 SAGE meeting. One component of this WG was to review available evidence on use of catch-up campaigns, including in the context of pneumococcal outbreaks. This will be written up in a revised WHO PCV position paper in 2018. We will also launch activities to analyze available data and use disease modeling to devise a strategy for responding to pneumococcal outbreaks, since the existing data is sparse. |
| Polio | The documentation for 'legacy planning' should include contributions from communities and front-line health workers on their experiences with the polio programme, what it has meant for them and how lessons learnt could further improve the routine vaccine and health programme. | Apr 2013 | Ongoing | GPEI partner agencies recently have launched two new projects to comprehensively document and disseminate lessons learned from polio eradication. The first one is a 5 year project led by Johns Hopkins Bloomberg School of Public Health document, preserve, and disseminate the polio program's best practices to help inform future global health policy and implementation. Collaborating with academic institutions from around the world, the team will develop short courses and hands-on clinics for public health students and professionals, by conducting a variety of activities from literature review to in-person surveys. Frontline workers involved in polio eradication efforts will be an intricate part of the process to gather "first hand" experience on success and challenges. As a part of a multimedia lessons-learned project, GPEI is also collecting stories focusing on inspiring individuals, who were key to innovations in the history of polio eradication. The project involves interviews with community leaders and front-line health workers, who made a difference in changing strategies, when stakes were high and there was need for a paradigm shift in the programme. |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|-------|--|--------------|---------|--|
| Polio | SAGE encouraged further engagement of WHO regional offices in regard to the polio legacy planning to ensure adequate technical support to countries. | Oct 2015 | Ongoing | WHO Regional Offices from AFRO, EMRO and SEARO have been an integral part of the polio transition planning exercise at the country level. For the last two years, the Regional Offices have been guiding and providing technical support to the countries to develop their national transition plans. In many cases, Regional Offices have integrated polio transition planning into broader region-specific immunization initiatives and strategies (e.g. Addis Declaration for Immunization). In addition, the Regional Offices are a part of a cross-cluster WHO team set up to finalize the "Strategic Action Plan on Polio Transition" which will be presented to the World Health Assembly in May. As a part of this effort, the regional offices have provided substantive input into a comprehensive planning exercise, looking at functions that need to be sustained to keep the world polio-free, to strengthen immunization and to strengthen outbreak preparedness, detection and response, including the estimated costs of sustaining these functions. The Regional Offices will play an important role in the implementation of the Strategic Action Plan and its Monitoring and Evaluation Framework. |
| Polio | SAGE advised GPEI to develop a targeted advocacy and communication plan to engage key countries and stakeholders to ensure completion of phase I and implementation of phase II, including establishment of national containment authority and national regulation for containment of poliovirus in designated essential poliovirus facilities. | Oct 2015 | Ongoing | A communications officer to focus on containment has been recruited and will join the WHO Containment team in March. Sweden has submitted to GCC the first and so far only certificate of participation (CP) in the containment certification activities. At their meeting of 23-25 Oct 2017, GCC has recommended WHO to consider an EB request for a WHA 2018 resolution urging countries hosting PEFs to accelerate the appointment of a competent NAC as soon as possible and no later than 31 Dec 2018 and to process all CP applications as soon as possible and no later than 30 June 2019, stating that after June 2019, new PEF applications will not be considered unless under exceptional circumstances. The report is published and has been shared with stakeholders in all regions. |
| Polio | SAGE advised GPEI to accelerate implementation of the WHO Global Action Plan for containment (GAP/II) including: a) all countries completing phase I; b) regional focal points closely monitoring country activities and ensuring each country completes its inventories of facilities that hold or handle polioviruses, and destroys or commits to destroying WPV2 by end 2015 and any other type 2 containing materials including Sabin poliovirus by July 2016. | Oct 2015 | Ongoing | As of January 2018, countries still pending completion of Phase I are awaiting the publication of the 'Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses'. For Phase II, 28 countries reported the intention to retain PV2 materials (WPV2 or OPV2/Sabin2) in 91 designated poliovirus-essential facilities (PEFs). 18 of these countries have nominated a national authority for containment (NAC). So far, only one designated facility, in Sweden, has requested to engage in the containment certification process. |
| Polio | SAGE requested WHO to complete the guidance on identification of potentially infectious materials (including stool and respiratory specimens) into 3 groups based on likelihood of being contaminated with VDPV2 or WPV2. | Oct 2016 | Ongoing | A revised draft of the 'Guidance for non-polio facilities to minimize risk of sample collections potentially infectious for polioviruses' has been approved by the Containment Advisory Group (CAG) at their second meeting of 28-30 November 2017, pending minor adjustments and completion of annex 3 listing country-specific data. The guidance is planned to be completed shortly. |
| Polio | SAGE urged WHO to facilitate discussions and decision-making by National Immunization Technical Advisory Groups (NITAGs) to introduce IPV intradermal fractional dose use by providing necessary technical information. | Oct 2016 | Ongoing | WHO prepared the communication and technical materials to National Immunization Technical Advisory Groups (NITAGs). The WHO secretariat is advocating for the use of fractional dose IPV at both regional and country technical advisory group meetings (TAGs). |
| Polio | SAGE noted that the IPV supply situation is further deteriorating. Therefore, the programme should explore the possible use of devices facilitating intradermal administration (e.g. jet injectors, intradermal adapters). | Oct 2016 | Ongoing | WHO is working on pre-qualification of both jet injectors and intradermal adapters. In addition, WHO has conducted several pilots of the use of these devices in immunization campaigns (e.g. Karachi, Pakistan). These results were presented to the scientific stakeholders in polio program and to countries considering introduction of fIPV. |
| Polio | SAGE requested its Polio Working Group (WG) to provide urgent guidance on optimal management of IPV supply and mitigation of other risks in case the IPV supply is further reduced. | Oct 2015 | Ongoing | The IPV supply situation is being closely monitored. An update from the September Polio Working Group meeting, including on discussions with vaccine producers, was provided during the October 2017 SAGE meeting. |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
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| Polio | SAGE requested that WHO review its tier classification of countries with respect to prioritization of IPV to take into account the size of the population with no IPV protection and the recent VDPV2 events. | Apr 2017 | Ongoing | WHO, in collaboration with partners, is working on updating its tier classification of countries with respect to prioritization of IPV. It will be presented to the SAGE Working Group in September 2017 and to SAGE in October 2017. |
| Preferred Product Characteristics | SAGE noted the utility of Preferred Product Characteristics (PPCs) to developers and funders, and proposed that the opportunity for input into future PPCs at an early stage for any vaccine of public health importance could be included as part of SAGE's global public health mandate. | Apr 2013 | Ongoing | Since this recommendation, the Product Development for Vaccines Advisory Committee (PDVAC) has been created, and identified as the WHO committee responsible for overseeing the PPC generation process and content. PDVAC has emphasized the need for several PPC documents to be developed by WHO IVR. PPCs for Group B streptococcus and RSV vaccines have been finalized. Target Product Profiles for emerging pathogens have been developed as part of the Blueprint initiative. PPCs for new tuberculosis vaccines, next-generation influenza vaccines, Group A streptococcus, ETEC, Shigella and Herpes Simplex Virus 2 are under development. PPCs when finalized and ready for public circulation are posted on the WHO IVR website. |
| Private sector engagement with national immunization programmes | SAGE applauded the development of the draft guidance as an initial step in tackling this area of work and urged WHO to finalize a common framework starting with a set of core principles. | Apr 2017 | Completed | As requested by SAGE the "WHO Guidance Note: Engagement of private providers in immunization service delivery. Considerations for National Immunization Programmes" has been revised and particularly shortened. The WHO Guidance Note was published in September 2017 and can be retrieved through the following link: http://www.who.int/immunization/programmes_systems/policies_strategies/Private_sector_immunization.pdf?ua=1 |
| Regulatory | SAGE recommended that the further development of the Emergency Use Assessment and Listing procedure being developed by WHO, which would allow use of a vaccine in the context of a Public Health Emergency of International Concern, be done in close consultation with relevant regulatory authorities, including those of the affected countries. | Apr 2015 | Ongoing | Regarding the Emergency Use Assessment and Listing (EUAL) procedure, the WHO Prequalification Team took note of SAGE recommendation and further development of the EUAL will consider relevant regulatory authorities including those of impacted countries. Further, a document entitled, "Vaccine evaluation in public health emergencies – review of regulatory pathways in selected countries" was prepared and presented to SAGE working group (WG) on Ebola vaccines in Aug 2015. In Oct 2015, the document was submitted to the Expert Committee on Biological Standardization (ECBS) for review and advice. The Committee considered that a guidance document might be of value to National Regulatory Authorities (NRAs) and other public health organizations. However, it also recognized the complexity of emergency situations, each of which is essentially unique, and that decisions ultimately rest on a benefit/risk assessment. The ECBS reviewed the document's progress in 2016. Evaluation of vaccines for public health emergencies was discussed in the 3rd meeting of the WHO Collaborating Centers Network on Vaccines in Seoul, in July 2016. Lessons learned from the Ebola crisis in West Africa and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in Korea were discussed and several activities of the CC network were proposed. In addition, new initiative called the Coalition for Epidemic Product Innovation (CEPI) was discussed as a framework in which a number of partners will work together to assure better preparedness for public health emergencies in future. The ECBS was also briefed about the CEPI in Oct 2016. The CEPI initiative led to the establishment of a Regulatory Working Group in 2017 with the focus on data requirements for product development in the absence of an outbreak, regulatory issues related to stockpiling and the use of stockpiled products during the outbreaks. |
| Reports from other advisory committees on immunization | WHO and NIBSC should develop with other stakeholders, a business plan to assure long-term security of the development of WHO reference preparations as a global public health resource and additional efforts should be undertaken to disseminate outcomes of the committees deliberations and to explain the relevance of its work to the broader immunization community. | Nov 2006 | Pending | A network of WHO Collaborating Centres (CC) on the Standardization of Vaccines has been established. At its 3rd meeting, the network agreed to establish a "Core Expert Group (CEG)" to assist the Expert Committee on Biological Standardization (ECBS) to review selected proposals for measurements standards. Proposals for replacement measurement standards are usually straightforward, with few strategic or scientific issues, and they would be the initial focus of the CEG. The ECBS agreed that the CEG could pre-review selected measurement standards in the vaccines area and thus help to streamline the ECBS review process. A drafting group on Men B guidelines was established as a part of CEG activity on written standard and report will be submitted to ECBS for discussion. Review of measurement standards will be conducted in September and feedback from CEG will be submitted to the ECBS. Further discussion on the activities of the CEG is going to take place at the ECBS meeting from 17 to 20 October 2017. |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
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| RSV | SAGE asked for preparations to be made to support global policy-making for respiratory syncytial virus (RSV) maternal immunization as well as passive immunization with long-acting mAb. SAGE emphasized the need to link maternal immunization platform strengthening with influenza, tetanus and pertussis vaccines along with preparations for potential country introductions of RSV vaccine. | Apr 2016 | Ongoing | Further discussions have been held with the WHO Prequalifications (PQ) team with regard to prequalification processes for both respiratory syncytial virus (RSV) vaccines and monoclonal antibodies (mAbs). The ECBS Guidelines for RSV vaccines are planned for development and possible adoption at Expert Committee on Biological Standardization (ECBS) 2018, as these are a prerequisite for consideration for PQ. The Essential Medicines and Health Products (EMP) department is considering an approach to PQ of mAbs. Intensive discussions continue about the most appropriate way to prepare for policy-making in Low and Middle Income Countries (LMICs), without any results yet available for efficacy trials in these settings. A Phase 3 trial of the Novavax RSV F Vaccine in 11,856 older adults (60 years of age and older, enrolled in the USA), did not meet the pre-specified primary or the secondary efficacy objectives, and did not demonstrate vaccine efficacy. Efficacy may differ between elderly and healthy pregnant women target groups. The Novavax Phase 3 trial in late 2nd/early 3rd trimester pregnant women continues with endpoints accruing in neonates and young infants. Novavax announced that a planned interim data analysis was favorable, supporting trial continuation. Results from a MedImmune candidate vaccine tested in adults showed negative results and the possibility of increased severity in a subset of participants, which led to the discontinuation of an important part of this program. The RSV vaccine pipeline remains very active and can be accessed at the IVR Vaccine Pipeline Tracker: http://who.int/immunization/research/clinicaltrials_newvaccinepipeline/en/ (open the page then navigate to the RSV tab of the spreadsheet). A WHO Preferred Product Characteristics for RSV vaccines document has been finalized under PDVAC oversight, and is now publicly available on the WHO IVR website. WHO is actively developing its activities related to the preparation of policy decisions related to RSV vaccines, with funding support from the Gates foundation. |
| Second year of life (2YL) | A recommendation was made for consideration of a platform for immunization coverage in the 2nd year of life, in view of potential necessary booster doses and opportunities to catch up with incomplete vaccination, and removing the artificial barrier often experienced after the 1st birthday. | Apr 2014 | Ongoing | Two country case studies (Zambia, presented to SAGE in April 2016, and Senegal) (WHO, JSI) and a global landscape analysis and literature review (UNICEF) have been conducted; learnings from these as well as country demonstration projects in Ghana and Malawi (CDC) have been used to inform the draft global guidance on Establishing and strengthening immunization in the second year of life: practices for immunization beyond infancy. An advanced draft of the guidance document was shared with the Immunization Practices Advisory Committee (IPAC) in Feb 2017 and the document was circulated for a final round of review in September 2017. Advocacy and demand creation packages targeting decision makers, planners, health workers and caretakers are also under development and will be published, along with the guidelines and a companion Handbook for planning, implementing, and strengthening vaccination into the 2YL, in Q1 2018. With the guidelines on track, WHO and UNICEF are moving ahead to develop training materials for country-level staff and for building a pool of consultants trained to identify gaps and facilitate actions needed to maximize coverage of vaccines scheduled in the second year of life. |
| Smallpox vaccines | SAGE recommended that WHO initiate discussions with countries in possession of smallpox vaccine to establish mechanisms for replenishment of the WHO stockpile in case of need. | Nov 2013 | Ongoing | In December 2017, WHO published the 'Operational framework for the deployment of the WHO Smallpox Vaccine Emergency Stockpile (SVES) in response to a smallpox event.' This document lays out the considerations and processes needed for countries to request vaccine in the event of a smallpox outbreak. It also describes the processes by which donors can deploy vaccine to the WHO SVES, and WHO can deploy vaccine to requesting countries. WHO continues discussion with countries for their donation and replenishment of the stockpile. |
| Standardization of BCG strains | SAGE requested ECBS to review and report whether manufacturers have implemented their guidelines for characterization of BCG vaccines on strain, product and batch related characteristics. | Oct 2017 | ongoing | |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|-------------------------|--|--------------|---------|--|
| Strengthening of NITAGs | SAGE requested a regular update on the number of established National Immunization Technical Advisory Groups (NITAGs). | Apr 2016 | Ongoing | This information is collected via the WHO/UNICEF joint reporting form and analyzed every year. The figures are included in the GVAP secretariat report, which is made available to the SAGE DoV working group and then to SAGE. By the end of 2016, 127 Member States reported the existence of a NITAG and 82 Member States (including 27 GAVI-eligible and 25 non GAVI supported Middle Income countries) the existence of a NITAG that meets all 6 basic process indicators included in the JRF and used as part of the GVAP indicator. These figures can also be included in the global report on a yearly basis. A specific NITAG session was held at the April 2017 SAGE meeting. |
| Supply shortages | SAGE recommended that WHO could play a key role in setting up an "Exchange Forum", helping to collect demand information from all Member States and to enhance dialogue between countries' demand (including anticipation of schedule evolution and new introductions) and manufacturers' supply availability and risks. | Apr 2016 | Ongoing | Concerns about ongoing shortages of vaccines persist. This has been stressed through the SAGE session on vaccine shortages held in April 2016, resolution 69.25 on "Addressing the global shortage of medicines and vaccines", the fifth objective of the Global Vaccine Action Plan (GVAP), the Middle Income Country (MIC) Strategy endorsed by SAGE in April 2015 and the 68th World Health Assembly (WHA) resolution on the GVAP in May 2015. WHO IVB Department, in collaboration with Essential medicines and health products (EMP) and with support from Linkbridge consulting funded by the Bill & Melinda Gates Foundation and MMGH consulting, has leading a Vaccine Shortage Project over the years 2016-2017. The aim of the project was to act upon the recommendations and requests of SAGE and WHA by providing concrete proposals on WHO's role and actions to enhance information sharing for pre-empting and managing vaccine supply shortages. While all countries can benefit from this work, particular attention is paid to countries not supported by UNICEF Supply Division, PAHO, or Gavi. To ensure that any potential solution in this space builds on existing data, knowledge and processes, a first phase of the project, the Analysis of Assets, aimed to understand the extent of information available to WHO to be able to predict, pre-empt and act upon vaccine shortages. This includes both internal and external information. This phase also aimed to understand the extent of current project/mitigation work within WHO, vaccine by vaccine. This phase has been completed and a project report is available upon request. Based on the findings from Phase 1, Phase 2 of the project was focusing on development of concrete solutions to enhance WHO's ability to address vaccine shortages with a focus on filling current gaps in information sharing and supporting self-procuring countries. Using Bacillus Calmette-Guérin (BCG) and D&T containing vaccines to prototype solutions, an informed proposal on WHO's functions and operating model with regards to vaccine supply/demand/price data input, market analytics, output material and distribution was developed. The proposal was successfully submitted to the Bill and Melinda Gates foundation for funding and the new project, Market Information for Access to Vaccines (MI4A) was kicked off in January 2018. Under this project, WHO commits to conduct to enhance available GLOBAL vaccine market information to enhance timely access to affordable vaccines. The work will entail: i) two global vaccine market studies per year in collaboration with Linkbridge SPC and MMGH Consulting to assess global supply, demand and pricing challenges of vaccines at risk (availability & affordability). ii) development of tools and materials for countries to improve market knowledge and enhance procurement outcomes. iii) creation of an information sharing ecosystem for enhanced information exchange among key stakeholders. iv) development of guidance and strategies for suppliers and countries aimed at enhancing access. |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|--------------|--|--------------|---------|---|
| Surveillance | <p>SAGE endorsed the recommendations of the ad hoc TAG for improving the quality of the IB-VPD surveillance network and urged that the objectives of this network be more clearly defined, that collaboration with other surveillance systems and laboratory networks (i.e. the polio/measles laboratory networks) be continued, and that, where feasible, activities be linked with other programmes enhancing country capacity, including implementation of the International Health Regulations. SAGE urged greater attention to integration of data systems, which would facilitate real-time analysis and performance monitoring. SAGE also noted the opportunities for integration by building upon the enhanced capacity developed by these networks to conduct surveillance for other diseases using a similar case-definition and personnel trained in applying and adhering to rigorous surveillance protocols. Both networks should continue to share experiences with the polio surveillance network. Integration efforts must be strategically designed in ways that are logical and synergistic.</p> | Nov 2013 | Ongoing | <p>Since 2013, significant progress has been made to strengthen the Global IB-VPD and Rotavirus Surveillance Networks through recommendations from the 2013 global strategic review and annual meetings and consultations. By the end of 2017, we have made significant progress toward strengthening the Networks and meeting those goals. In 2016, the Global Rotavirus Surveillance Network comprised 133 sentinel surveillance sites in 58 countries and the Global IB-VPD Surveillance Network comprised 124 sentinel sites in 57 countries. This continued through 2017. Data management processes continue to be improved toward a more systematic approach in reporting, cleaning, analysing and interpreting data. The reference laboratories are appropriately supporting sites and network laboratory performance has been successfully monitored by the global external quality assessment program as well as quality control programmes. Sentinel site and laboratory assessments are ongoing at priority sites. The most recent complete year of data available is from 2017, and it reflects the strength of the data and the network. Network data has contributed to vaccine introduction decisions, such as choice of pneumococcal conjugate vaccine (PCV) formulation, and the surveillance networks have been used as platforms for vaccine impact evaluations, particularly for rotavirus vaccines (RV). The surveillance platform has also been leveraged to monitor other VPDs, such as typhoid using the IB-VPD surveillance sites and other enteric pathogens such as norovirus, Shigella, and ETEC using the rotavirus network. Moving forward, the rapid introduction of PCV and RV by Member States now requires the surveillance networks to focus on improving baseline data for sites in non-vaccine using Member States and to ensure consistent surveillance practices to monitor impact for sites that meet inclusion criteria in vaccine-using Member States, especially for pediatric diarrhea and rotavirus. A web-based data management tool is being rolled out in one Region (PAHO) and has great potential to improve data quality and sharing across the Network. We are discussing how to better integrate IB-VPD meningitis surveillance with existing meningococcal meningitis surveillance systems. We also continue to support sites where PCV and/or RV vaccine impact evaluations may be feasible due to sufficient pre- and post-vaccine introduction data, including using secondary data sources such as hospital administrative data. Finally, one of our main activities is to work with countries on making surveillance sustainable in the long term.</p> |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|-------------------------------|---|--------------|---------|---|
| Sustainable Development Goals | Approval of a vaccination coverage indicator under the child mortality target of the Sustainable Development Goals (SDGs) has not yet been obtained. SAGE urged WHO and countries to request an aspirational immunization indicator under the SDGs. | Apr 2016 | Ongoing | <p>Several immunization partners (Gavi, Unicef, BMGF, US-CDC, WHO, Center for Vaccine Ethics and Policy NYU) have worked together to explore possible indicators to be added to the SDGs monitoring framework in addition to the currently included ones (Target 3.8.1 Universal Health Coverage composite indicator, and the Hepatitis B control strategy, three doses of Hep B vaccine). It was agreed to propose Global Vaccine Action Plan (GVAP) G2 Indicator Coverage for all vaccines in national schedule to be included for SDGs sustainability and access to health and essential medicines & vaccines goal (3.b).1. The choice of this indicator has been validated by the SAGE Decade of Vaccine Working Group. In November 2016, at the 4th meeting of the Inter-agency and Expert Group on Sustainable Development Goal Indicators (IAEG-SDG), the new accepted immunization indicator was defined as 3.b.1 Proportion of the target population covered by all vaccines included in their national programme.</p> <p>WHO and UNICEF were identified as co-custodians for this indicator. The indicator definition was presented to SAGE in October and was reclassified to Tier II at IAEG-SDG meeting on 28 November. The indicator definition is:</p> <ul style="list-style-type: none"> - Coverage of DTP containing vaccine (third dose): Percentage of surviving infants who received the 3 doses of diphtheria and tetanus toxoid with pertussis containing vaccine in a given year. - Coverage of Measles containing vaccine (2nd dose): Percentage of children who received two dose of measles containing vaccine according to nationally recommended schedule through routine immunization services. - Coverage of Pneumococcal conjugate vaccine (last dose in the schedule): Percentage of surviving infants who received the recommended doses of pneumococcal conjugate vaccine. - Coverage of HPV vaccine (last dose in the schedule) : Percentage of 15 years old girls received the recommended doses of HPV vaccine. <p>This indicator aims to measure access to vaccines, including the newly available or underutilized vaccines, at the national level over the life course.</p> <p>Indicator was reported for DTP3, MCV2 and PCV3 in February 2018 and will be part of next SDG report.</p> |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|-----------------------|---|--------------|---------|--|
| Tuberculosis vaccines | SAGE endorsed the establishment of a WHO TB vaccine technical expert group with representation from SAGE. An annual written report on TB vaccine developments should be provided to SAGE. SAGE would be provided with two-page summaries of progress every year. TB would only be included on the agenda of SAGE when there is a meaningful development of decision from SAGE required. | Nov 2011 | Ongoing | <p>WHO IVR, with the support from an TB vaccine expert working group, with further advice from PDVAC, continues to progress its activities on TB vaccine development</p> <p>Several tuberculosis efficacy trial results are awaited in the coming months.</p> <p>The most advanced vaccine candidates are GSK M72/AS01E, the recombinant BCG VPM1002, M. Vaccae™.</p> <p>M.vaccae is a heat killed homogenized lysate developed by Anhui Zhifei Longcom, China, which has been evaluated in Phase 3 for prevention of tuberculosis in healthy adults with latent TB infection, as well as as adjunctive immunotherapy with the aim to shorten TB treatment. Results have not been communicated.</p> <p>VPM 1002 is a recombinant BCG, originally developed by the Max Planck Institute; now licensed to the Serum Institute of India (SII) and being developed with Vakzine Projekt Management (VPM), Hannover, Germany. It is currently in Phase IIb/III trials, being compared to BCG in neonates in South Africa, as well as being tested for prevention of TB recurrence in adults in India. Discussions are ongoing about neonatal BCG comparison phase 3 study design to ensure appropriate data is generated, supporting robust policy decision on possible BCG replacement.</p> <p>M72/AS01E a GSK adjuvanted protein vaccine candidate in phase IIb evaluation in Southern Africa, being tested for prevention of pulmonary TB. Primary results are awaited in the coming months. Secondary endpoints include safety and immunogenicity.</p> <p>H4/IC31 is an adjuvanted recombinant protein under development by Sanofi Pasteur, SSI and Aeras, currently in a Phase II prevention of infection study in adolescents (Phase II) with data expected in the coming months.</p> <p>Upon PDVAC recommendation, WHO has developed guidance on preferred product characteristics for TB vaccines, with support from the Bill and Melinda Gates Foundation. The document has gone through a thorough consensus building consultation process including a vast stakeholder meeting organized late 2017, and is now available for public review through the WHO IVR website: http://www.who.int/immunization/research/development/tuberculosis/en/.</p> |

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| Typhoid | Establish a SAGE working group on typhoid conjugate vaccines in 2016 to prepare for a SAGE review of the evidence in 2017. | Oct 2015 | Ongoing | <p>The SAGE Working Group (WG) on Typhoid Vaccines was established in Mar 2016 and will report its evidence review and draft policy recommendations for typhoid vaccines to SAGE at the Oct 2017 meeting. Data on the safety of typhoid vaccines was reviewed by the Global Advisory Committee on Vaccine Safety (GACVS) in Dec 2016. New modelling data on the dynamics of diseases transmission and economic evaluation of typhoid burden and of vaccination strategies have also been reviewed by the Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC) in Feb and Sept 2017. Important new data have also been generated in recent and ongoing studies on areas such as the epidemiology and burden of typhoid fever; trends in antimicrobial resistance of S. Typhi and implications for typhoid control. These data have provided critical information to inform the SAGE Working Group's evidence review, or are anticipated to provide data in the next few years to support country level decisions on typhoid control. Currently, one licensed typhoid conjugate vaccine is undergoing WHO prequalification review. The position Paper is published end of March 2018.</p> |
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| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
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| Un/under-immunized children | SAGE requested that WHO quickly roll out tools so that other countries can address low coverage of vaccination. | Nov 2010 | Ongoing | <p>Work is ongoing on the tool to assess "Missed Opportunities for Vaccination" (see item 284). On a broader level, a companion document to the Global Vaccine Action Plan (GVAP) focusing on Routine Immunization entitled "Global Routine Immunization Strategies and Practices" (GRISP) has been presented to the SAGE WG on DoV twice, and in Aug 2016 was published.</p> <p>Additionally, a range of additional guidance materials are under development and close to finalization. These include a health worker 'knowledge, attitudes, and practices' (KAP) tool, training materials for health workers on conversations with hesitant parents/caregivers, and addressing concerns regarding multiple injections and pain. A global field guide for 'Tailoring immunization programmes', based on the original guide from EURO, is being finalized. General guidance is also planned for development in 2018 to outline a range of evidence-informed interventions that may be considered when working to identify, assess, and address hesitancy in specific populations.</p> <p>Possibilities of using the SAGE framework in other public health areas and emergency settings are being explored.</p> |
| Vaccination during humanitarian emergencies | SAGE also suggested that the framework approach to vaccine decision-making could be considered for other health interventions in emergencies. | Apr 2012 | Ongoing | <p>A WHO meeting on implementation of vaccination during humanitarian emergency situations was convened in Cairo from 12-14 January 2016. The objectives were to:</p> <ul style="list-style-type: none"> -reflect on the experience of EMR countries in implementing vaccination in humanitarian emergencies and the issues, challenges, best approaches and existing country guidance documents to ensure satisfactory vaccination of the target populations. -reflect on countries experience using vaccination in acute humanitarian emergencies: a framework for decision making. -build on countries experience to initiate development of a draft guidance document on the implementation of vaccination in humanitarian emergency situations. <p>A draft guidance document on implementation issues was initially produced by EMRO, adjusted some as a result of limited preliminary peer-review, and then distributed for a much broader peer review. 'Vaccination in acute humanitarian emergencies: a framework for decision making' has also been adjusted/updated based on the feedback received during the Cairo meeting and a draft operational manual is being developed. Finally, although there was no separate specific session during the Apr 2016 SAGE meeting an update was featured in the IVB Director's global report at this meeting. A meeting was jointly organized with MSF on 20 June to tackle the issue of supply and procurement obstacles in humanitarian emergencies:</p> <ol style="list-style-type: none"> Discuss/map the obstacles to necessary access to affordable vaccines in a timely manner in emergency and humanitarian crisis situations. Discuss proposed solutions for addressing the key barriers to timely provision of affordable vaccines in humanitarian crisis situations. Agree upon a set of priority issues to be addressed by partners with a proposed plan of action/timeframe for follow up. <p>A follow-up meeting took place on 10-11 Oct to develop consensus on the various guidance and priorities mentioned above and discuss how to best communicate and advocate for their implementation. Feedback from the meeting included that the envisaged operational manual missed important features while still being too long. Therefore the participants concluded that with having the revised and edited framework for decision-making along with the web-based tools, the operational manual was obsolete.</p> <p>The updated framework for decision-making has been published and is available at http://apps.who.int/iris/bitstream/10665/255575/1/WHO-IVB-17.03-eng.pdf and implementation guide was finalized and is available at http://apps.who.int/iris/bitstream/10665/258719/1/WHO-IVB-17.13-eng.pdf. Work is ongoing with UNICEF for the development of web based interactive tools to support its use and facilitate further updating. These tools should be available by Q3 2017. Attempts are currently being made to have a proactive dissemination and communication plan to ensure adequate distribution of the tools.</p> |
| Vaccination during humanitarian emergencies | SAGE emphasized the need to advance work on refining guidance in delivering continuous immunization services during humanitarian conflicts. A session on human emergencies will tentatively be slotted at the April 2016 SAGE meeting. | Oct 2015 | Ongoing | |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
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| Vaccine coverage | SAGE recommended that WHO support new research for biological specimen collection including rapid on-site diagnostics that could improve coverage and susceptibility estimates. Improved serological surveillance techniques could be integrated with existing population-based surveys such as DHS or MICS. These research topics should be included on the QUIVER (now IVIR-AC) agenda. | Nov 2011 | Ongoing | With the support from the Bill and Melinda Gates Foundation (BMGF), a point-of-care testing (POCT) prototype sample OraLight collection device and POCT test system based on lateral flow and a reader combined with mobile phone, has been developed for the detection of measles specific antibodies in serum and oral fluid. The prototype showed high sensitivity and specificity (91 and 94% respectively for serum and 90 and 96% for OF). On top of that, measles virus genome could be reliably detected in the POCT strips and used for genotyping, even after prolonged storage for more than a month at 20-25°C. The added advantage was that the POCT was highly thermostable and the results showed high concordance with gold standard assay used in the Global Measles Rubella Laboratory Network (GMLRN). The assay is particularly useful in endemic settings as well as in settings near elimination of even post elimination and re-introduction. During a recent meeting of the Measles Rubella Initiative on Research and Innovation POCT came out as one of the top research priorities. It will allow monitoring disease using effective surveillance and evaluate programmatic efforts to ensure progress. It will also aid in developing and maintaining outbreak preparedness, and respond rapidly to outbreaks and manage cases. Field studies are now in phase 2 in different epidemiological and health care settings, including countries in different phases of measles control and with different health care infrastructures (Africa and South East Asia). Particularly the operational feasibility of using POCT/OF in a field setting needs to be determined. Currently, besides the measles IgM assay for oral fluid, capillary blood and serum, a POCT for rubella IgM is being developed. POCT for measles and tetanus IgG are being evaluated for the use on oral fluid and dried blood spots on filter paper. |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|------------------|--|--------------|---------|---|
| Vaccine coverage | SAGE recommended that WHO explore alternative survey methods to improve the precision, reduce the cost and improve the usefulness of survey results to national and local immunization programmes. | Nov 2011 | Ongoing | <p>To improve the quality, precision and usefulness of survey results and to reduce the cost of surveys, the Strategic Information Group (SIG) at EPI (IVB) explored recent advances in sampling methodology; new technologies for constructing sampling frames, supervision of field work, data collection, and analysis; and alternative content, collection, analysis, presentation and linkages with other health household surveys. The development of a revised WHO Vaccination Coverage Survey Reference Manual followed a thorough process. In short, several recommendations were made to WHO, countries and partners seeking to improve the quality of surveys and their use. The WHO Vaccination Coverage Survey Reference Manual was finalized at the end of 2017. The revised recommendations will likely improve accuracy, by decreasing selection bias and reliance on maternal recall, and should also increase likelihood for adequate power, increase rigor and quality. The cost of the various trade-offs is being explored. All survey related materials are available here: http://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/index2.html</p> <p>Finally, several capacity building activities around vaccination coverage surveys have been conducted. In Dec 2015, a briefing workshop on the WHO Vaccination Coverage Survey methodology for regional focal points and consultants was done. In 2016, countries in the African and Eastern Mediterranean regions were briefed. Between 2016 and early 2017, WHO in collaboration with UNICEF and CDC conducted trainings that brought together statisticians from developing countries (one Anglophone and one Francophone training), along with immunization program officers and consultants were conducted for countries from all regions, except EUR. A separate training was done in China for all provinces. An additional training was conducted in Nepal in Feb 2017, with the objective to train persons working on Immunization and a cadre of statistics professionals who, in partnership with Immunization Programmes, can conduct secondary immunization analyses from existing surveys. Participants included NSO and Immunization persons from SEAR and WPR countries, as well as consultants that work mainly in Asia. In this hands-on training in Nepal, the tool "Vaccination Coverage Quality Indicators (VCQI)" was introduced. VCQI is set of Stata programs intended to be used by statisticians and epidemiologist to analyze survey data; and for survey analysts to add further modifications and additional indicators. VCQI allows conducting analysis not only from surveys done using WHO Vaccination Coverage Cluster Surveys, but also from existing survey databases, such as DHS and MICS. Going forward, WHO envisions providing this tool VCQI for others to code it in R and other statistical packages. The largest initiative to develop capacities on the new WHO survey recommendations was the design and successful implementation of the Survey Scholar distance-learning initiative, using an approach that is based on evidence-based adult-learning methodologies for distance learning. The distance-based portion of this training initiative, Modules A was conducted from August to December 2017. Survey Scholar participants, from almost 50 countries, were engaged A community of Survey Scholar Alumni was created.</p> |

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| Vaccine coverage | WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage. | Nov 2011 | Ongoing | <p>Currently, WHO is developing global guidelines on conducting serosurvey studies on measles and rubella to identify immunity gaps in the population. An expert working group has been assembled, based on the expertise in the various fields of each of the members needed to conduct such studies, including statisticians, epidemiologists, laboratory experts, and program experts, given sub-tasks in developing parts of these guidelines that pertain to their respective expertise. A working draft has been circulated for comments and was finished by the end of 2015. It was tested subsequently in pilot studies in two different settings (post campaign/post outbreak in Mongolia, and at elimination in Bhutan). The data collection part of a pilot study has been conducted in Mongolia in 2016; analysis of the survey results is underway. The data collection has been completed in Bhutan and laboratory testing is ongoing; this study was an integrated study alongside hepatitis B/C. Based on the field work, the working draft guidelines are being adjusted, amended and corrected where needed. The final document is planned to be ready and published by end of 2017 and to be rolled out as a tool to evaluate the immune status of the target or targeted population.</p> |
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| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
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| Vaccine delivery research | SAGE requested that IVIR-AC explore research studies and methods including behavioural science studies for ranking reasons behind lack of vaccine delivery and other 'barriers to access'. | Oct 2015 | Ongoing | IVIR-AC reviewed methods, and encourages studies on vaccine delivery costing and financing (human papillomavirus (HPV), influenza and oral cholera vaccine (OCV)) and vaccine uptake/hesitancy. Non-specific effects (NSE) of vaccination and missed opportunities for vaccination sessions were on the IVIR-AC agenda in 2016 and 2017. Economic tools for influenza vaccines were presented at the June 2016 meeting. A malaria costing tool to help countries cost and plan RTS,S vaccine in their country will be reviewed at the Sep 2017 meeting. |
| Vaccine demand / acceptance /hesitancy | Acceptance and demand: Each country should develop a strategy to increase acceptance and demand for vaccination, which should include ongoing community engagement and trust-building, active hesitancy prevention, regular national assessment of vaccine concerns, and crisis response planning. | Oct 2017 | ongoing | The role of legislation in promoting vaccination - need to review current experiences. |
| Vaccine Hesitancy | SAGE acknowledged the necessity to develop core capacities at headquarters and regional level for gaining behavioural insights that can be applied in an integrated fashion for prevention of many communicable and non-communicable diseases, as well as vaccine hesitancy. This will require the involvement of sociologists, psychologists, anthropologists, experts in social marketing, communication experts, and specific disease and vaccine experts. | Oct 2014 | Ongoing | A range of activities are now ongoing in this area. With added capacity in this area at WHO HQ since late 2017, a number of initiatives are now scaling up, e.g. development and dissemination of further guidance on applying behavioural insights to assess and address hesitancy, and coordination with a group of global experts to support initiatives and capacity building in a variety of regions and countries. One of the key pillars of this work is "Tailoring Immunization Programmes (TIP)" which is now being used in at least 9 countries in the European Region, and as of December 2017 in Mauritania. A updated TIP guide is due to be published by WHO EURO in 2018. TIP has also been presented at regional meetings and features in regional guidance for WHO SEAR and WHO WPR. Lastly, in 2018 a range of new activities and materials are planned, with a focus on building capacity among regional staff, sharing lessons learned and experiences, and promoting and scaling up use globally of the various tools and guidance developed by EURO on boosting acceptance and addressing hesitancy. Collaborations in this field are also being fostered with a number of experts and researchers from a diverse range of disciplinary backgrounds to informally help support WHO efforts in this area. Coordination with UNICEF, CDC, Gavi, and other partners is also taking place to ensure alignment of efforts. |
| Vaccine Hesitancy | SAGE encourages validation of the developed compendium of survey questions on vaccine hesitancy, which have been assessed and validated only in some high-income countries or not at all. | Oct 2014 | Ongoing | Discussions with various stakeholders are ongoing (Centre for Disease Control CDC, WHO EURO, Middle Income Countries MIC task force) on the ways forward to identify partners to take on the validation of the survey questions. The MIC task force framework was presented to SAGE during the April 2014 meeting, which highlighted the importance to advance this initiative. Currently, how to secure funding from donors in support of the listed activities and advance validation of the questions in LMIC settings is being explored. The survey questions have been translated in Arab and French and are available on the WHO hesitancy website: http://www.who.int/immunization/programmes_systems/vaccine_hesitancy/en/ The promotion of their use and necessity to validate the research questions will be discussed further internally at WHO. |

| Topic | Recommendations/Action item | Meeting Date | Status | Comments and Follow up |
|-------------------|--|--------------|---------|---|
| Vaccine Hesitancy | SAGE underlined the importance of distributing the matrix of determinants, the definition of hesitancy and the other deliverables to countries and partners. | Oct 2014 | Closed | Discussions and presentations were held in the context of the immunization managers' meeting in the Eastern Mediterranean Region (EMR) and the African Region (AFR) Task force on immunization(TFI) meetings in 2014 and 2015. A Special Issue on Vaccine Hesitancy has been published in Aug 2015 in the journal Vaccine with a series of 10 full papers plus one editorial. In conjunction, a WHO press briefing was held on 18 Aug 2015 to emphasize WHO initiatives addressing vaccine hesitancy. This generated much positive media coverage. A compilation of centers to assist countries in addressing vaccine hesitancy has been finalized and sent to WHO regions to disseminate to countries. A paper which outlines the results of the 2015 Joint Reporting Form (JRF) indicators on vaccine hesitancy and contains the matrix of determinants and the definition of vaccine hesitancy was published open access on 1 Mar 2017: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0172310 . |
| Yellow Fever | SAGE prioritized head to head non-inferiority studies of all 4 WHO prequalified Yellow Fever vaccines, as well non-inferiority studies in special populations. Of particular importance, given the consequences for international travel involving IHR requirements is the duration of protection with fractional dosing, including the potential need for revaccination. Safety and effectiveness assessments should be put in place when minimal effective doses are used. | Oct 2016 | Ongoing | IVR actively promotes the research agenda, and several relevant studies are in planning or execution phase. A technical consultation was held in NOV 2017, and the report is available on WHO's website. Fractional dose non-inferiority studies for all 4 prequalified vaccines will be conducted (funded, Africa), and long term immunogenicity have been studied (manuscript submitted). Immunogenicity study in DRC is on track, and 1 month immunogenicity data have been published, 1 year data to follow soon. |

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DRAFT REPORT ON

MEETING OF THE EASTERN MEDITERRANEAN REGIONAL TECHNICAL ADVISORY GROUP (RTAG) ON IMMUNIZATION, Muscat, Oman, 14 December 2017

1. Introduction

The World Health Organization (WHO) Regional Office for the Eastern Mediterranean (EMRO), organized first meeting of the reconstituted Regional Technical Advisory Group (RTAG) on immunization in Muscat, Oman, 14 December 2017

The objectives of the meeting were to:

- discuss the Terms of Reference and operating procedures of the reconstituted regional technical advisory group (RTAG)
- review regional progress, challenges and constraints facing achieving of goals of the Eastern Mediterranean Vaccine Action Plan (EMVAP) and advice on the way forward.

The meeting was attended by 10 out of the 12 members of the RTAG, Director of department of communicable diseases prevention and control and VPI staff, WHO EMRO. In addition, participants from WHO HQ, UNICEF ROs and HQ, Gavi secretariat and CDC Atlanta attended the meeting (list of participants is attached)

Dr Rana Hajjeh, director, department of communicable diseases prevention and control, opened the meeting, welcomed members of the RTAG and thanked them for their willingness to support immunization programmes in the EMR through their membership in the RTAG. Dr Hajjeh underlined the crucial role the RTAG would play for strengthening immunization programmes in the Region and achieving goals of the Regional Vaccine Action Plan, specially at this difficult point of time where several countries in the region are facing acute or protracted humanitarian emergency situation.

Dr Ziad Memish, Director of Research Department, Prince Mohammed Bin Abdulaziz Hospital, Saudi Arabia, was appointed as Chairman of RTAG

2. Discussion and conclusion

The following were the topics included and main discussion points of the meeting:

1) RTAG: INTRODUCTION AND EXPECTED SUPPORT

Dr R. Hajjeh introduced the subject highlighting role of the RTAG as part of the three levels advisory bodies (SAGE, RTAGs and NITAGs). Terms of reference and expected support of the RTAG, mode of function, communication modalities, meetings and methods of reporting of the RTAG and rotation of RTAG membership were discussed in details. The following were the main discussion points:

- In view of the demanding situation of the region, there might be a need for more than one RTAG meeting per year. Virtual meetings were suggested.
- Formulating recommendations of the RTAG: the Region is very heterogeneous, so general recommendations may not be the best approach. Specific recommendations for certain country/groups of countries will be more beneficial
- Decision making process of RTAG: making decisions by full consensus is desirable but not always possible. . In such situations decisions will be made through majority vote of the members of the RTAG.
- Working Groups within RTAG should be established to focus on specific themes. WGs should not be too many (not more than 3) and can also include non-RTAG experts relevant to the WG subject.
- Establishing RTAG website with an interactive component where there could be a forum to discuss specific issues e.g. disease outbreaks
- RTAG can help facilitate research and help establish linkages between research institutes and public health.
- Need to strengthen RTAG secretariat capacity as planning and coordinating RTAG activities is demanding. Wider secretariat, that includes partners and has the capacity to help with the technical work, should be considered.
- Linking with SAGE and specific SAGE WGs to help address region-specific policy issues.
- Establishing explicit linkages between RTAG and NITAGs to ensure coherence of regional immunization policy application and enhancing leverage of NITAGs in shaping national policies.

2) VPI STRUCTURE AND FUNCTIONS

Dr N. Teleb, RA/VPI, introduced the subject describing the organogram of VPI unit at WHO RO and COs vis-a-vis the workload of the unit and the increasing demand of the member states for technical support, especially in view of the expanding areas of work of EPI and the challenging situation in several countries. The RTAG was requested to advise on the following questions: 1) Is the current structure of VPI adequate for the functions?; 2) Is the current staffing of VPI at RO and COs adequate?; and 3) How to ensure provision of optimum support to the member states in view of current WHO human resource capacity at RO and CO?

The following were the main discussion points:

- The current structure of VPI is adequate but the number of staff is not enough to cover the various areas of work and the increasing countries' demand for technical support (in particular those facing acute and or protracted emergencies).. Resource mobilization is required for recruitment of additional staff
- Increasing the staff in VPI should not be done in isolation of polio eradication activities and transition planning. Ongoing polio eradication activities in countries with major

programme gaps have opportunities for synergies and collaboration that are being missed. Moreover, Polio Transition planning is an opportunity for optimizing staffing for VPI at regional and countries levels. Pakistan and Afghanistan are particular priorities in this regard.

- Traditional recruitment methods are not always effective. There are challenges of finding well qualified people.
- Exploring other mechanisms of increasing human resource capacity at the RO such as fellowship programs, JPO, secondments. Fellowship programs can be at two levels, mid-career and early career professionals. It will serve both supporting the implementation and investing in next generation of leaders.
- Maximizing use of regional capacities such as collaborating centres and centres of excellence

3) EASTERN MEDITERRANEAN VACCINE ACTION PLAN (EMVAP) 2016-2020:

Dr N. Teleb provided brief description of the different sections of the EMVAP with emphasis on EMVAP goals. The RTAG was requested to advise on the following questions: 1) Are the EMVAP goals still valid/applicable in view of the current situation in the region?; 2) How can we increase visibility of EMVAP goals at the highest levels in the countries and among the partners?; 3) How can more resources be allocated/mobilized for implementation of activities pertaining to EMVAP goals, specially for the Middle Income Countries (MICs)

The following were the main discussion points:

- Goals of EMVAP are still valid but the feasibility of achievement of EMVAP goals is in question in countries facing humanitarian emergency situation.
- Need to advocate for increasing commitments to the programme and mobilize resources for implementation of related activities. To advocate and mobilize resources, there is a need to demonstrate VPDs burden in terms of morbidity and mortality, and make an economic case showing the economic benefits of achieving these goals.
- Need to address the barriers in the region hindering the achievement of the goals.
- Need to articulate the national and international risks and costs of failure to achieve EMVAP goals.
- To reduce and eliminate donor-dependency, increasing national resource allocation is required. Fund raising from within the region, including, high income countries, foundations, individuals and the private sector, is required.
- Strengthening partnerships and agreeing on a clear distribution of roles and responsibilities between all potential partners involved in immunization in the Region in order to accelerate EMVAP implementation
- Need to work more on communicating progress and challenges towards achieving the targets

4) ROUTINE IMMUNIZATION:

Dr I. Chaudhri, MO/VPI, briefed the RTAG on situation of routine immunization coverage in countries of the EMR and highlighted the continued success in 14 out of the 22 countries, whereas achieving the EMVAP coverage target is still far in remaining countries, particularly those facing various degrees of humanitarian emergency.

The RTAG was requested to provide guidance on how to address the challenges in the countries with large number of unvaccinated children (AFG, IRQ, PAK, SOM, SYR, YEM).

The following were the main discussion points:

- The large number of unvaccinated children in the region is of great concern. There is a need to map who and where they are and why they are not reached. A number of countries will need TA and resources to perform this exercise.
- Need for concrete strategic plan for countries with high number of unvaccinated children, based on above mentioned mapping exercise, and with specific focused approach and allocation of funds required for reaching the unreached.
- NITAG should be empowered to monitor routine activities for reaching the unvaccinated children in each country
- Need for ensuring accountability in countries with large numbers of unvaccinated children. High quality disaggregated data are required to monitor progress and judge accountability. Accountability frameworks need to be developed for EPI in all low coverage countries, learning from polio experience and utilizing some of its channels and assets.
- Engaging directly with provincial leadership, in addition to Federal leadership in Pakistan. Need to form a multi partner taskforce, learning lessons from polio, focused on addressing RI gaps in Pakistan.

5) MEASLES/RUBELLA CONTROL AND ELIMINATION

Dr N. Musa, MO/VPI, briefed the RTAG on progress towards achieving measles elimination in the region the challenges being faced. She proposed classification of the EMR countries into four groups according to their progress towards achieving measles elimination, based on burden of measles, measles vaccine coverage, performance of measles case based surveillance system as well as the country situation (i.e., political stability, armed conflict, civil strife, humanitarian crisis). The RTAG was requested to provide guidance on how to address measles elimination goal by 2020 in view of the current situation in the region.

The following were the main discussion points:

- Low performing countries may need more realistic substantive milestones for measles elimination

- Maintaining the target date of measles elimination would be an incentive to the well performing countries and will encourage the low performing ones.
- Need to raise the visibility of measles to help increase political commitment. Keeping the RC informed of the issues that will impact the region's efforts for achieving the measles goal.
- Countries need to assess population immunity, predict and anticipate outbreaks and address immunity gaps to mitigate outbreaks. For example, apply cohort analyses, revive and use the measles strategic Planning (MSP) tool, etc.
- Enhancing measles and rubella surveillance through using e technology and mobile phones.
- Introducing rubella vaccine more widely in the region, where suitable, and building on the opportunity of measles elimination to eliminate rubella together with regional elimination of measles.
- As countries verify measles elimination, they should also aim to verify elimination of rubella.

6) INTRODUCTION OF NEW AND UNDERUTILIZED VACCINES:

Dr K. Fahmy, MO/VPI, provided brief notes on progress in introduction of the different types of the new and underutilized vaccines in countries of the EMR. The RTAG was requested to provide guidance on how to accelerate introduction of HPV in the EMR

The following were the main discussion points:

- Need to discuss/address introduction of new vaccines according to their regional/national priority order in relation to disease burden. Accordingly PCV vaccine should come first, followed by Rotavirus vaccine then HPV. NITAG need to be well informed to take the appropriate decision on that.
- HPV infection might be much more common in the Region than it's known. Need to document the real burden and use the data for advocacy for HPV introduction.
- HPV introduction is difficult as there is no adolescent vaccination platform in several countries. Need to develop a platform for adolescent vaccination.
- Other barriers to HPV vaccine introduction in the region may explain the slow uptake of this vaccine (lack of data on disease burden, vaccine price, etc) and need to be assessed
- Use advocacy for SDGs for introduction of new vaccines especially HPV

7) POLIO TRANSITION

Dr N. Abid, Team Leader, Cross Cutting Functions, Polio Eradication initiative, briefed the RTAG on polio transition. He explained that Polio Transition process involves carefully analyzing the risks and opportunities associated with ramping down or transitioning the assets, functions and knowledge of the polio programme at all levels, with ensuring that the world remains polio-free, that the programme's

benefits continue, and that lessons learned by the Global Polio Eradication Initiative (GPEI) are transferred and applied. Sixteen countries globally are considered priorities for transition planning, 4 of them are in the EMR: Afghanistan, Pakistan, Somalia and Sudan. Sudan and Somalia are expected to complete their transition plan by end of 2nd quarter 2018, while Afghanistan and Pakistan should do it within a year of stopping wild poliovirus transmission. The Regional Steering Committee on Polio Transition decided, in 2017, to add Yemen, Iraq and Syria to the list of transition priority countries in the Region.

The following were the main discussion points:

- GPEI will begin to phase out 6-12 months after the certification of interruption of wild poliovirus transmission which will impact the size and availability of Polio assets. Concern about rapidity of change as part of the transition, especially in the field.
- Pakistan and Afghanistan will not be affected by polio transition in the immediate future, as they remain endemic for polio.
- Huge investments were put in polio. Concern about losing the polio infrastructure due to diminishing funding. Resources need to be mobilized to maintain and adapt this infrastructure for elimination/eradication of other diseases (e.g. measles) and sustain eradication of polio.
- A concrete transition plans for polio resources with operational aspects and specific milestones, taking into account that transition planning is country-specific, is required.
- The Region needs to develop a resource mobilization plan that will address immunization and surveillance gaps in the region in the aftermath of polio transition.
- RTAG needs clarity on what the transition means for the VPI team and for the polio team, how it will happen in the field and how the 2 streams would come together as polio eradication assets begin to ramp down.
- RTAG is willing to play a role in monitoring the implementation of the polio transition roadmap, if considered helpful and necessary.

3. RECOMMENDATIONS

Preamble:

RTAG noted the following achievements in the region with appreciation:

1. Maintaining high coverage with all antigens provided by the national EPI in 14 countries in the region¹.
2. Maintaining of EPI functions under extremely challenging situation and active conflict in some areas in countries facing humanitarian emergency situation (Iraq, Libya, Syria and

¹ Bahrain, Egypt, Iran, Jordan, Kuwait, Libya, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Sudan, Tunisia and UAE. Concerns are raised about validity of the immunization data quality and coverage estimates of Libya

- Yemen). The region has developed vast experience and best practices for delivering immunization in areas of armed conflict and various phases and types of humanitarian crises.
3. Progress of the region towards measles/rubella control/elimination with achievement of very low incidence of endemic measles virus transmission (<1/million population) in 7 countries in 2017²
 4. The remarkable progress the region has made towards polio eradication, particularly in Pakistan and Afghanistan, the two remaining endemic countries and the commencing of planning for polio transition in the region.

RTAG noted the following issues with concern:

1. The large number of unvaccinated/under-vaccinated children in the region who are concentrated in six countries, namely, Afghanistan, Pakistan, Iraq, Somalia, Syria and Yemen,
2. The slow progress towards achieving the EMVAP goals.
3. The delayed introduction of the new and underutilized vaccines in the region.
4. The current staffing at VPI unit is inadequate for delivering the required technical support to the member countries, in view of the expanding areas of work of EPI and the challenging situation in several countries of the region

Accordingly, RTAG members recommended the following:

1) RTAG: Introduction and expected support

- 1.1. Revise TORs of RTAG to include addressing VPD control and immunization during acute and protracted humanitarian emergency situations
- 1.2. Establishing RTAG website with an interactive component open for Qs and As
- 1.3. Including engagement of NITAGs as an agenda item at the next RTAG meeting
- 1.4. Establishing RTAG working groups on the following:
 - EMVAP – meeting immunization coverage targets
 - Conflicts and complex situations
 - New vaccines introduction

2) VPI STRUCTURE AND FUNCTIONS

Recognizing that strengthening EMRO/VPI capacity is indispensable to the success of the country immunization programs, and that its essential functions are at risk of being compromised due to understaffing, the RTAG recommends that the regional office should urgently focus on filling this human resource gap through the following actions:

- 2.1. Providing/mobilizing resources for filling in the core positions
- 2.2. Collaborating with Polio Eradication to identify and leverage current opportunities to fill human resource gaps in countries with substantial polio eradication assets.

² Bahrain, Egypt, Iran, Jordan, Morocco, Palestine and Tunisia

- 2.3. Ensure that Regional Polio Transition Plan closes the human resources gap in VPI (which I think will definitely happen once polio assets transitioned)
- 2.4. Creating an internship and mid-career programme fellowship for countries-funded immunization professionals and trainees from academic centres within the region, in order to provide additional human resource to VPI and develop practical experience to the next generation of vaccine program leaders in the EMR.
- 2.5. Working with international partners (e.g. CDC) to facilitate secondment of technical staff to the region.
- 2.6. Optimizing and aligning utilization of all potential partners (UNICEF, CDC, EMPHNET,...) , collaborating and academic institutions to help implementation of EMVAP-related activities.
- 2.7. Engaging actively with prominent academic institutions in the region to attract their top graduates to work in immunization programmes.

3) EASTERN MEDITERRANEAN VACCINE ACTION PLAN (EMVAP)

- 3.1. Developing comprehensive advocacy and resource mobilization strategy to increase national commitments to the programme and mobilize resources for implementation of EMVAP-related activities.
- 3.2. Develop business case to demonstrate VPDs burden in terms of morbidity and mortality, demonstrate the economic benefits of achieving the EMVAP goals and the cost of implementation of related activities.
- 3.3. RTAG should utilize any opportunity, with governments and partners, for advocacy to raise commitment to and visibility of immunization goals in the Region.

4) ROUTINE IMMUNIZATION

- 4.1. WHO is to take immediate action for working with the countries and related partners for mapping the unvaccinated children in each country: who and where they are and why they are not reached.
- 4.2. Developing a concrete strategic plan for countries with high number of unvaccinated children with a specific focused approach, with allocation of required funds, for reaching the unreached.
- 4.3. Working with the countries to ensure empowering NITAGs to monitor activities related to identifying and reaching the unvaccinated children in each country
- 4.4. EMRO should engage directly with provincial leadership, in addition to Federal leadership, in Pakistan. If possible, WHO should support the country for forming and leading a multi partner taskforce, learning from polio experience, focused on addressing RI gaps in Pakistan.
- 4.5. As the region has developed vast experience and best practices for delivering immunization in areas of armed conflict and various phases and types of humanitarian crises, these lessons and best practices should be systematically documented and widely shared.

5) MEASLES/RUBELLA CONTROL AND ELIMINATION

RTAG recognizes that countries of the EMR are at different situations and capacities for achieving measles elimination. While some countries are progressing well, the situation in other countries is not conducive for achieving elimination by the target date. Accordingly, RTAG recommends the following:

- 5.1. Maintaining the measles elimination target of 2020 and verifying elimination in countries that might meet the criteria for verification.
- 5.2. Establishing progress milestones on the path to elimination for countries facing high endemicity/outbreaks of measles. Attaining at least 90% MCV1 coverage in Djibouti, Pakistan, Sudan, Syria, Yemen and at least 80% MCV1 coverage in Afghanistan, Somalia and Yemen by WUENIC estimates by 2020, as a milestone towards measles elimination.
- 5.3. RTAG commends EMRO on steps taken to establish the Regional Verification Committee and encourages setting the dates for the first meeting in the first half of 2018.
- 5.4. Member countries that are close to measles elimination should assess whether rubella has been eliminated or is close to elimination and take appropriate steps to achieve both measles and rubella elimination.
- 5.5. Jordan, Palestine, Oman and Bahrain are to submit for measles (and rubella if applicable) elimination verification at the earliest opportunity and no later than end 2018.
- 5.6. Egypt, Morocco, Tunisia, Kuwait, Iran, Libya and KSA should begin preparation of documentation for verification of measles (and rubella if applicable) elimination and complete the documentation by 2019.
- 5.7. RTAG notes that the current funding climate for measles and rubella elimination goals is sub-optimal and recognizes the key role that the region plays in promoting measles and rubella elimination. RTAG recommends that EMRO and partners make every effort to increase the visibility of measles and rubella elimination in the region and globally.
- 5.8. Member countries that have not yet introduced RCV and potentially meet the criteria for introduction (Afghanistan, Djibouti, Pakistan and Sudan) should introduce RCV into their national program by 2020. A risk – benefit analysis including estimates of accumulating cases of Congenital Rubella Syndrome (CRS) is to be conducted and used as an advocacy tool for the introduction of RCV in those countries.
- 5.9. All countries should establish/strengthen CRS surveillance.

6) INTRODUCTION OF NEW AND UNDERUTILIZED VACCINES

- 6.1. Member countries, who haven't done so, should add the following new vaccines on their EPI schedule in the order of priority determined by NITAGs:

pneumococcal conjugate vaccine, rotavirus vaccine, chicken pox vaccine, hepatitis A vaccine and human papillomavirus vaccine.

- 6.2. Member countries where at birth Hepatitis B immunization has not been implemented, should take necessary steps to make that introduction as soon as feasible. VPI should provide guidance to countries on the necessary steps and on implementing or, at least piloting, the new tools and opportunities and including in the neonatal care kits and training of birth attendants in administering the vaccine.
- 6.3. Member countries that have not introduced HPV vaccination should initiate efforts of quantification of the HPV-related burden of diseases (including cervical and other genital cancers, cervical intraepithelial neoplasia, prevalence of HPV infections, and genital warts), enhancing advocacy for HPV vaccination and raising public and physician awareness and education.
- 6.4. Member countries should plan on establishing an Adolescent vaccination platform where this is absent. This platform is necessary to implement the pre-teen tetanus/diphtheria/pertussis booster and introduce the HPV vaccine.
- 6.5. WHO should work with countries to generate data on HPV burden and costs and health and economic benefits of HPV vaccine introduction in the region.

7) POLIO TRANSITION

Recognizing that countries with substantial polio infrastructure can further leverage these resources to meet their broader immunization goals, including measles elimination goal, the RTAG recommends that:

- 7.1. A regional multi-year roadmap be prepared by mid-2018 that articulates how the polio-funded human and material resources in the regional office and within countries - taking into consideration the country context - will be leveraged to help meet the EMVAP goals, without jeopardizing the focused efforts to interrupt poliovirus transmission in the region;
- 7.2. RO should identify mechanisms and responsible focal points for coordination between VPI and Polio Eradication Initiative and include clear milestones for monitoring progress.
- 7.3. RO should systematically identify and leverage synergies between EPI and ongoing polio eradication activities before the commencement of polio transition.

Report of the Regional Immunization Technical Advisory Group Meeting

Johannesburg, South Africa

5–7 December 2017

Executive Summary

The second 2017 meeting of the Regional Immunization Technical Advisory Group (RITAG), the principal advisory group to the WHO Regional Office for Africa took place at the Protea Balalaika Hotel Sandton, in Johannesburg, South Africa, on 5–7 December 2017. The meeting focused on progress towards regional immunization goals, maternal & neonatal tetanus elimination, polio eradication & end-game strategy, challenges facing middle-income countries, cholera control and immunization research in the African Region.

The **annual progress report** on immunization in the African Region highlighted some progress in 2017 but concluded that much remains to be done if regional 2020 immunization targets are to be met. The ten countries that collectively account for 80% of under-immunized children present a particular challenge. Furthermore, national data can mask significant variation in vaccination coverage within countries, highlighting the need to map and respond to variation in service provision at a more granular subnational level.

Despite commitments made in the Addis Declaration on Immunization, and although some countries have invested significantly in new vaccine introductions, the proportion of countries supporting financially their immunization programmes wholly or mostly through domestic resources remains virtually unchanged since the previous year. With external funding declining as the Global Polio Eradication Initiative (GPEI) winds down and countries transition out of Gavi support, it is increasingly important that countries honour their investment commitments, and explore the use of innovative approaches to boost domestic funding.

The **mid-term review of the Regional Strategic Plan for Immunization**, carried out by an independent expert panel, was presented to the RITAG meeting. The Regional Strategic Plan seeks to energize efforts to bring the benefits of immunization to all target groups of the African region, particularly those in underserved and hard-to-reach populations. The mid-term review highlighted areas of progress but concluded that the region was not on track to achieve most of its 2020 targets. The review was well received by RITAG and, once feedback from RITAG members has been incorporated, it will be adopted by RITAG and its recommendations endorsed.

Middle-income countries (MICs) are home to two-thirds of the world's poorest people and two-thirds of vaccine-preventable deaths occur in these countries. Gavi-ineligible MICs and Gavi-graduating countries, including those in the African Region, face particular challenges. These were addressed in a Middle-Income Country Strategy developed by WHO and partners which was endorsed by the WHO's Strategic Advisory Group of Experts on Immunization (SAGE) but has not been adequately funded or implemented.

Pooled procurement mechanisms may be one approach for facilitating vaccine access in such countries. There is also a need to address regulatory issues that may affect timely access to vaccines for routine and emergency use and evaluation in clinical trials.

The implications of Gavi transitions are of concern, including the risk that countries enter transitions ill-prepared to absorb increasing co-financing commitments and eventually to assume full responsibility for immunization systems. This could potentially lead to reversals of new vaccine introductions.

There is real hope that **polio** can soon be eradicated in the region. No new cases of wild poliovirus have been detected in the African Region since August 2016. RITAG applauds the emergency response launched in Nigeria and the countries surrounding Lake Chad. Technologies and approaches applied here may have application in control of other infectious diseases. Nevertheless, concerns remain about the possible continued transmission of wild polioviruses and the emergence of vaccine-derived polioviruses in areas where insecurity constrains high-quality surveillance and high vaccination coverage.

As GPEI funding declines, it is vital that polio transition plans safeguard essential surveillance functions for polio and other vaccine-preventable diseases and routine immunization activities, to protect national populations and regional health security. Declining levels of human and financial resources for surveillance in the region may potentially compromise the quality and completeness of data and jeopardize the regional certification of polio eradication, as well as complicate efforts to achieve measles and rubella elimination.

Affordable **oral cholera vaccines** (OCVs) combined with water, sanitation and hygiene (WaSH) and other control strategies represent a valuable new tool for cholera control, and it is essential that they are used effectively in the region. It is important that procedures for accessing the OCV global stockpile facilitate rapid access in emergency situations, and in particular do not impose impractical data collection requirements on countries. Countries also need to ensure that their vaccine regulatory policy frameworks enable the rapid importation of OCV when required, to establish effective surveillance systems to underpin timely disease control, and to collect and analyse the data required to develop evidence-driven policies and programmes, including the use of OCVs, to mitigate the risk of cholera outbreaks.

Great progress has been made towards achieving and maintaining **maternal and neonatal tetanus elimination** (MNTE). Nevertheless, the region is off-track to reach its elimination target in 2020. The seven countries yet to achieve MNTE face significant challenges, including civil conflicts and infectious disease outbreaks, and require support during a final push towards elimination. Although it has been suggested that MNTE could be accelerated through greater use of compact pre-filled auto-disable devices, which can be used by individuals with minimal training and enhance access to hard-to-reach populations, question marks remain about the true demand and appropriateness of this technology and the likelihood of reliable supply.

A further important theme was **research** – particularly the need for research driven by local priorities and involving or led by African researchers. These are core principles of the draft **Strategic Framework for Research on Immunization in the African Region**. Once finalized, the Strategic Framework will provide a key resource to support the generation and use of evidence required to prioritize and support new vaccine

development, in order to strengthen national immunization programmes and bring its benefits to larger numbers of people, including those currently being missed.

Recommendations

Annual progress

Recommendation 1.1: Targeting priority countries

A stronger advocacy strategy, including targeting of senior government officials, should be developed and implemented for the ten priority countries with the greatest numbers of under-immunized children, to ensure that each country implements a remedial plan to ensure that regional targets are met by 2020

Deliverable/outcome measure and timescale: Draft advocacy strategy to be presented to

RITAG in June 2018

Main responsibility: WHO Regional Office; other key stakeholders: countries, partners, RITAG

Recommendation 1.2: Optimizing use of subnational data

Countries should be supported to use subnational data to identify low-coverage areas and populations (including the urban poor), and to conduct and evaluate the impact of activities targeting such groups

Support plan to be presented to RITAG in June 2018

Main responsibility: WHO Regional Office; other key stakeholders: countries

Recommendation 1.3: Securing political commitment

WHO should engage with the African Union to request regular progress reports from member states on Addis Declaration commitments, including a summary of domestic financial commitments

Progress reports to be initiated by Q2 2018

Main responsibility: WHO Regional Office; other key stakeholders: African Union, countries: political leaders, ministers of health, ministers of finance

Recommendation 1.4: Exploring innovative financial instruments

A comprehensive review of best practice in innovative domestic financing of immunization and other aspects of healthcare provision should be undertaken and findings shared with countries

Draft review to be presented to RITAG in December 2018

Main responsibility: WHO Regional Office; other key stakeholders: partners, health economists

Mid-term review of the Regional Strategic Plan for Immunization 2014–2020

Recommendation 2.1: Mid-term review

RITAG should provide comments on and oversee finalization of the mid-term review, and support its dissemination

Finalization of mid-term review by end of January 2018

Main responsibility: WHO Regional Office; other key stakeholders: RITAG, mid-term review panel

Middle-income countries and vaccine procurement

Recommendation 3.1: Middle-Income Country Strategy

Given the crucial importance of MICs to achieving 2020 goals, the existing Middle-Income Country Strategy should be fully resourced and implemented

Implementation of strategy initiated by end of 2018

Main responsibility: partners; other key stakeholders: WHO Regional Office, countries

Recommendation 3.2: Gavi transitioning

In countries projected to transition out of Gavi support, advanced planning should be undertaken up to 5 years ahead, to systematically address all relevant issues well in advance of the initial stages of Gavi transitions

Summary of proposed dialogue to be presented to RITAG in June 2018; countries to be approached by end of 2018

Main responsibility: WHO Regional Office; other key stakeholders: countries, Gavi, other partners

Recommendation 3.3: Regional pooled procurement

A consultative study should be undertaken to explore the potential of pooled vaccine procurement, for example at a sub-regional level, and to identify and address potential barriers to the development of such mechanisms and potential solutions

Summary of study to be presented to RITAG in December 2018

Main responsibility: WHO Regional Office, UNICEF Supply Division; other key stakeholders: countries, NGOs engaged in pooled pharmaceutical procurement

Recommendation 3.4: Vaccine procurement

To explore the potential for cost savings in vaccine procurement, countries should be offered support to develop an analysis of financial options, including transition to UNICEF reimbursable procurement, and the possibility of creating a revolving fund to enable countries to make advance payments should be investigated

Option analysis to be reported to MICs consultation Q1 2018

Main responsibility: WHO Regional Office, UNICEF Supply Division; other key stakeholders: countries

Polio eradication and endgame strategy**Recommendation 4.1: Leveraging innovative practices**

Innovative practices and technologies deployed in Nigeria and other countries as part of the GPEI should be documented and shared to encourage their adaptation for other vaccine-preventable disease control and elimination activities, including emergency responses, and to raise routine vaccination coverage in hard-to-reach populations

Plan for documentation and dissemination to be presented to RITAG in June 2018

Main responsibility: WHO Regional Office; other key stakeholders: partners

Recommendation 4.2: Transition planning

Summaries of polio transition plans for the seven priority countries in the African Region should be reviewed by RITAG, so it can assess their implications for regional health security including surveillance

Summaries to be presented to RITAG in June 2018

Main responsibility: WHO Regional Office; other key stakeholders: countries

Recommendation 4.3: Polio surveillance

Subnational-level reporting of acute flaccid paralysis cases, as specified in the WHO-recommended surveillance standard of poliomyelitis, should be enforced in all countries, in light of its importance to regional certification of polio eradication

Monitored through annual review of national surveillance data

Main responsibility: countries; other key stakeholders: WHO Regional Office

Cholera control

Recommendation 5.1: Stockpile applications

The process for developing the dossier to apply for OCV stock should be simplified to provide speedier response to outbreaks and humanitarian emergencies

WHO Regional Office to initiate dialogue with International Coordinating Group Q1 2018

Main responsibility: International Coordinating Group; other key stakeholders: WHO HQ, OCV stockpile partners, WHO Regional Office

Recommendation 5.2: Regulatory frameworks

Countries should ensure that their regulatory frameworks facilitate the rapid importation of OCV (and other unregistered vaccines required for emergencies), by encouraging manufacturers to register OCV in advance and adopting mechanisms developed by the African Vaccine Regulatory Forum (AVAREF) for use of unlicensed products

Dialogue with national regulatory authorities to begin by Q2 2018; summary of progress to be reported to RITAG in December 2018

Main responsibility: countries; other key stakeholders: WHO Regional Office, OCV vaccine manufacturers, AVAREF

Recommendation 5.3: Cholera surveillance

Countries at risk of cholera outbreaks should strengthen their cholera surveillance capacity at the district level, including laboratory capacity, ideally integrating cholera surveillance into routine surveillance activities, to facilitate rapid responses to outbreaks

WHO Regional Office to initiate communication with countries Q1 2018; summary of progress to be reported to RITAG in December 2018

Main responsibility: countries; other key stakeholders: WHO Regional Office, partners

Recommendation 5.4: OCV research agenda

Countries at risk of cholera outbreaks should identify the evidence required to establish a national strategy for use of OCV and other measures, developing and implementing a cholera control research and evaluation agenda, and ensuring that African institutions and scientists play a lead role in the resulting agenda

WHO Regional Office to initiate communication with countries Q1 2018; summary of progress to be reported to RITAG in December 2018

Main responsibility: countries; other key stakeholders: WHO Regional Office, partners

Maternal and neonatal tetanus elimination (MNTE)

Recommendation 6.1: Resourcing for MNTE

WHO should engage with partners to ensure that adequate resources, including human resources, are available to drive forward the final stages of MNTE elimination in the region, including the development of business case to justify funding efforts.

Resources to be secured by Q2 2018

Main responsibility: WHO Regional Office; UNICEF, other key stakeholders: partners, countries

Recommendation 6.2: Progress reports

In the seven high-priority countries yet to achieve MNTE¹, RITAG should receive annual progress reviews on maternal and neonatal tetanus elimination, including district-level data on tetanus and diphtheria disease mortality noting the WHO recommended use of Td, incidence and vaccination coverage

First progress report to be presented to RITAG in June 2018

Main responsibility: WHO Regional Office; other key stakeholders: UNICEF, countries

Recommendation 6.3: Compact pre-filled auto-disable devices

A review should be undertaken to clarify the price, availability and demand for compact pre-filled auto-disable devices in the region and to synthesize the views of manufacturers and other stakeholders, to identify a route out of the current impasse

Review to be presented to RITAG in June 2018

Main responsibility: WHO Regional Office; other key stakeholders: WHO HQ, Immunization Practices Advisory Committee, UNICEF Supply Division, countries, partners, manufacturers

Regional research agenda**Recommendation 7.1: Strategic Framework for Research**

A RITAG working group should be established to revise the draft Strategic Framework for Research on Immunization and oversee its dissemination across and beyond the region with a view of raising interest among research bodies and potential funding sources

Working group established by end of 2017; revised draft presented to RITAG in June 2018

Main responsibility: WHO Regional Office; other key stakeholders: framework authors and advisers

¹Angola, Central African Republic, Democratic Republic of Congo, Guinea, Mali, Nigeria, South Sudan.

Introduction

The Regional Immunization Technical Advisory Group (RITAG) serves as the principal advisory group to the WHO Regional Office for Africa, providing strategic guidance on regional immunization policies and programmes. It holds two meetings a year, in June and December. The December 2017 RITAG meeting took place at the Protea Balalaika Hotel Sandton, in Johannesburg, South Africa, on 5–7 December 2017.

The meeting was chaired by **Professor Helen Rees**, RITAG Chair and Founder and Executive Director of the Wits Reproductive Health and HIV Institute at the University of Witwatersrand, Johannesburg, South Africa, with **Dr Felicitas Zawaira**, Director of Family and Reproductive Health Cluster at the WHO Regional Office for Africa, **Dr Richard Mihigo**, WHO Programme Coordinator, Immunization and Vaccine Development in attendance throughout the meeting. Dr Zawaira welcomed participants on behalf of the WHO Regional Director **Dr Matshidiso Moeti**, and an introductory address was delivered by **Dr Yogan Pillay**, Deputy Director-General of Health in South Africa, whose responsibilities include maternal, child and women's health, on behalf of the Minister of Health.

“Every \$1 spent on childhood immunization in Africa returns \$44 in economic and social benefits, proving that once again that immunization is one of the best buys in public health.”

Dr Felicitas Zawaira

Director of Family and Reproductive Health Cluster at the WHO Regional Office for Africa

“The issue of the ‘last mile’ is becoming more and more important. We need to spend more time working out how to get vaccines to those at the periphery of society.”

Dr Yogan Pillay

Deputy Director-General of Health in South Africa]

The agenda for the meeting included annual progress towards the goals set out in the Regional Strategic Plan for Immunization 2014–2020, as well as a mid-term review of the Regional Strategic Plan. Other topics discussed were the challenges facing middle-income countries, polio eradication, maternal and neonatal tetanus elimination, cholera control, and the regional immunization research agenda.

Summary of technical sessions

Regional Strategic Plan for Immunization 2014–2020

Annual progress report on implementation of the Regional Strategic Plan for Immunization

Dr Richard Mihigo, WHO/AFRO

Progress toward the objectives outlined in the Regional Strategic Plan for Immunization 2014–2020 is slow against a challenging backdrop, with much of the continent affected by conflict and insecurity, natural disasters and disease outbreaks. With its relatively young population, Africa will also experience marked demographic changes in coming years, alongside mass migration to urban centres.

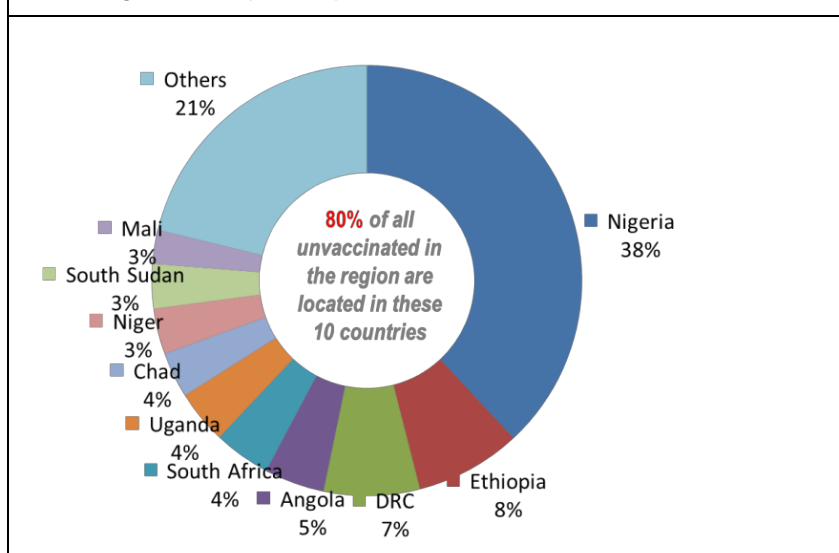
Infectious disease continues to pose a major threat – to health, wellbeing and economic development: just four vaccine-preventable diseases (pneumococcal disease, measles, rubella and rotavirus) account for an annual economic burden of US\$13 billion. The region also faces the challenge of the ramp down and closure

of the GPEI funding by 2020, while some countries will be affected at the same time by transitions out of Gavi support.

Yet there is considerable momentum for change. The Addis Declaration on Immunization, signed by heads of state in January 2017, signaled the highest possible level of political commitment to immunization in Africa. The transformation agenda instigated by WHO Regional Director Dr Matshidiso Moeti is providing new impetus and strategic direction to WHO activities. Moreover, the potential returns on investment in immunization are immense: between 2020 and 2030, control of four key vaccine-preventable diseases could save 1.9 million lives, avert 167 million cases of disease, and deliver US\$58 billion in total economic benefits².

While some progress has been made towards regional immunization objectives, much remains to be done. Immunization coverage rates remain below targets.

The figure below shows the location of missed children having missed DPT₃ in the African Region in 2016 (WUENIC)



Countries with large populations pose a particular challenge – just 10 countries account for 80% of unvaccinated children. Equity targets have also not been achieved and, while males and females benefit equally from immunization, rural/urban location, education and wealth still have a significant impact on access.

Major progress has been seen in polio eradication, with the last case of wild poliovirus reported in the region in August 2016 (see below). Circulating vaccine-derived poliovirus (cVDPV) outbreaks were reported in one country (Democratic Republic of the Congo) in 2017 and concerns persist about the quality of surveillance in the Lake Chad region and Northern Nigeria. Although coverage with the first dose of measles-containing vaccine (MCV1) has plateaued at around 75%, MCV2 coverage has been on a sharp upwards trajectory (albeit from low levels). New vaccine introductions have been a regional success story – pneumococcal conjugate vaccine has been introduced by 39 countries and rotavirus vaccine by 32 countries.

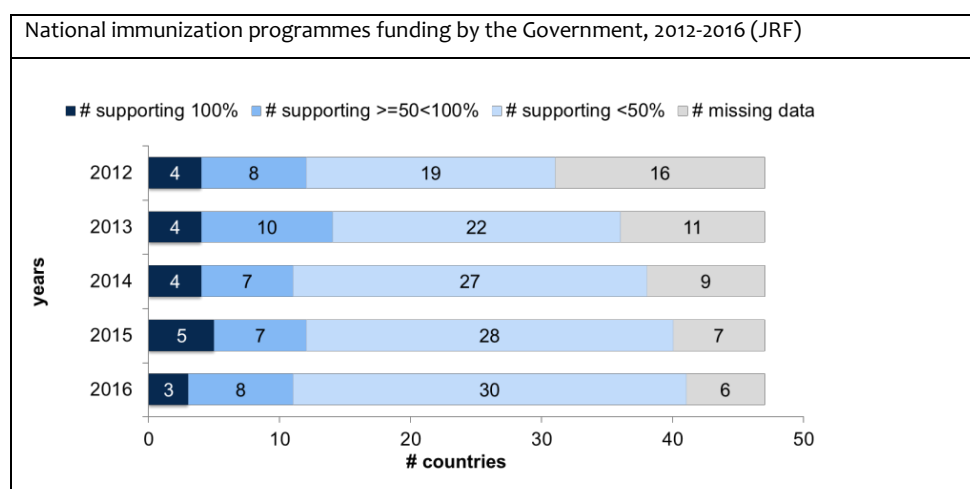
² Deloitte health economic impact calculator, 2017.

Studies have generated important data on the impact of new vaccines in Africa – use of rotavirus vaccine, for example, averted an estimated 135,000 hospitalizations and 21,000 deaths in 2016. In addition, use of MenA vaccine has prevented an estimated 300,000 cases of meningitis A and 30,000 deaths.

Some progress has been made on achieving and maintaining MNTE, with 38 countries and one zone in Nigeria validated for MNTE by December 2017 (see below). However, the region remains off-track for elimination by 2020. An updated risk map has been developed for yellow fever, but vaccination coverage remains low in many high-risk countries.

More encouragingly, the numbers of countries with national immunization technical advisory committees (NITAGs) has more than doubled since 2012; 23 NITAGs now exist, including 13 achieving six key process indicators suggesting that they are functioning effectively.

Less positively, the proportion of countries funding most or all of their national immunization programmes has scarcely changed over the past five years, with just 11 providing more than 50% financial support in 2016.



Vaccine shortages and stockouts have been on the rise, often due to internal factors such as funding delays and forecasting errors.

Looking forward, the new WHO strategy being developed by Director-General Dr Tedros, with its strong focus on universal health coverage, should favour immunization as a global priority. On the ground, a revised Reaching Every District (RED) manual provides updated guidance on enhancing access and closing equity gaps, while addressing missed opportunities for vaccination has the potential to significantly improve routine coverage. A major programme of work with partners is examining data quality and the need for greater use of subnational data where it is generated, while efforts are being made to align and integrate immunization with other global health agendas such as health security, health systems strengthening/universal health coverage and the Sustainable Development Goals.

RITAG members emphasized the importance of addressing coverage in the ten priority countries with the most under-immunized children³. Furthermore, while rural populations have typically been underserved relative to urban populations, rapid urbanization is creating marginalized urban populations at risk of

³ Angola, Chad, Democratic Republic of Congo, Ethiopia, Mali, Niger, Nigeria, South Africa, South Sudan, Uganda.

exclusion from immunization services. More granular subnational data should be analysed to identify underserved populations, as well as the underlying social and environmental factors affecting access to services. Such data could underpin targeted immunization programmes in order to close gaps in equitable service delivery.

With external funding from, for example, the GPEI projected to decline and stop, the importance of countries honouring their immunization investment commitments was stressed. Opportunities may exist to explore the use of innovative approaches to domestic funding, such as greater involvement of the private sector, health insurance schemes, trust funds and taxation, and to deepen engagement with other potential partners such as the World Bank or the African Development Bank.

RITAG members also focused on the importance of community mobilization and engagement. Civil society can play a key role in stimulating demand for vaccination but also in promoting political accountability. It was also suggested that emphasis may need to shift from individual behaviour change to more societally oriented norm-shifting in order to internalize the value immunization more effectively.

Report of the independent mid-term review of the Regional Strategic Plan for Immunization

Professor Jeffrey Mphahlele, South African Medical Research Council and Chair of the mid-term review panel

The forerunner of RITAG asked the WHO Regional Office to coordinate a mid-term review to assess progress towards the objectives set out in the Regional Strategic Plan for Immunization 2014–2020. The review was carried out by an independent panel supported by the WHO Regional Office for Africa.

The Review confirmed the continuing relevance of the Regional Strategic Plan and its alignment with the Global Vaccine Action Plan, including its monitoring and evaluation framework. However, it identified shortcomings in the achievement of several strategic targets and recommended their revision based on the current state of progress.

For the first strategic objective, on immunization coverage, the review panel found that coverage with traditional vaccines had plateaued in recent years. Progress has been achieved towards the second strategic objective, polio eradication. There was great concern that the third strategic objective, measles elimination and rubella control, would not be achieved by 2020. Finally, variable progress has been seen towards the fourth strategic objective, control of other vaccine-preventable diseases. The Regional Strategic Plan also identified six strategic directions, covering national commitments to immunization, community awareness, equitable access, integration with other health services, funding and vaccine supply, and research and development. Mixed progress was seen in these areas, and there may also be a need to develop a more appropriate range of indicators.

The review panel made specific recommendations in six areas: (1) leveraging commitments made in the Addis Declaration; (2) defining community-centered approaches to improve equitable access; (3) fostering a universal health coverage approach with immunization at the core of primary health care; (4) improving the availability and quality of data; (5) involving new players and approaches to enhance human resource

capacity; and (6) employing innovative instruments to sustain financing.

The review was warmly welcomed by RITAG. Once feedback from RITAG members has been incorporated, the review will be adopted by RITAG and its recommendations endorsed after a further round of review.

Middle-income countries: improving access to affordable vaccines

Tania Cernuschi, WHO HQ

The world's 107 MICs are home to two-thirds of the world's poorest people and two-thirds of vaccine-preventable deaths occur in these countries. Globally, there are also concerning signs of declining vaccination coverage in Gavi-ineligible MICs. Of the 65 Gavi-ineligible MICs, ten are in the African Region, including three transitioning out of Gavi support⁴. Gavi-ineligible MICs have limited access to other sources of financial support, and may struggle to sustain the delivery of newly introduced vaccines.

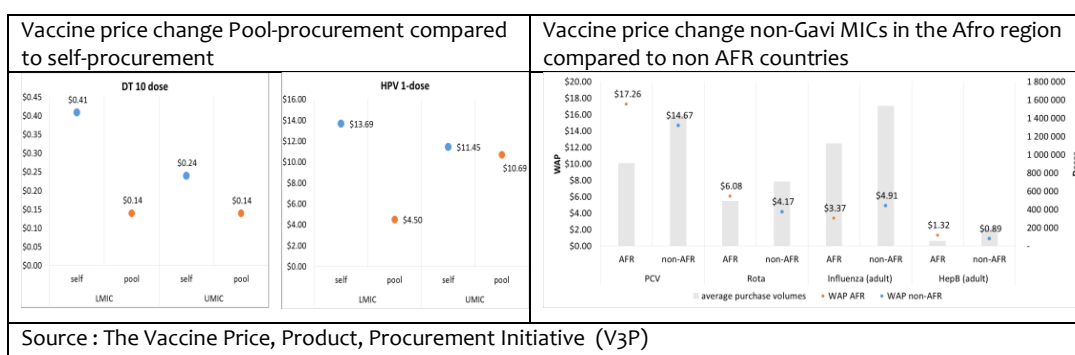
In light of the challenges facing these countries, particularly those around vaccine procurement, in 2015 WHO and partners developed a Middle-Income Country Strategy, with the aim of enhancing coverage and enabling the introduction of new vaccines. Although the strategy was endorsed by SAGE in 2015, it has not been adequately funded or implemented.

Vaccines represent the largest single budget item for national immunization programmes. Gavi-eligible countries benefit from Gavi vaccine procurement mechanisms, while the Revolving Fund of the Pan-American Health Organization operates pooled procurement for the Region of the Americas, and countries can also use the UNICEF reimbursable procurement mechanism. Alternatively, many countries self-procure directly from suppliers.

A lack of market information is a major disadvantage for self-procuring countries. To enhance price transparency, WHO has developed the Vaccine Price, Product and Procurement (V3P) database (www.who.int/immunization/programmes_systems/procurement/v3p/platform/en/), which collates information on prices, volumes, procurement methods and other key data. By the end of 2017, some 144 countries were contributing information, including all but one country in the African Region.

⁴ Gavi-ineligible MICs: Algeria, Botswana, Cape Verde, Equatorial Guinea, Gabon, Mauritius, Namibia, Seychelles, South Africa, and Swaziland. Transitioning countries: Angola, Republic of Congo, and Nigeria.

Analysis of V3P data has revealed that self-procuring countries pay considerably more for most vaccines. For several vaccines, countries in the African Region are paying higher prices than equivalent countries in other regions



V3P data also suggest that volume alone is a poor predictor of price – factors such as contract length and timing of payments are also key factors.

WHO offers a range of mechanisms to support more effective self-procurement. Alternative options include adoption of UNICEF reimbursable procurement or sub-regional pooled procurement agreements, such as the arrangement successfully used by small Baltic States in the European Region to achieve costs savings.

RITAG members focused on the possibility of establishing pooled vaccine procurement for the African Region. An attempt to develop such a mechanism in the Eastern Mediterranean Region has not been successful to date, and a consultation exercise within the African Region in 2008 identified significant barriers to pooled procurement. However, sub-regional collaboration has improved (for example through Regional Economic Communities such as the Economic Community of West African States and the Southern African Development Community), suggesting there may be emerging opportunities for cooperation in procurement.

It was also suggested that countries could be supported to undertake an option analysis as carried out in Swaziland, to explore the possible benefits of UNICEF reimbursable procurement. Innovative funding mechanisms might be required to address one potential obstacle to UNICEF procurement – the need for advance payments. It was also suggested that valuable lessons could be learned from, and collaborative opportunities explored with, NGOs that have experience of procurement of pharmaceutical products.

Discussions also covered the importance of simplicity of national regulatory systems processes to facilitate timely vaccine access, for routine and emergency use and evaluation in clinical trials. During the 2016 Ebola outbreak, it became clear that many national regulatory authorities (NRAs) and ethics committees did not have policies and procedures in place to support rapid clearance for clinical trials. In addition, in some countries, access to cholera vaccines has been hampered by the reluctance of industry to apply for registration. The legal framework governing NRAs in the region together with certain regulatory practices may discourage vaccine manufacturers from applying for licensure of important vaccines (unfavorable ratio of cost and complexity of registration versus the expected financial return). If a limited number of vaccine products are registered in a country, this can lead to a dependence on a small number of suppliers, increasing the risk of vaccine stockouts. Building on WHO's ongoing activities to strengthen NRAs through the AVAREF

network, countries need to identify and eliminate unnecessary regulatory obstacles that limit vaccine availability. In addition, the harmonization of regulatory systems between countries could deliver efficiencies and generate more sustainable vaccine marketplaces.

RITAG members also welcomed Gavi's recent acknowledgement of the challenges that some countries (including those in the Africa region) were experiencing in their transitions out of Gavi support. A range of supportive measures has been announced, including the development of a tailored plan for Nigeria, the possibility of funding for new vaccine introductions and targeted technical support during transitions, and an analysis of the risks to successful transitions in Angola and Republic of Congo.

COUNTRY CASE STUDY

Swaziland: Experiences in vaccine procurement

Dr Njabuliso Lukhele, Ministry of Health, Swaziland

Swaziland is classified as a lower middle-income country but is ineligible for Gavi support. The Government fully funds vaccine procurement and 96% of routine immunization costs. Expenditure on immunization has increased significantly since 2010.

As a relatively small country, Swaziland faces several challenges in vaccine procurement. Orders are small and payment sometimes delayed, which deters some suppliers. This can lead to a dependence on a limited number of suppliers and difficulty in negotiating fair prices.

To identify more efficient methods of procurement, in April 2017 the country was visited by representatives from the UNICEF Supply Division. A cross-departmental task team was established, including WHO and external partners, and a forecast of vaccine needs was developed. Following the signing of a memorandum of understanding between the Ministry of Health and UNICEF, this information was used to generate cost estimates for vaccine supply through UNICEF.

Preliminary analysis suggests that UNICEF reimbursable procurement system could deliver annual cost savings of more than US\$1 million (almost 25% of the total vaccine budget). Should Swaziland adopt this mechanism, it would need to adapt some of its policies and procedures, as UNICEF requires full payment in advance and waivers would be required to address tendering regulations.

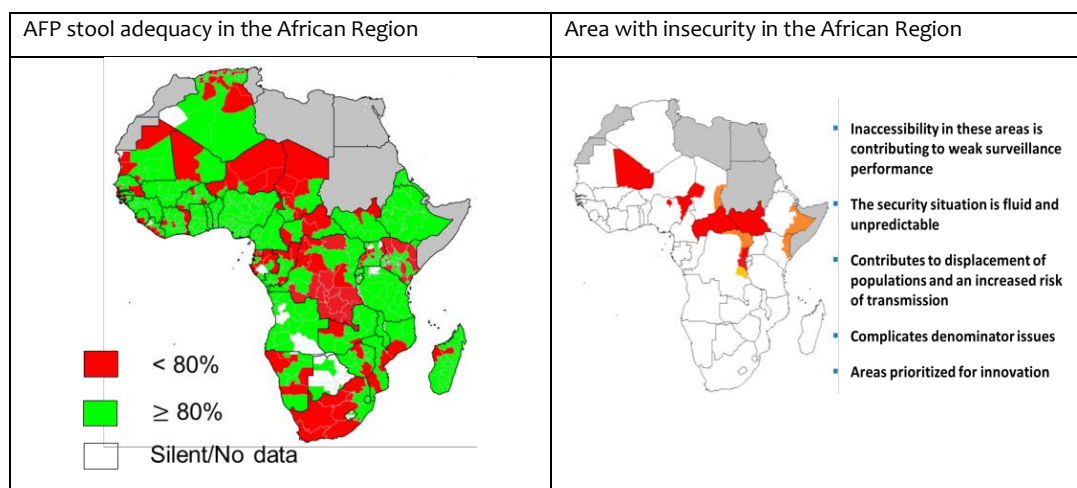
Polio eradication and endgame strategy

Polio eradication in the African Region: updates and way forward

Dr Pascal Mkanda, WHO/AFRO

The prospect of certification of polio eradication in the African Region has been raised by the absence of any confirmed cases of wild poliovirus since August 2016. Cases of type 2 circulating vaccine-derived poliovirus (cVDPV2) were however detected in the Lake Chad area in 2016 and in the Democratic Republic of Congo in 2017. Nevertheless, in much of the Africa Region, the impact of ongoing civil conflict, insecurity and population displacements on vaccination coverage and vaccine-preventable disease surveillance poses a significant risk to polio eradication. Furthermore the substitution of tOPV with bOPV combined with low immunisation coverage has increased the threat of cVDPV as evidenced by the outbreak in the DRC.

There are particular concerns over polio surveillance due to localized performance gaps in detection of AFP cases and stool adequacy, which are mostly attributed to insecurity (inaccessibility) and weak surveillance networks, particularly at sub-national levels.



Several innovations have been introduced to improve surveillance. For example, in areas with weak health systems, the Auto-Visual AFP Detection and Reporting (AVADAR) system enables members of local communities to use mobile phones to report AFP cases for investigation. Approaches based on geographic information system (GIS)-enabled devices, such as eSurv and Integrated Supported Supervision (ISS), have been used to enhance surveillance and to collect data on immunization facilities in more than 20 countries. These tools have made possible the identification of AFP cases not detected through conventional surveillance, and improved reporting from insecure areas and silent districts.

After wild poliovirus was detected in northern Nigeria in August 2016, an emergency response was launched in Nigeria and countries surrounding Lake Chad. An Outbreak Response Assessment (OBRA) was completed in these countries as well as in the Democratic Republic of the Congo and in the Central African Republic in October 2017. In December 2017, the Lake Chad Technical Advisory Group highlighted a continuing risk of transmission, and recommended that control efforts be extended to mid-2018, using a variety of innovative approaches to access hard-to-reach populations in challenging circumstances (see Box).

Inactivated poliovirus vaccine (IPV) has been widely introduced in the African Region, and the remaining 11 countries have made a formal commitment to introduce IPV. Ten countries experienced IPV stockouts in 2017, but global supply of IPV is expected to improve in 2018. IPV shortages led to a recommendation for use of fractional intradermal dosing; with supplies improving, some countries are reverting to administering the full intramuscular dose, although fractional dosing remains an option when suitably trained health workers are available.

Progress has continued on implementation of the Global Action Plan on polio containment (GAP III). Just one country has yet to complete containment phases 1a and 1b. South Africa is the only country in the Region that plans to maintain wild poliovirus samples in secure poliovirus-essential facilities.

In terms of certification of polio-free status, nine countries have yet to present evidence of interruption to the Africa Region Certification Commission (Gabon was certified after the RITAG meeting).

Polio-free certification status in the African Region, as of December 2017



Regional certification could be threatened by the declining quality and completeness of AFP surveillance in several countries, while a continuing risk of wild virus reintroduction has been highlighted in some countries certified as polio-free.

Polio transition planning continues in the seven priority countries hosting the majority of polio infrastructure in the Region, all of which are now developing transition plans (see Box). A reduction in WHO human resources in the region began in 2017.

Future priorities include the continuing efforts to improve surveillance and immunisation coverage around Lake Chad, including increased use of innovative new technologies, sharing of lessons learned from GPEI, and further progress on transition planning.

Lake Chad Technical Advisory Group

Professor Daniel Tarantola, RITAG member and chair of the polio Lake Chad TAG

Following the detection of wild poliovirus in Borno state in Nigeria in August 2016, a Declaration of Emergency was signed by health ministers in five countries in the Lake Chad region (Cameroon, Central African Republic, Chad, Niger and Nigeria). The Lake Chad Coordination was put in place to organize local activities, initially focused on outbreak response supplementary immunization activities (SIAs).

The latest OBRA (outbreak response assessment), carried out in October–November 2017 in the northern Nigerian states of Borno, Sokoto and Adamawa, sought to determine whether transmission had been interrupted. Key criteria include the absence of any confirmed cases of wild poliovirus for six months, the adequacy of surveillance, and plans for targeting high-risk populations.

Although no new wild polio or cVDPV cases have been reported in 2017, population displacements due to civil unrest make it hard to judge the reliability of vaccination coverage figures. Furthermore, the completeness of surveillance is open to question. On the balance of evidence, OBRA could not conclude that transmission had

been interrupted and recommended that activities around Lake Chad be extended, intensified and re-assessed in 2019, and that greater attention to the vulnerability of other Nigerian states close to the Lake Chad area and challenged by insecurity (e.g. Yobe State) be included in this re-assessment.

These conclusions were echoed by the Lake Chad Technical Advisory Group (TAG). While applauding the efforts of the Lake Chad Coordination, the TAG identified a range of issues, including the need for more granular analysis of surveillance data, the need to ensure adequate quality of samples sent to laboratories, and the need to remove trivalent oral polio vaccine from some facilities. The TAG also supported targeting of high-risk populations, particularly those living on Lake Chad's islands and nomadic populations.

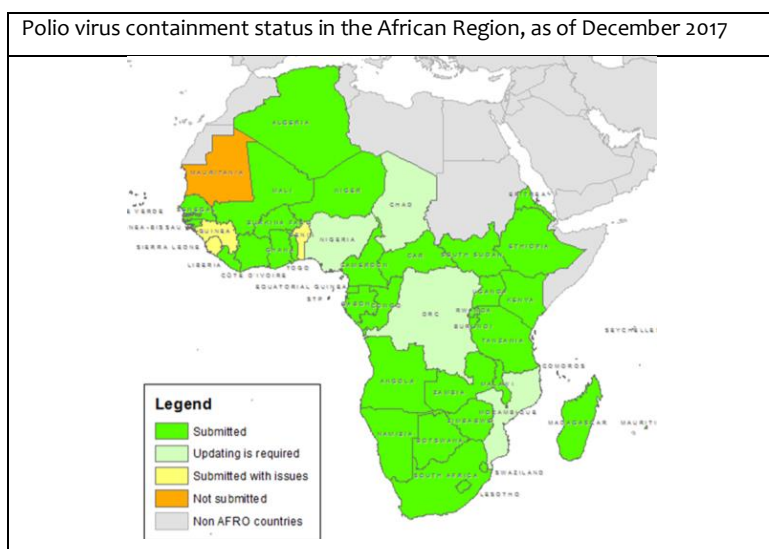
Post-Certification Strategy

Dr Michel Zaffran, Polio Eradication, WHO HQ

The Polio Post-Certification Strategy has two aims: to define the functions required to maintain a polio-free world and to identify and address potential impacts on other health programmes drawing on GPEI support. The GPEI leads in the former area while countries are expected to take the lead in the latter.

A draft Post-Certification Strategic Plan provides high-level guidance on how a polio-free world can be maintained after eradication. Once endemic transmission has been interrupted globally, a three-year pre-certification period is envisaged, the last year of which will see an overlap between GPEI and post-GPEI programmes; the GPEI will be dissolved at certification.

Key risks after certification will initially be the emergence of cVDPV, until oral vaccine use is discontinued, then the shedding of VDPV from immunocompromised individuals. In the longer term, the major risk is the circulation of virus following a laboratory containment breach.



The goals of the Post-Certification Strategy are to contain wild and live vaccine poliovirus sources; to protect populations by switching from oral vaccine to IPV; and to maintain systems to detect and respond rapidly to any reintroduction. Each goal is supported by specific responsibilities at global, regional and national levels.

The Post-Certification Strategy is due to be reviewed by the SAGE Polio Working Group and SAGE itself, before presentation to the World Health Assembly in May 2018. However, it is intended to be a ‘living document’ updated as circumstances demand prior to certification.

Among the key discussion points on polio eradication was the need to analyse polio surveillance data at a more granular level, to identify gaps in surveillance, and in particular to distinguish between zero-reporting wards (‘silent’ wards) and wards that do not report at all (‘mute’ wards). As emphasized by the Lake Chad Technical Advisory Group, this analysis needs to extend below district level, to ward level or its equivalent.

RITAG applauded the emergency response launched around Lake Chad. The innovative approaches and technologies used were felt to have applicability in other areas of infectious disease control. Lessons might also be learned from Nigeria on the targeting of under-served populations in its emergency plan for routine immunization. The coordinated response also illustrates the importance of cross-border collaboration and of strong political leadership in response to health emergencies – essential in the battle against infectious diseases that are unconstrained by national borders.

A recurring theme in this and other RITAG sessions was the importance of vaccine-preventable disease surveillance. Effective surveillance will be essential for certification of polio eradication, measles and rubella elimination and MNTE, but also for timely use of vaccines to control outbreaks (for example, of cholera and yellow fever), and more generally to inform national immunization activities. Surveillance and immunization are both critical components of national and regional health security, and the IHR Joint External Evaluations that countries are now undertaking provide a measure of countries’ ability to deliver on both these aspects of public health – as well as an opportunity to strengthen systems through the resulting national action plans.

COUNTRY CASE STUDY

Nigeria: Innovations to reach children in accessible areas

Fiona Braka, WHO/Nigeria

Polio eradication efforts in Nigeria have focused on Borno state, where the last case of wild poliovirus was detected in August 2016. Innovative approaches have been adopted to improve coverage in difficult-to-access populations in areas of high insecurity.

Settlements have been divided into three groups – accessible, partially accessible and inaccessible. Accessible settlements have been reached through house-to-house campaigns, while immunization workers received the protection of civilians with military experience to visit partially accessible settlements. The only feasible strategy in inaccessible areas was for the Nigerian army to conduct immunization exercises, which ensured that nearly 50,000 children were vaccinated in 2,500 inaccessible settlements.

Although these three strategies have improved coverage, many gaps remain. Following advocacy visits to the military commander and the Executive Governor of Borno State, a plan has been agreed to increase the use of military teams to reach additional inaccessible settlements.

Alongside these efforts, other innovative approaches have been adopted. For example, various locations have been targeted to reach migrating children at checkpoints and transit points, leading to the vaccination of nearly 300,000 children since January 2017.

Satellite imaging has also been used to track the persistence, growth or abandonment of settlements, giving a clearer picture of population size and distribution and population movements. GIS-based technologies will be used to support the next wave of activities to reach remaining unvaccinated populations.

The Government of Nigeria has also recognized that gains are not sustainable without a strengthening of routine immunizations systems. A state of public health concern was announced and an emergency plan for routine immunization was introduced in June 2017, focusing on priority states with low coverage.

COUNTRY CASE STUDY

Ethiopia: Polio transition planning

Dr Getnet Bayih Endalew, Ministry of Health, Ethiopia

As envisaged in the Polio Eradication and Endgame Strategic Plan 2013–2018, Ethiopia has been working with WHO to develop a national polio transition plan to manage the withdrawal of GPEI resources.

A multisectoral national Polio Transition Planning Committee has been established, with the representation of external stakeholders. This committee has overseen the development of a range of documents feeding into a draft Polio Transition Plan for Ethiopia (2018–2020). The development of the plan was significantly influenced by a desktop polio transition simulation exercise.

Analyses have included a detailed breakdown of GPEI-funded resources and their contributions to polio and other immunization activities. The annual polio fund amounted to US\$39.8 million in 2016, with GPEI donors contributing US\$21.7 million; this is projected to be reduced to US\$4.6 million in 2018.

Ethiopia has conducted a risk analysis to prioritize future activities to maintain its polio-free status. Of particular concern is the possibility of the introduction of poliovirus from neighboring fragile states such as Somalia, in view of extensive population movements. This risk is compounded by low levels of vaccination coverage and weak surveillance in hard-to-reach and nomadic populations living near Ethiopia's borders.

The transition plan has been developed to maintain minimal assets until certification is achieved, with responsibilities then transferring to the Ethiopian Government from 2020. Strengthening surveillance and immunization activities in the border regions will be a particular focus. The transition plan includes a detailed budget breakdown, and a significant projected budget gap is being discussed with potential partners.

Cholera in the African Region

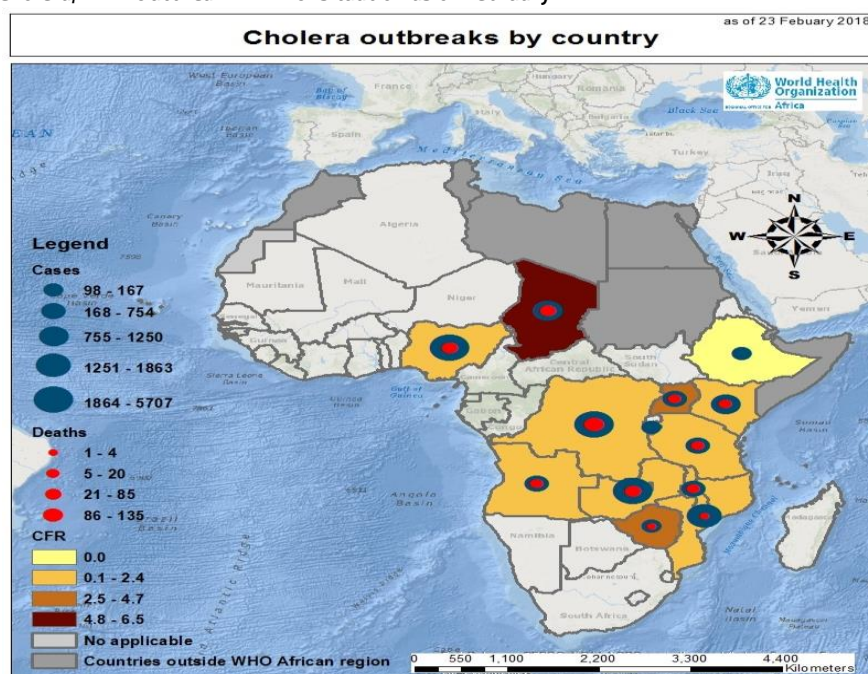
Dr Linda Omar, WHO/AFRO

Sub-Saharan Africa experiences a high burden of cholera. By mid-September 2017, more than 139,000 cases and 3,000 deaths had been reported; numbers that likely underestimate the true situation. Multiple factors increase the risk of cholera outbreaks in the region, including conflict and population displacements, lack of access to clean water, poor health infrastructure and climatic factors. Cholera control is further challenged by a lack of political commitment, weaknesses in disease surveillance and laboratory capacity, and limited national water, sanitation and hygiene (WASH) initiatives.

Affordable oral cholera vaccines (OCVs) represent an emerging tool for effective cholera control. Available vaccines have shown adequate efficacy and safety profiles, although they have drawbacks, including limited protection of young children, a need for two doses and unpleasant taste; improved OCVs are being developed.

OCVs have potential use in both emergency (humanitarian emergencies and cholera outbreaks) and non-emergency (endemic cholera) situations. A global OCV stockpile has been established, with an International Coordinating Group enabling rapid access in emergency situations and the OCV Working Group of the Global Task Force on Cholera Control overseeing access to non-emergency supplies. Since 2013, OCV use has increased rapidly, with humanitarian crises accounting for most use in 2017.

Cholera/AWD Outbreak in AFRO: situation as of February 2018



The Global Task Force has developed a plan for eradicating cholera epidemics that occur repeatedly in the same geographic areas by 2030 (*Ending Cholera: A Global Roadmap to 2030*). This envisages a greater emphasis on long-term WaSH-based prevention and control, with effective case management and OCVs playing a critical role in this transition. A Cholera Implementation Framework has been developed for the Africa Region, based on an integrated multisectoral strategy incorporating intensified surveillance and effective case management alongside OCV use, to underpin national cholera control programmes.

RITAG members stressed the need for the application procedure to the global stockpile to be fit for purpose and not to impose unrealistic data requirements on applicants. The importance of effective cholera surveillance and laboratory capacity was stressed, and concerns were expressed about the impact of the withdrawal of GPEI resources on this surveillance. It was also recognized that NRAs need to ensure that national policy frameworks are compatible with the rapid import of OCV when required; importation can be delayed if OCVs have not been registered in advance or if regulatory requirements are obstacles to the rapid importation of unregistered vaccines in emergency situations.

COUNTRY CASE STUDY

OCV in emergencies: experiences from Freetown, Sierra Leone

Dr Dennis Marke, Ministry of Health, Sierra Leone

In 2017, Sierra Leone deployed OCV for the first time to prevent a cholera epidemic in Freetown, following flooding and a landslide that displaced nearly 6,000 people. The country has had a history of outbreaks – the last major one, in 2012, affecting more than 23,000 people.

With partners, the Ministry of Health rapidly developed an emergency response, and within 72 hours secured approval from the International Coordinating Group to access OCV from the global stockpile. Two rounds of vaccination targeted more than 500,000 people at risk, with health workers moving house to house and visiting schools, and operating from fixed health facilities.

Reported vaccination coverage was high (generally above 95%). A follow-up coverage verification survey of nearly 7,000 individuals found slightly lower coverage (around 80%), particularly among adolescents. Of those vaccinated, around 30% received only one dose. Concerns about cholera were by far the most commonly cited reason for presenting for vaccination. Reasons given for non-vaccination were almost all practical; there was little evidence of vaccine hesitancy.

A range of factors were suggested to be important to the success of emergency OCV campaigns. These included central coordination and planning, training of vaccinators, community engagement, detailed implementation plans, and rapid post-campaign monitoring. Despite significant technical difficulties inherent to study design, an attempt is being made to evaluate the impact of the OCV mass campaign on cholera mortality and morbidity in the targeted population.

COUNTRY CASE STUDY

Cholera control: lessons learned from Tanzania

Mr Christopher Kamugisha, WHO Tanzania

An ongoing cholera outbreak in Tanzania began in Dar es Salaam in August 2015 and rapidly spread throughout the country. A Public Health Emergency Operations Centre was established in the Ministry of Health and a national task force meets weekly. Daily surveillance reports provide a snapshot of the epidemic, although periodic nationwide data validation exercises suggest some under-reporting of cases. Control responses have focused on social mobilization and promotion of WaSH practices.

Tanzania used OCV to control a cholera outbreak affecting refugees at Kagunga village in Kigoma District on the shores of Lake Tanganyika in April 2015. UNHCR moved refugees by boat to Kigoma Port then to a refugee camp at Nyarugusu. By September 2015, the camp was home to more than 150,000 people.

In May 2015, a cholera outbreak occurred at Kagunga and the transit camp and spread to the main camp at Nyarugusu. Within days, cholera had also spread to local village communities. The Ministry of Health and WHO jointly developed an application to the global stockpile, with vaccine being delivered within a week. An emergency national inter-agency coordinating committee (ICC) meeting endorsed use of two doses as an emergency response and Tanzania's NRA fast-tracked registration enabling an import permit to be issued. The ICC also decreed that local communities as well as individuals in camps should be vaccinated. By July, the outbreak had been brought under control in the camps and local communities.

The vaccination exercise was considered to have been successful, largely thanks to effective social mobilization and micro-planning. However, the fact that the vaccine had not been registered prior to the outbreak had delayed implementation. It was also felt that the application process to the global stockpile was challenging, calling for data that were not easily available.

Maternal and neonatal tetanus elimination (MNTE)

Attaining and maintaining MNTE in the African Region

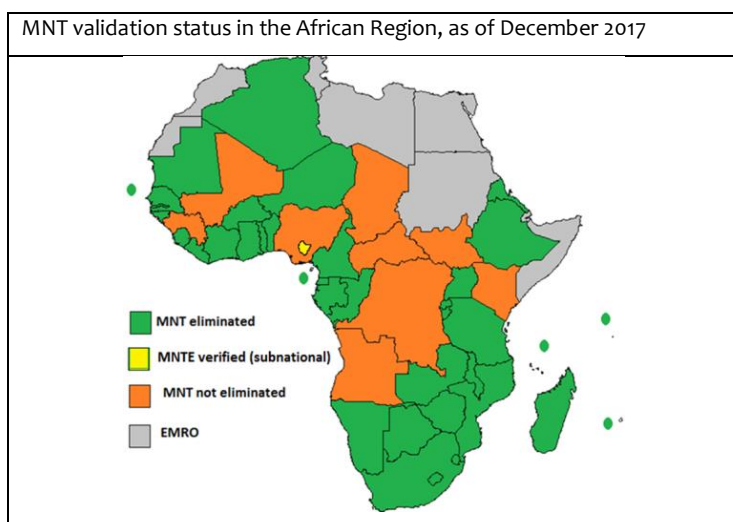
Dr Balcha Masresha, WHO/AFRO

MNTE is one of the objectives of the Regional Strategic Plan for Immunization. Although more countries have achieved MNTE, the region did not achieve its target of MNTE in 42 countries by 2017 and is off-track to reach its target of all 47 countries by 2020.

The strategy for MNTE is based on tetanus toxoid (TT) vaccination in pregnancy supported by SIAs in high-risk areas (alongside clean delivery practices and surveillance for neonatal tetanus). WHO now recommends a six-dose vaccination strategy (three doses initially and three boosters in childhood and adolescence). WHO also recommends tetanus–diphtheria (Td) for the booster doses, which have been introduced by 18 countries. This is especially relevant as globally there have been several outbreaks of diphtheria particularly in areas of civil conflict including in the African region. .

Vaccination coverage at birth has been relatively stable at around 80%. During 2014–17, 13.3 million women of childbearing age received two or more TT doses in SIAs targeting 390 high-risk districts in nine countries. Not all these activities could be completed, due to funding and security issues.

By December 2017, 38 countries and one zone in Nigeria had been validated for MNTE; two (Kenya and Chad) are likely to be validated early in 2018.



A range of activities are being planned in the remaining seven countries⁵, many of which are affected by civil conflict and/or infectious disease outbreaks.

A global investment case for MNTE is currently being finalized, targeting 16 countries, including nine in the African Region. This will include consideration of the use of compact auto-disable devices, which can be used by vaccinators with minimal training, facilitating access to hard-to-reach populations.

MNTE was identified as a key issue in equitable access to health services – infection typically affects the most disadvantaged families. As well as the need to drive forward MNTE, it was also emphasized that vaccination coverage must be sustained to prevent disease resurgence – maintaining MNTE must still be a priority in countries validated for MNTE. Elimination strategies must combine safe clean delivery practices with strengthening routine immunization and SIAs in situations where vaccination coverage among pregnant women is inadequate. Implementation of the six-dose strategy, which should reduce the need for SIAs, and the drive towards increased Td use will be challenging.

RITAG members also focused on the potential value of compact pre-filled auto-disable devices. A ‘catch 22’ situation currently exists, with manufacturers reluctant to commit to large-scale production in the absence of clear demand, and programmes unwilling to adopt the technology in the absence of price data. There is an urgent need to assimilate the extensive dialogue that has taken place between manufacturers and other stakeholders to generate clarity on demand, pricing and the likelihood of reliable supply, noting that these devices have also been identified as a potentially important technology for hepatitis B vaccine delivery. RITAG requested clarity on the status on prefilled auto-disabled devices as they felt that this technology would increase immunisation coverage in hard to reach areas.

⁵ Angola, Central African Republic, Democratic Republic of Congo, Guinea, Mali, Nigeria, South Sudan.

COUNTRY CASE STUDY

Challenges in achieving MNTE: the South Sudan experience*Dr Anthony Laku, Ministry of Health, South Sudan*

South Sudan has been affected by a protracted civil conflict that has significantly affected healthcare delivery – more than half the country's population of 12.3 million people do not have access to health facilities. An estimated 7.4 million people have been affected by conflict, with 3.9 million displaced. South Sudan has been affected by multiple disease outbreaks and food insecurity, and the country is experiencing a severe shortage of health workers.

Given these challenges, the country has struggled to achieve its routine immunization and SIA objectives: 61% of counties had less than 80% coverage in a third round of TT SIAs and 27 out of 80 counties were not accessible at a. Similarly, routine vaccination coverage has been in decline, although estimated protection against tetanus at birth was 68% in 2016, a small increase on previous years.

Promoting clean delivery practices has been challenging, with only 13% of mothers having access to skilled delivery services, in part because of a chronic shortage of health workers and attacks on health services. Surveillance is suboptimal, with no case-based surveillance and incomplete reporting from counties.

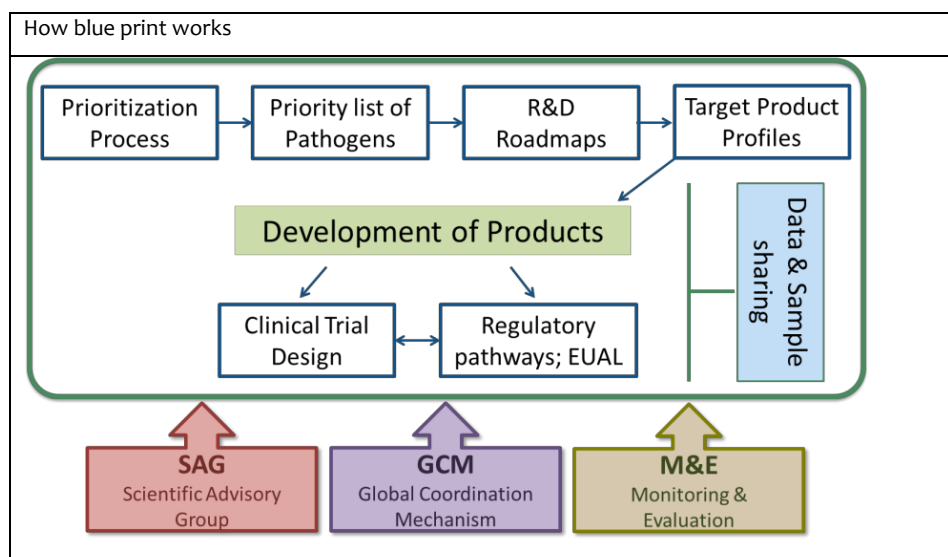
The country has developed strategies to enhance vaccination coverage, including 'hit and run' approaches for insecure areas and targeted strengthening of routine services in specific geographic areas. A new comprehensive multiyear plan for MNTE has been developed for 2018–2022, spanning SIAs, routine immunization services, a switch from TT to Td, and case-based surveillance. The aim is also to enhance integration with other health services and with an overarching health human resourcing plan.

Immunization research**A Research & Development (R&D) Blueprint for action to prevent epidemics***Dr Joachim Hombach, WHO HQ*

The R&D Blueprint is being developed by WHO in response to the uncoordinated R&D response to the Ebola epidemic. It is intended to provide a global framework to support more rapid and coordinated R&D responses to emerging infectious disease outbreaks, and more effective and equitable collaboration among partners. Agreement on the terms of the Blueprint in advance would ensure that data of public health value on vaccines and other interventions could be generated more rapidly when outbreaks occur.

The Blueprint will encompass three areas: improving coordination, accelerating R&D, and developing new norms and standards. To facilitate product development, a list of priority pathogens has been established, alongside an R&D roadmap and target product profiles. Discussions are being held on appropriate and standardized clinical trial designs and harmonization of regulatory mechanisms.

Activities are guided by a Scientific Advisory Group, a Global Coordination Mechanism, and Monitoring and Evaluation structures.



The ongoing process includes discussion of the methodological tools used to evaluate vaccines, as well as the current level of preparedness of NRAs. The norms and standards strand is also developing guidance and practical tools to facilitate collaboration and data and sample sharing.

RITAG members emphasized the importance not just of the region being prepared to carry out clinical trials in outbreak situations but also of ensuring that African researchers are at the heart of such research. The Ebola experience also revealed significant issues related to specimen ownership and data sharing that need to be addressed. The important role of AVAREF in developing the capacity of NRAs, promoting consistency in clinical trial evaluation and licensure of vaccines and enhancing regulatory preparedness was also acknowledged.

Strategic Framework for Research on Immunization in the WHO African Region

Dr Joseph Okeibunor, WHO AFRO

Research is a powerful tool for achieving the objectives of the Regional Strategic Plan for Immunization. Yet research on immunization in the Africa Region does not always reflect regional and national priorities, often being driven by the interests of external sponsors. To address this issue, in 2013 the forerunner of RITAG proposed that a Strategic Framework for Research be developed to set the agenda for immunization research in the region.

Following an extensive consultation, a working group has developed a draft Strategic Framework, designed to enable countries to design and undertake high-quality immunization-related research relevant to their needs and to disseminate evidence to inform policy and practice. Ultimately, this should accelerate the development of vaccines and improve the delivery of immunization services.

The Strategic Framework covers all stages of the research process, including formulation of research questions, design and conduct of research studies, and dissemination of results. It identifies three priority research areas: epidemiology of disease and impact of vaccines; clinical trials; and implementation research and community participation. Once finalized, it will provide essential guidance on the development of needs-led immunization research in the region.

As well as identifying the need for RITAG to provide feedback for the finalization of the Strategic Framework and to advise on its dissemination, discussions also emphasized that African researchers should play a leading role in national programmes of immunization research. It was recognized that this would depend on the long-term development of research capacity in the region, including approaches to attract back and retain African researchers who are working outside the region.

While RITAG commended WHO AFRO for the progress made towards developing a Regional Strategic Framework for Research on Immunization, it recommended that further input should be solicited from additional stakeholders to reflect the broad spectrum of research needs in the region.

Conclusion

To conclude the meeting, Professor Rees presented a summary of the draft recommendations and thanked participants for contributing so full to discussions throughout the meeting. Her comments were reinforced by Dr Mihigo, who also identified the important contributions made by representatives of national immunization technical advisory groups. Closing the meeting, Dr Zawaira urged all participants to seize the moment and build on the momentum created by the Addis Declaration and the reinvigoration of the WHO Regional Office to drive forward the immunization agenda in Africa.

RITAG members

| | | |
|----|-----------------------|--------------|
| 1 | Helen Rees | RITAG Chair |
| 2 | Mohamed-Mahmoud Hacen | RITAG Member |
| 3 | Stephen Lwanga | RITAG Member |
| 4 | Daniel Tarantola | RITAG Member |
| 5 | Robert Linkins | RITAG Member |
| 6 | Bill Brieger | RITAG Member |
| 7 | Ekoe Tetanye | RITAG Member |
| 8 | Ephrem Tekle Lemango | RITAG Member |
| 9 | Rose Agatha Kambarami | RITAG Member |
| 10 | Haroon Saloojee | RITAG Member |
| 11 | Folake Olayinka | RITAG Member |
| 12 | Robin Biellik | RITAG Member |

Session 4: Malaria vaccine implementation programme (MVIP)

Executive summary

1. Background

In January 2016, WHO published its position paper for RTS,S/AS01, the first malaria vaccine, officially adopting the joint recommendation by SAGE and the Malaria Policy Advisory Committee (MPAC). WHO recommends pilot implementation of the RTS,S vaccine in distinct settings in sub-Saharan Africa in order to generate critical evidence to enable decision-making about potential wider scale use.

2. Purpose of session 4

The aim of this session is two-fold:

- 1) To provide a comprehensive update to SAGE on how the recommendation for pilot implementation has been taken forward by WHO since 2016. Following a brief recap of the considerations that have led to the recommendation for pilots, the malaria vaccine implementation programme (MVIP) will be presented and a status update of preparatory activities given.
- 2) To provide an update on the development of the policy decision framework for RTS,S/AS01 which was first presented to SAGE during the breakfast meeting in October 2017.

3. Malaria vaccine implementation programme – progress update

Following the WHO recommendation for pilot implementation in January 2016, a team at WHO, with support from PATH, developed a funding proposal which was submitted to prospective donors in view of securing the required resources for the MVIP. Funding commitments from Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Malaria and Tuberculosis and Unitaid were secured and donor agreements fully signed by the end of 2017.

Following a WHO call for expression of interest, three countries (Ghana, Kenya, Malawi) were selected to participate in the MVIP, introducing the RTS,S/AS01 malaria vaccine in pilot implementations.

The MVIP aims to support the introduction of the vaccine in selected areas of the three countries through routine immunization programmes and to evaluate the outstanding questions related to the public health use of the vaccine. The MVIP consists of three components:

- **Vaccine introduction:** National immunization programmes in Ghana, Kenya, and Malawi will lead the pilot introduction of the malaria vaccine in areas with moderate to high malaria transmission. The aim is to reach approximately 360 000 children per year in the selected areas.
- **Pilot evaluation:** A master protocol has been developed and will be implemented by country-based research partners to evaluate: (1) the programmatic feasibility of delivering RTS,S/AS01 with new immunization contacts, including the fourth dose in the second year of life; (2) the vaccine's impact on mortality and (3) the vaccine's safety in the context of routine immunization, with an emphasis on meningitis and cerebral malaria.

- **GSK Phase 4 study:** The GSK-sponsored observational Phase 4 studies form part of the RTS,S/AS01 Risk Management Plan agreed between GSK and EMA to further assess vaccine safety, effectiveness and impact in routine use. The WHO-led pilot evaluation has been designed to complement the GSK Phase 4 study that will take place in a small sub-set of the pilot areas.

The MVIP will be implemented over approximately 6 years from 2017 to 2022. Preparatory work for regulatory approval, vaccine introduction and pilot evaluation has started in all countries. RTS,S/AS01 introduction is anticipated in 2018 in the first country, upon confirmation of readiness of all relevant components.

4. Framework for policy decision

SAGE welcomed the idea of developing a framework for policy decision for RTS,S/AS01. The framework will aim to clarify how data collected through the MVIP might be used to inform future policy. Criteria will be established that would likely lead to a favorable or an unfavorable recommendation for vaccine use. Discussion and deliberation on the framework by SAGE and MPAC will provide an opportunity to clarify the relative contribution of the collected data (e.g. feasibility as measured by vaccine coverage, impact on severe malaria, impact on mortality, safety) in light of potential changes in SAGE/MPAC membership between the time the recommendation for pilots was made (2015) and the programme end (2022). Examples of the type of questions that will be presented as part of the framework include :

- What constitutes ‘favorable implementation data’? In particular, what levels of coverage (especially of the fourth dose) achieved in a routine setting would be considered good public health value?
- If impact on severe disease is demonstrated despite only moderate vaccine coverage levels, would WHO recommend vaccine implementation?
- Is demonstration of impact on mortality through the MVIP required for a policy recommendation or would evidence of impact on severe disease and modelled impact on survival suffice?

To help with question 1 above, two modelling groups (Swiss TPH and Imperial College) have been engaged to assist in estimating the impact on severe malaria and mortality of different vaccine coverage levels that might be achieved in the MVIP. Feedback from IVIR-AC was sought in March 2018 to ensure that the methods and assumptions of the modeling work proposed for the framework for policy decision are appropriate.

SAGE will be presented with a status update on this work and asked for feedback on the proposed inputs and output measures for modelling.

Malaria vaccine implementation programme (MVIP)

Progress update

1. Background

In 2016, the World Health Organization (WHO) estimated that 216 million cases of malaria occurred worldwide (95% confidence interval [CI]: 196–263 million) leading to an estimated 445 000 deaths.¹ Children under the age of five in sub-Saharan Africa are especially vulnerable, accounting for approximately two thirds of all global deaths due to malaria. *Plasmodium falciparum* is the most prevalent malaria parasite in sub-Saharan Africa, accounting for 99% of estimated malaria cases in 2016.

African countries have made tremendous progress in the fight against malaria using core disease-prevention tools such as insecticide-treated mosquito nets, indoor spraying with insecticides and prompt diagnosis and treatment with antimalarial medicines. However, the rate of decline in malaria case incidence and mortality has stalled and even reversed in some regions. All current malaria control tools are only partially effective, and all are based on insecticides or drugs, which are increasingly threatened by resistance. In some areas, available tools are unable to drive down malaria further. New and complementary tools are needed to further drive down the disease burden with a view to achieving — ultimately — the vision of a world free of malaria.

2. The malaria vaccine RTS,S/AS01

The Phase 3 trial of RTS,S/AS01 was conducted over 5 years (2009–2014) in 7 sub-Saharan African countries: Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and the United Republic of Tanzania. The trial enrolled approximately 15 500 infants and young children in two target age groups:

- Older children received their first dose of the malaria vaccine between 5 and 17 months of age.
- Infants received the vaccine together with other routine childhood vaccines at 6, 10 and 14 weeks of age

Efficacy: Among children aged 5–17 months who received three doses of RTS,S administered at 1-month intervals, followed by a fourth dose 18 months later, the vaccine reduced malaria episodes by 39% (95% CI, 34-43), equivalent to preventing nearly 4 in 10 malaria cases.² In addition, the 4-dose vaccine schedule reduced severe malaria by 32% (95% CI 9 -48) in this age group, with reductions also confirmed in malaria hospitalizations (37%, 95% CI, 24-49), all-cause hospitalization (15%, 95% CI 4-25) and severe anaemia (62%, 95% CI 27 -81). In addition, blood transfusions were reduced by 29% (95% CI 4 - 47) in children randomized to receive four doses of RTS,S compared with those who received none.

¹ World Malaria Report 2017, World Health Organization, Geneva, 2017

² RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *Lancet*. 2015;386(9988):31–45.

Among children aged 5–17 months who did not receive a fourth dose of the vaccine, the protective benefit against severe malaria was lost, highlighting the importance of the fourth dose of this vaccine to maximise its benefits.

Impact: The impact of RTS,S/AS01 vaccination has been assessed by an estimation of cases averted in the Phase 3 clinical trial,² and by use of mathematical models to predict the impact of RTS,S/AS01 when administered through the routine EPI programme.³ The estimated number of cases averted by RTS,S/AS01 in the trial was the sum of differences in the number of cases between the control and the RTS,S/AS01 groups, expressed per 1000 participants vaccinated. Among participants in the 5–17 month age category who received a 3-dose schedule or a 4-dose schedule, the estimated numbers of cases of clinical malaria averted by study end (M2.5-SE) were 1363 (95% CI, 995–1797) and 1774 (95% CI, 1387–2186) per 1000 vaccinees, respectively. The largest numbers of cases averted per 1000 vaccinees were at sites with the greatest disease burden, reaching more than 6500 cases averted per 1000 children vaccinated with 4 doses.

A comparison of 4 mathematical models of the potential impact of RTS,S/AS01 was carried out.³ The models assumed that vaccine implementation was added to existing levels of malaria control interventions and treatment. With an assumed coverage of 90% for the first 3 doses, with 80% of these individuals receiving the fourth dose (72% coverage overall), all models predict a substantial additional public health impact of RTS,S/AS01 in settings with PfPR_{2–10} between 10% and 65%.⁴ In these settings, median modelled estimates range from 200 to 700 deaths averted per 100 000 children vaccinated with a 4 dose schedule, and 10% to 28% of all malaria deaths averted in vaccinated children aged <5 years. Public health impact and cost-effectiveness tended to be greater at higher levels of transmission.

Safety: No fatal adverse events were assessed as causally related to RTS,S/AS01 vaccination. In the 5–17 month age category, from the first dose to the trial end, serious adverse events (SAEs) were slightly less frequent in the RTS,S/AS01 groups than in the control group. In this age group, febrile convulsions were an identified risk in RTS,S/AS01 recipients in the 7 days following vaccination. In the same age group, meningitis was identified as a potential risk, with more cases of meningitis in RTS,S/AS01 recipients, compared to the control group (relative risk (RR) 8.0 (95% Confidence Interval (CI) 1.1–60.3)). Unplanned, exploratory analyses in children in the 5–17 month age category revealed more cerebral malaria cases in the RTS,S/AS01 group and, for both age categories, more deaths in vaccinated girls compared to the control group. A relationship between the RTS,S vaccine and these findings has not been established. The pilot evaluations and a Phase IV study (further explained below) have been designed to provide further information.

3. WHO position

In January 2016, WHO published its position paper for RTS,S/AS01, adopting the joint recommendation by the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC).⁵ WHO recommends pilot implementation of the RTS,S/AS01 vaccine in 3–5 distinct epidemiological settings in sub-Saharan Africa, at subnational

³ Penny MA, et al. Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. *Lancet* ([http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(15\)00725-4.pdf](http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(15)00725-4.pdf), accessed January 2016).

⁴ Prevalence of infection as measured by cross-sectional surveys in those aged 2–10 years. Prevalence of infection in children is a commonly used measure of malaria parasite transmission.

⁵ Weekly Epidemiological Record No4, 2016, 91, 33–52, Malaria vaccine: WHO Position paper.

level, covering moderate-to-high transmission settings, in order to generate critical evidence to enable decision-making about potential wider scale use.

These pilot implementations should be done with phased designs and in the context of ongoing high coverage of other proven malaria control measures. A highly critical issue is the extent to which the protection demonstrated in children aged 5–17 months in the Phase 3 trial can be replicated in the context of routine health systems, particularly in view of the need for a 4-dose schedule that requires new immunization contacts. Other questions that should be addressed as part of pilot implementations include the extent to which RTS,S/AS01 vaccination impacts all-cause mortality (including gender-specific mortality), which could not be adequately assessed in the Phase 3 trial owing to the very low overall mortality in the trial; and whether the excess cases of meningitis and cerebral malaria identified during the Phase 3 trial are causally related to RTS,S/AS01 vaccination.

Based on the efficacy data from the Phase 3 trial, WHO does not recommend the use of the RTS,S vaccine in the younger (6–12 weeks) age category, as the vaccine efficacy was found to be low in this age category.

4. Regulatory review of RTS,S/AS01

The European Medicines Agency (EMA), under a process known as Article 58, has reviewed data on the quality, safety and efficacy of RTS,S/AS01 and issued a positive scientific opinion in July 2015. The positive opinion means that the quality of the vaccine and its risk/benefit profile is favourable from a regulatory perspective. In its assessment, the EMA applies the same rigorous standards as for medicines to be marketed within the EU. The EMA's assessment is being updated as new data become available and has remained valid since the original issuance.

As a prerequisite for vaccine implementation in pilot countries, RTS,S/AS01 must be authorized for use by the respective National Regulatory Authorities (see status update in subsequent sections).

5. Malaria Vaccine Implementation Programme

The Malaria Vaccine Implementation Programme (MVIP) was established by WHO to coordinate and support the introduction of the vaccine in selected areas of Africa through country-led routine immunization programmes and to evaluate the outstanding questions related to the public health use of the vaccine. The MVIP consists of three components:

- **Vaccine introduction:** National immunization programmes in Ghana, Kenya, and Malawi will lead the pilot introduction of the malaria vaccine in areas with moderate to high malaria transmission. The aim is to reach approximately 360 000 children per year in the selected areas.
- **Pilot evaluation:** A master protocol has been developed and will be implemented by country-based research partners to evaluate: (1) the programmatic feasibility of delivering RTS,S/AS01 with new immunization contacts, including the fourth dose in the second year of life; (2) the vaccine's impact on mortality and (3) the vaccine's safety in the context of routine immunization, with an emphasis on meningitis and cerebral malaria.
- **GSK Phase 4 study:** The GSK-sponsored observational Phase 4 studies form part of the RTS,S/AS01 Risk Management Plan agreed between GSK and EMA to further assess vaccine safety, effectiveness and impact in routine use. The WHO-led pilot evaluation has been designed to complement the GSK Phase 4 study.

Evidence and experience from the MVIP will be provided to SAGE and MPAC to inform recommendations on the vaccine's potential use on a wider scale in Africa.

5.1. Malaria vaccine implementation

The malaria vaccine introduction is country-led. RTS,S/AS01 will be implemented by the Ministry of Health through the national immunization programme in selected areas characterized by medium-to-high malaria transmission. Immunization authorities in the 3 pilot countries will specify the exact vaccination schedule, based on WHO recommendations. A 4-dose schedule is required, with the first dose given as soon as possible after 5 months of age followed by doses 2 and 3 at approximately monthly intervals and the fourth dose near the child's second birthday. RTS,S/AS01 can be co-administered with other vaccines in the national immunization programme.

Close collaboration with the national malaria control programme will ensure that existing WHO-recommended prevention tools, such as long-lasting insecticidal nets (LLINs) and artemisinin-based combination therapies (ACTs), continue to be deployed on a wide scale.

5.2. Pilot evaluation

While it is critical that the MVIP represents routine vaccine implementation through the national immunization programmes, the evaluation components must be conducted in a scientifically rigorous manner to generate answers to the remaining questions. For this reason, RTS,S/AS01 will be introduced in some areas at the beginning of the programme with other areas, initially without RTS,S/AS01 introduction, acting as comparison. The division into vaccine implementation or comparison areas will be randomized in order to generate the strongest possible evidence on the impact and safety of the vaccine. Identical monitoring systems will be established in both implementation and comparison areas to record impact and safety outcomes through observational and cross sectional studies. Surveillance systems will be established and cross-sectional surveys conducted at time periods to allow evaluation of key variables more than 1 year following the administration of the fourth vaccine dose in a sufficiently large number of children to meet sample size needs.

A master protocol for the pilot evaluations was developed by WHO and received approval by the WHO Research Ethics Review Committee in February 2018. Country-based research partners will be contracted to implement country-specific protocols. The subsequent sections provide further information about the three evaluation components.

5.2.1. Feasibility evaluation

The operational feasibility of providing RTS,S/AS01 at the recommended four-dose schedule will be evaluated in the context of routine health service delivery. The primary objective of the feasibility evaluation will be to estimate the coverage of RTS,S/AS01 in the implementation areas, defined as the proportion of children aged 12-23 months who had received 3 doses of RTS,S/AS01 by 12 months of age, and the proportion of children aged 27-38 months who had received their fourth dose of RTS,S/AS01 by 27 months of age. Secondary feasibility objectives will measure, in implementation and comparison areas, the coverage of recommended EPI vaccines; the coverage and utilization of ITN/LLIN and IRS; changes in malaria diagnosis and treatment practices; and the patterns of health-seeking behaviour for febrile children. In addition to ongoing monitoring of

facility-based administrative uptake and coverage data, three cross-sectional household surveys will be conducted in each pilot country over the course of the programme.

As for most new vaccine introductions, a New Vaccine Post-Introduction Evaluation (PIE) will be conducted approximately 6 to 12 months after introduction of RTS,S/AS01 to evaluate programmatic performance.

In addition, a qualitative study will explore a range of factors (socio-economic, cultural, demographic, systemic and health-related) that may impact on how the vaccine is delivered and received at district and local level. Using Qualitative Longitudinal (QL) methods, the study will run alongside and track the introduction of the vaccine, following health care professionals as they promote and deliver the new vaccine, and following households as they receive it. In particular, it will track a panel of households with eligible children over time, as the programme is introduced and established. In this way, the study will shed light on the factors that influence the sustained engagement of families in the vaccine programme, and what (if any) impact the introduction of the vaccine has on their health-related practices and understandings.

Finally, the Programme will collect economic data to estimate the incremental cost of adding RTS,S/AS01 to the routine schedule, its budgetary impact and to provide updated estimates of the vaccine's impact and cost-effectiveness.

5.2.2. Impact evaluation

The second evaluation component aims to estimate the impact of RTS,S/AS01 on all-cause mortality in children aged 5-39 months, malaria mortality, and rate of hospitalization with malaria (as an indicator of severe malaria) and the gender-specific effect of RTS,S/AS01 on all cause child mortality. Data will be captured at the community level through resident Village Reporters (VR) specially trained to document and report deaths in the target age group. Trained VR supervisors will conduct Verbal Autopsies, using WHO-recommended methods.

Malaria mortality and the rate of hospitalization with malaria will be captured at sentinel hospitals on all children in the relevant age group presenting to the hospital. The randomized vaccine introduction will enable a comparison of the rate of these events between the areas that have introduced RTS,S/AS01 and those which have not yet introduced the vaccine.

5.2.3. Safety evaluation

In addition to strengthened routine pharmacovigilance, safety data will be captured in up to 24 sentinel hospitals across the three pilot countries by means of systematic, prospective, monitoring of all paediatric admissions, paying particular attention to meningitis and cerebral malaria.

Data collected in the pilot evaluations will be complemented by data collected by GSK in Phase IV post-approval studies. The observational Phase IV studies form part of the RTS,S/AS01 Risk Management Plan agreed between GSK and EMA and aim to monitor vaccine safety, effectiveness and impact in routine use. In addition to enhanced hospitalization surveillance, the Phase IV study will include active surveillance through home visits and continuous monitoring of outpatient visits and hospitalisations at health care facilities in a subset of implementing and comparison areas.

Safety data from routine pharmacovigilance, the pilot evaluations and the Phase IV studies will be reviewed regularly by a Data Safety and Monitoring Board (DSMB) to identify, assess causality and monitor any accumulating safety signals.

6. Country selection

WHO initiated the country selection process by issuing a call for expressions of interest addressed to Ministries of Health in Sub-Saharan Africa in December 2015. Of the ten countries that expressed interest, three were selected for the Programme based on pre-specified criteria. Key among these criteria was the desire to engage in the MVIP by national stakeholders – particularly the Ministry of Health – and well-functioning malaria and immunization programmes. Other criteria included: good coverage of recommended malaria control interventions and childhood vaccinations; moderate-to-high malaria transmission despite good implementation of WHO-recommended malaria interventions; a sufficient number of infants living in the malaria-transmission areas where the vaccine will be introduced; strong implementation research or evaluation experience in the country; and capacity to assess safety outcomes. Participation in the Phase 3 RTS,S/AS01 trial was an additional element considered during the country selection process.

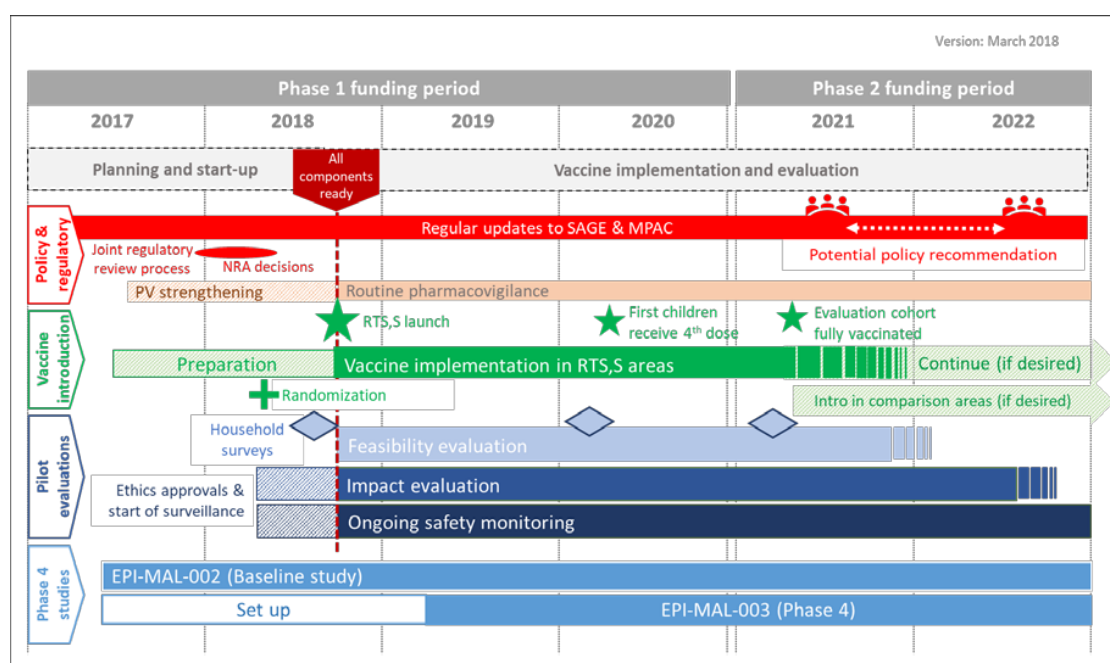
The selection of Ghana, Kenya and Malawi to participate in the MVIP was made public on 24 April 2017, just ahead of World Malaria Day and during African Vaccination Week.⁶

7. Programme timeline

The MVIP will be implemented over approximately 6 years from 2017 to 2022. RTS,S/AS01 introduction is anticipated in 2018 in the first country, upon confirmation of readiness of all relevant components (see Figure 1).

Data on programmatic feasibility, vaccine safety, and impact will accumulate over time. Regular updates will be provided to SAGE and MPAC to ultimately inform recommendations on the vaccine's potential use on a wider scale in Africa.

Figure 1. MVIP timeline



⁶ Pilot country announcement by WHO AFRO (April 2017) <http://www.afro.who.int/news/historic-launch-malaria-vaccine-pilots-africa>

8. Financial support

Financing for the MVIP up until 2020 has been mobilized through an unprecedented collaboration between three major global health funding bodies: Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaïd. WHO is providing additional in-kind contributions and PATH's activities are also supported by the Bill & Melinda Gates Foundation. GSK is contributing through the provision of vaccine doses free of charge for the MVIP and is covering the costs of the Phase IV studies.

9. Programme coordination and oversight

The Programme is jointly coordinated by the Global Malaria Programme (GMP), the Immunization, Vaccines & Biologicals (IVB) department and the WHO Regional Office for Africa, collaborating closely with other WHO departments and country offices, ministries of health in pilot countries and PATH. Relevant activities are coordinated with the vaccine manufacturer, GSK, based on a MVIP Collaboration Agreement signed between WHO, PATH and GSK in October 2017.

The malaria vaccine introduction is led by pilot countries' Ministry of Health through the national immunization programme, with technical support provided by WHO as appropriate.

A MVIP Programme Advisory Group (PAG) has been established to regularly review progress and to provide technical advice and recommendations to WHO on Programme-specific issues (see PAG membership in Annex 1).

To safeguard the well-being of children participating in the MVIP a Programme-specific Data Safety and Monitoring Board (DSMB) has been set up (see DSMB membership in Annex 2). The DSMB will regularly review relevant safety data from the pilot evaluation, the GSK-sponsored Phase IV studies and routine pharmacovigilance across the three countries and provide advice and recommendations to WHO.

Regular MVIP updates will continue to be provided to the Global Advisory Committee on Vaccine Safety (GACVS), the Regional Immunization Technical Advisory Group in Africa (RITAG), as well as SAGE and MPAC.

10. Current status of the malaria vaccine implementation programme

Following the WHO recommendation for pilot implementation in January 2016, a team at WHO with support from PATH has taken the lead in developing a funding proposal to prospective donors in view of securing the required resources for the MVIP. Funding commitments from Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Malaria and Tuberculosis and Unitaïd were secured by the end of 2016 and donor agreements fully signed by the end of 2017. Various preparatory activities have taken place since 2016 as further described in the following section.

10.1. Regulatory review by national authorities

The use of RTS,S/AS01 in the MVIP will require approval by national regulatory authorities (NRA) of the three pilot countries prior to vaccine introduction. A joint regulatory review by the three NRAs, convened under the African Vaccine Regulatory Forum (AVAREF), took place in February 2018. The joint review was based on the EMA assessment reports leading to the positive scientific opinion in accordance with Article 58. Timelines for the post-review steps leading to special authorization of the vaccine by national agencies have been agreed upon.

10.2. Preparation for vaccine introduction

In-country stakeholders in all three countries have provided recommendations on the most suitable sub-national areas for the pilot, based on a review of available data and guiding criteria set by WHO. The selection process is currently being finalized.

The national immunization programmes of the three countries have developed RTS,S/AS01 vaccine introduction plans and budgets. These plans specify how the four doses of RTS,S/AS01 will be included into the national immunization schedule and outline strategies and activities to ensure successful introduction, covering communication, social mobilization, health worker training, vaccine supply, cold chain and logistics, adaptation of monitoring tools, and strengthening of routine pharmacovigilance, amongst other topics. While similar planning approaches have been used as for other new vaccine introductions, particular attention was given to the inclusion of relevant stakeholders from the national malaria control programme. The plans are currently being finalized with technical support from WHO and PATH.

10.3. Supply planning

As part of the MVIP Collaboration Agreement, GSK has committed to supply sufficient quantities of the RTS,S/AS01 vaccine, free of charge to the Programme, to allow sound implementation of the MVIP, up to a maximum of 10 million doses. Operational planning with UNICEF as the delivery partner is ongoing.

10.4. Preparation for pilot evaluations

A master protocol for the malaria vaccine pilot evaluation was developed by the WHO MVIP team with inputs from external experts. The protocol received final approval from the WHO Research Ethics Review Committee (ERC) in February 2018. Adaptation into country-specific protocols by the local research partners is expected in the coming months.

On 18 May 2017, WHO released a Request for Proposals (RFP) to identify suitable research partners to conduct the evaluations. A lead bidder consortium of partners has been identified for each pilot country and contracts are currently being finalized.

10.5. Readiness for MVIP start

Various elements need to be in place before vaccine introduction and pilot evaluations can begin in each country. The WHO MVIP team is actively supporting the components within its remit (i.e. support for vaccine introduction; support for pilot evaluation set-up, etc.) while monitoring closely the aspects outside of its control and their impact on timelines, such as the special approval by national regulators for use of the vaccine, competing priorities for the national Immunization Programmes, etc. At present, the first vaccine introduction is expected to occur in 2018.

11. Framework for Policy Decision

In 2015, the Joint Technical Expert Group on Malaria Vaccines (JTEG) recommended that WHO should monitor emerging findings from pilot implementation, so that countrywide introduction may be recommended *“if concerns about safety have been resolved, and if favorable implementation data become available, including high coverage of the fourth dose”*. However, neither JTEG nor SAGE/MPAC did specify how the collected data would be used to inform a policy recommendation,

e.g. what coverage levels may be considered favorable and whether demonstration of impact on mortality is required for a policy recommendation.

The WHO MVIP team therefore proposed to develop a framework for policy decision on RTS,S/AS01 that describes how data collected through the MVIP would be used to inform policy. Both SAGE and MPAC were in favor of development of such a framework.

SAGE will be updated on the status of framework development during its meeting in April 2018 and a separate background document on this topic has been provided.

12. More information

Further information on the MVIP is available on the WHO web site:

<http://www.who.int/malaria/media/malaria-vaccine-implementation-qa/en/>

Annex 1: Malaria Vaccine Implementation Programme Advisory Group (PAG) membership

The role of the Programme Advisory Group is to provide technical advice and recommendations to WHO on issues concerning the Malaria Vaccine Implementation Programme.

Membership as of March 2018

Professor Nick Andrews, Public Health England, United Kingdom

Dr Dominique A. Caugant, WHO Collaborating Centre on Meningococci, National Institute of Public Health, Norway

Dr Corine Karema, Swiss Tropical and Public Health Institute and University of Basel, Switzerland

Dr Eusebio Macete, Manhica Health Research Centre (CISM), Mozambique

Professor Kim Mulholland, London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom and MCRI, Australia

Professor Francine Ntoumi, Fondation Congolaise pour la Recherche Médicale (FORM), Republic of the Congo

Ms Adelaide Eleanor Shearley, Maternal and Child Health Integrated Programme (MCHIP), Zimbabwe

Professor Peter Smith, London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom

Professor Frederick Were, University of Nairobi, Kenya

Annex 2: Malaria Vaccine Implementation Programme Data Safety and Monitoring Board (DSMB) membership

The role of the Data Safety and Monitoring Board (DSMB) is to safeguard the well-being of children participating in the Malaria Vaccine Implementation Programme and to provide advice and recommendations on issues concerning the safety of RTS,S/AS01 in the MVIP to WHO.

Membership as of March 2018

Dr Esperança Sevene, Eduardo Mondlane University, Mozambique

Prof. Alexander Doodoo, Ghana Standards Authority, Ghana

Dr Jane Achan, MRC Unit -The Gambia

Professor Charles Newton, KEMRI-Wellcome Trust Research Programme, Kenya

Professor Larry Moulton, The Johns Hopkins University, USA*

Professor Katherine O'Brien, Johns Hopkins Bloomberg School of Public Health, USA

Dr Cynthia Whitney, NCRID, U.S. Centers for Disease Control and Prevention (CDC), USA.

Framework for policy decision on the RTS,S/AS01 malaria vaccine

Rationale and process

1. Background

In January 2016, WHO published its first malaria vaccine position paper, officially adopting the joint recommendation by SAGE and the Malaria Policy Advisory Committee (MPAC). WHO recommends pilot implementation of the RTS,S/AS01 malaria vaccine in distinct settings in sub-Saharan Africa to generate the necessary evidence to enable consideration of a policy recommendation for broader scale use of the vaccine. The Malaria Vaccine Implementation Programme (MVIP) was designed to operationalize the recommendation for sub-national pilot implementation of the malaria vaccine in areas of moderate to high malaria transmission in Africa. Ghana, Kenya and Malawi will be piloting the malaria vaccine. Vaccine introduction will be led by the EPI Programmes in the three pilot countries and will be accompanied by an independent evaluation to address remaining questions to inform public health policy on wider use of the vaccine.

2. Rationale for developing a policy decision framework

In 2015, the Joint Technical Expert Group on Malaria Vaccines (JTEG) recommended to WHO advisory bodies the pilot implementation of the RTS,S/AS01 vaccine to:

- Assess the programmatic feasibility of delivering a four-dose schedule requiring new immunization contacts;
- Evaluate the vaccine's impact on mortality (overall and by gender); and
- Further characterize vaccine safety in the context of a routine immunization programme, with an emphasis on meningitis and cerebral malaria.

The JTEG advised WHO to monitor emerging findings from pilot implementation, and that countrywide introduction may be recommended *"if concerns about safety have been resolved, and if favorable implementation data become available, including high coverage of the fourth dose"*. However, neither JTEG nor SAGE/MPAC specified how the collected data would be used to inform a policy recommendation, e.g. what coverage levels may be considered favorable and whether demonstration of impact on mortality is required for a policy recommendation.

The WHO MVIP team has proposed to develop a framework for policy decision on RTS,S/AS01 that describes how data collected through the MVIP will be used to inform policy. Through the development of the framework:

- SAGE and MPAC members will have an opportunity to discuss and refine ideas on the relative contribution of the collected data (feasibility, safety, impact) to a future policy recommendation
- Clarity will be provided on the expected use of the data in anticipation of potential changes in SAGE/MPAC membership between the time the recommendation for pilots was made (2015) and the programme end (2022)
- Funders, potential funders, and manufacturers can refer to the framework for planning purposes, thereby reducing the risk of gaps in funding or vaccine availability should the vaccine be recommended for broader use

SAGE and MPAC welcomed the development of such a framework when the idea was presented during meetings in October 2017.

3. Outline of key questions to be included in the framework

Examples of the type of questions that will be considered through the framework include :

1. What constitutes ‘favorable implementation data’? In particular, what levels of coverage (overall and for the fourth dose) are sufficiently high to be considered good public health value?
2. Should WHO recommend wider introduction if impact on severe malaria is demonstrated despite only moderate vaccine coverage levels?
3. Is demonstration of impact on mortality through the MVIP required for a positive policy recommendation or would evidence of impact on severe disease suffice?

Supporting information to facilitate discussion of these questions, including estimated timelines for when critical data (on feasibility, safety signals, impact on severe disease, impact on mortality) become available, will be developed over the coming months.

4. Consultations

Published modelling efforts, based on data from the Phase 3 trial, estimated high vaccine impact and cost effectiveness (assuming a vaccine price of US\$5 per dose), at an assumed coverage of 90% for the first 3 doses and 72% for the 4th dose ¹. To inform the framework for policy decision, WHO would like to understand whether alternative and potentially lower vaccine coverage is likely to result in impact and cost effectiveness. To assist with this question, WHO, in collaboration with PATH, has engaged two modelling groups (Swiss TPH and Imperial College) to provide estimates of impact on severe malaria and mortality at a range of vaccine coverage levels that could be achieved in the MVIP. The modelling groups will similarly estimate vaccine impact at a range of parasite prevalences that are observed across sub-Saharan Africa.

Both modelling groups participated in the WHO harmonization and comparison project evaluating RTS,S/AS01 vaccine impact and cost-effectiveness estimates using the Phase 3 trial data, mentioned above, the results of which were published in Penny *et al*.¹ The process was overseen by the WHO JTEG/IVIR-AC sub-group over a period of four years from 2011-2015.

The IVIR-AC was consulted again in March 2018 to review the methods and assumptions of the modelling work proposed for the framework for policy decision, and to consider whether those methods are appropriate to address the relevant questions on the RTS,S/AS01 vaccine. The recommendations from IVIR-AC were incorporated into modelling plans, which were presented to the MVIP Programme Advisory Group in March 2018. IVIR-AC will be consulted again in September to review the results from the modelling effort. Subsequently, the framework for policy decision will be presented to the Programme Advisory Group, then to SAGE and MPAC in the October 2018 meetings.

¹ Penny MA, Verity R, Bever CA, Sauboin C, Galaktionova K, Flasche S, White MT, Wenger EA, Van de Velde N, Pemberton-Ross P, et al: **Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models.** *Lancet* 2016, **387**:367-375.

5. Modelling plans

To facilitate discussion about vaccine coverage thresholds, Swiss TPH and Imperial College will produce vaccine impact estimates for a range of vaccine coverage levels and propose a list of outcomes and outcome metrics that can be generated by their models. Modelled vaccine impact outcomes may include but are not limited to: severe malaria; hospitalized severe malaria; malaria deaths; and the incremental cost-effectiveness ratio (cost per DALY averted). The proposed list of outcomes and outcome metrics (e.g. events averted per 100,000 vaccinated children, events averted per vaccine dose, events averted per 100,000 population (all ages or 0-5 year olds) were presented to the IVIR-AC for review in March 2018.

6. Timelines for development and review of the framework

| Timeline | Activity |
|------------------------|---|
| October 2017 | Proposal to develop a policy decision framework presented to SAGE and MPAC |
| March 2018 | Feedback on the proposed modelling work received from IVIR-AC |
| March / April 2018 | Update on framework development and feedback on proposed modelling work from MVIP Programme Advisory Group, SAGE and MPAC |
| April – September 2018 | MVIP team to further develop key questions to be addressed in the framework, including timelines for when critical data (on feasibility, safety signals, impact on severe disease, impact on mortality) become available. Modelling groups to generate impact estimates for various coverage levels for inclusion in the framework |
| September 2018 | Presentation of modelling estimates to IVIR-AC |
| October 2018 | Presentation of proposed final framework for policy decision to MVIP Programme Advisory Group, SAGE and MPAC |

Overview of the Global Polio Eradication Initiative

The polio eradication program in 2017/2018 has succeeded to further decrease the number of detected poliomyelitis cases: in 2017, 22 cases of poliomyelitis caused by Wild Poliovirus Type 1 (WPV1) were reported worldwide (14 in Afghanistan, 8 in Pakistan), compared to 37 in 2016 (13 in Afghanistan, 20 in Pakistan, 4 in Nigeria). And in 2018, as of 12 March, 3 WPV1 cases were reported from Afghanistan and none from Pakistan. Despite the decrease in detection of symptomatic cases, WPV1 continues to be consistently detected through environmental surveillance (ES) in Afghanistan and Pakistan indicating ongoing transmission. Specifically in Pakistan, the rate of WPV1 detection through ES increased from 12% to 16% during 2017/2018, with genetic divergence between isolates indicating multiple chains of transmission. It should be noted, however, that during this period the frequency of sample collection and the total number of collected samples have increased. Regarding type 2 circulating vaccine derived polioviruses (cVDPV2), 95 paralytic cases were reported in 2017 (74 in Syria, 21 in DRC). Nigeria has not reported any WPV or cVDPV2 cases since September and August 2016, respectively. Since the switch from tOPV to bOPV in May 2016, cVDPV2 outbreaks have been detected in 5 countries (Nigeria, Pakistan, DRC, Syria and Somalia). The Global Polio Eradication Initiative (GPEI) considers that in 2018 there is a unique epidemiological chance to interrupt WPV1 transmission in the endemic areas; and thereafter the program will move towards transition of the GPEI anticipating certification of WPV eradication in 2021.

Post-Certification Strategy

Post-Certification Strategy Document (PCS) is presented to SAGE for review/endorsement with the intention to submit PCS for the World Health Assembly review in May 2018 [PCS is included as background document]. PCS is a high level working document which aims to sensitize and guide member states and key stakeholders on the polio-essential functions required to sustain a polio-free world after global certification of WPV eradication and subsequent dissolution of GPEI. PCS will not provide specific or detailed country level guidance and the implementation elements (including governance, management and financial costs) are not included in the PCS as these will be developed, owned and updated by the stakeholders who will take over the responsibility for implementation of the essential functions post certification. The aim of the PCS is to serve as a roadmap to ensure that the oversight, infrastructure and funding is in place to 1) contain polioviruses, 2) protect populations from polio, and 3) retain capacity to detect and respond to any poliovirus event, in the post certification era. Engaging key stakeholders occurred in 2017, during two rounds of extensive consultations which were undertaken, incorporating input from key polio partners groups, major donors, GCC, SAGE, disease modelling groups, GAVI, smallpox focal point, and global groups including IHR, GVAP, non-polio donors, core NGO focal points and member states and other immunization stakeholders. The PCS was endorsed by the Polio Oversight Board in January 2018; and by the SAGE Working Group in February 2018.

Report from SAGE Polio Working Group

The 15th face-to-face meeting of the SAGE Polio Working Group (WG) was held on 20-21 February, 2018 at the World Health Organization HQ in Geneva. The WG discussed or reviewed:

- Harmonization of recommendations on post-eradication polio immunization schedule between SAGE and GAP III;
 - SAGE WG endorsed the proposal to harmonize the IPV schedule for countries hosting Poliovirus Essential Facilities (PEFs), and recommended the same schedule, coverage targets and geographical scope for vaccination target for PEFs storing or manipulating Sabin/OPV or WPV. The WG recommended a routine schedule of 2 IPV doses (full or fractional) with the 1st dose administered at 4 months and the 2nd dose at an interval of at least 4 months after the 1st dose, and recommended achieving and maintaining high population immunity of $\geq 90\%$ IPV2 coverage in infants in the area surrounding the PEF defined as within a 100km commutable distance from the PEF
- Reviewed and provided recommendation on VDPV outbreak response protocol (at this meeting the SAGE is asked to provide recommendations on this protocol [included as background document]);
 - SAGE WG provided specific recommendations on scope, and timeliness of outbreak response
- Reviewed and provided recommendation/endorsement on proposed Polio Post-Certification Strategy (PCS);
 - The WG endorsed the content and approach of the PCS document as a high level working document which aims to alert member states and other key stakeholders to the essential functions required to sustain a polio free world after certification of eradication
- Initiated development of recommendations on preconditions for certification of poliovirus eradication and clarify, in this context, how vaccine derived polioviruses will be treated.
 - SAGE WG noted the proposed changes to the criteria for certification of WPV eradication and requested the Global Certification Commission (GCC) to maintain communication with other advisory bodies (such as IMB, IHR, CAG, etc.)

20-21 February | 2018

15th Meeting of the SAGE Polio Working Group

Conclusions and recommendations

Note for the Record



Background

The 15th face-to-face meeting of the SAGE Polio Working Group (WG) was held on 20-21 February, 2018 at the World Health Organization HQ in Geneva, Switzerland.

Agenda and the List of Participants are attached as Annexes 1 and 2.

Dr. Ilesh Jani and Dr. Peter Figueroa co-chaired the meeting.

This note presents a summary of the discussions and recommendations.

Context and topics

1. To harmonize recommendations between SAGE and GAP III on post-eradication polio immunization schedule
2. To review and provide recommendation on VDPV outbreak response protocol
3. To review and provide recommendation/endorsement on proposed Polio Post-Certification Strategy
4. To hear from GCC on revised requirements for certification of poliovirus eradication and clarify, in this context, how vaccine derived polioviruses will be treated

Minutes of the meeting and SAGE WG recommendations

Programme update

The WG reviewed the global epidemiology of WPV (wild poliovirus) and circulating vaccine derived poliovirus type 2 (cVDPV2).

In 2017, 22 WPV1 cases were reported worldwide (14 in Afghanistan, 8 in Pakistan), compared to 37 in 2016 (13 in Afghanistan, 20 in Pakistan, 4 in Nigeria). As of 28 February 2018, 3 WPV1 cases were reported from Afghanistan, an increase from 1 case for the same time period in the previous year. Regarding cVDPV, 95 cases of cVDPV2 were reported in 2017 (74 in Syria, 21 in DRC). Nigeria has not reported any WPV or cVDPV cases since September and August 2016, respectively.

WPV1 continues to be consistently detected through environmental surveillance (ES) in Afghanistan and Pakistan indicating ongoing transmission. Specifically in Pakistan, despite the decrease in number of WPV1 cases from 2016 to 2017, the rate of WPV1 detection through ES increased from 12% to 16% during this period, with genetic divergence demonstrated between isolates indicating multiple chains of transmission. It should be noted that during this period sensitivity of ES in Pakistan has improved with an increase of 23% in number of sites (43 to 53) and 21% in number of samples taken (543 to 659).

VDPV2 outbreaks were detected in 5 countries since the switch (Nigeria, Pakistan, DRC, Syria and Somalia). It was clarified that all VDPV2 events/outbreaks except for an outbreak in the Maniema province of DRC were caused by VDPV2 viruses that originated prior to the switch from trivalent OPV (tOPV) to bivalent OPV (bOPV) in May 2016. The Maniema outbreak appears to be related to an unauthorized use of tOPV after the switch because in

Maniema the nucleotide difference of the cVDPVs from Sabin PV2 was between 7-9 nucleotide changes suggesting <1 year of circulation when detected.

The GPEI provided in-depth review of the progress towards poliovirus detection and interruption in the endemic countries Afghanistan/Pakistan which are considered as one epidemiological block, and outbreak countries Syria, DRC, Nigeria and Lake Chad, and Somalia. The WG was updated regarding ongoing challenges to achieving interruption in transmission, specifically:

- Lack of access due to violence particularly in Pakistan (where healthcare workers and security forces protecting them are deliberately targeted) and conflict in Afghanistan (where insecurity has resulted in chronic inaccessibility of children, including an estimated 23,000 children in Kunar and Nangarhar provinces. Conflict has also resulted in high-risk mobile populations in Afghanistan (including 2 million returning Afghan refugees from Pakistan in 2018), and continues to affect Borno state in Nigeria (where an estimated 160,000 children remain unreachable) and Syria.
- Changing political climate, particularly the upcoming elections in Pakistan could disrupt programmatic activities
- Lack of political commitment, including the ban imposed by the Government in Niger on immunization activities in Lake Chad Basin islands; and the declining political and financial commitment evident in Nigeria
- Low universal healthcare and routine immunization (RI) coverage, including pockets in northern Nigeria where reported RI coverage is as low as 3%
- Significant surveillance gaps, particularly in conflict affected areas in Nigeria and neighbouring Lake Chad Basin countries

WG decisions/recommendations

- The WG acknowledged the ongoing efforts of the GPEI and the progress achieved in WPV eradication. However, concerns were raised regarding challenges to interrupting transmission in 2018, particularly lack of access, supervision and monitoring and surveillance activities in conflict affected areas. In this regard the WG urged the GPEI to work closely with local actors with specific expertise in implementing innovative programmatic operations in conflict areas, including community based organizations, networks with female workers and female leaders, and local NGOs in order to attempt reaching inaccessible children in conflict areas
- The WG expressed concern over continuing WPV transmission in Pakistan and Afghanistan through the active corridors of transmission, as manifested through the continued detection of genetically divergent WPV1 detected in environmental samples in Pakistan and detection of orphan viruses in east Afghanistan. The WG recommended that the GPEI intensify vaccination activities to reach populations with low immunity to rapidly raise population immunity as a priority, and sustain this high level of population immunity which is the only way to interrupt the circulation of WPV in its last endemic zones
- The WG emphasized the importance of achieving high quality AFP surveillance in high-risk areas, including implementing innovative targeted strategies such as testing stool in healthy children leaving conflict areas (as was undertaken in Nigeria for approximately 300 children). The WG urged the GPEI to prioritize expanding environmental surveillance in high risk areas particularly in AFRO and EMRO, and

highlighted the importance of maintaining high quality AFP and environmental surveillance activities into the post-eradication era.

- The WG reaffirmed that the GPEI continue to monitor dynamic geopolitical situations and where possible ensure programmatic accountability
- The WG acknowledged the significant progress made in controlling the cVDPV2 outbreak in Syria and noted the ongoing discussions to determine whether additional subnational or national mOPV2 campaigns will be implemented in future. The WG noted that despite ongoing complexities significant improvement had been made particularly related to timeliness of specimen collection and transportation.
- The WG discussed the evident decrease in WPV1 cases in Pakistan despite consistent detection in environmental surveillance and the possibility of use of IPV to target high risk populations was raised.
- The WG highlighted the importance of reaching remaining pockets of under-immunized children particularly in mobile populations. Particular reference was made to a serosurvey undertaken in Pakistan which demonstrated improved poliovirus type 1 immunity in Killa Abdullah district (92%); despite the high overall immunity one possible explanation of WPV1 circulation is that pockets of immunity gaps (susceptibility) in the mobile population exist which help maintain WPV1 transmission.
- The WG suggested that the GPEI undertake and share in-depth analysis of AFP cases in endemic and outbreak countries, specifically the number of doses of vaccine received and of zero dose children.

Update on Poliovirus Containment

The WG was updated on progress in activities related to poliovirus containment. Currently 28 countries worldwide plan to host 91 Polio-Essential Facilities (PEFs); these countries account for 54% of the global birth cohort. The containment oversight structure and functions of key groups, containment reference documents and the process of certification of eradication and containment certification were presented. It was highlighted that:

- The Technical Report Series (TRS) 926 will be aligned with GAP III and endorsed by the Expert Committee on Biologic Standardization (ECBS) in October 2018
- GAP III was endorsed by the WHA in 2015, and that GAP III Containment Certification Scheme (CCS) supersedes Annex 4 of GAP III, which was endorsed by SAGE in 2016
- All PEFs will be certified through their National Authority for Containment (NAC) in consultation with the Global Commission for Certification (GCC) (through the process of obtaining Certificate of Participation (CP), Intermediate Certificate of Containment (ICC), and Certificate of Containment (CC)

Immunization Requirements for Countries with PEFs

At the request of the Containment Advisory Group (CAG), the WG reviewed the secondary safeguards in countries hosting PEFs, in order to align GAP III and SAGE recommendations on IPV schedule, vaccine coverage and geographical scope of vaccine coverage targets. The importance of reaching a consensus on this topic was emphasized as it was highlighted that countries hosting PEFs may be reluctant to submit their CP application due to uncertainty

regarding obligations included by statutory requirements as outlined in GAP III for population immunity.

The SAGE WG reviewed the proposal to harmonize the post-certification IPV schedule recommendation for all previously OPV- only using countries (including for countries hosting a PEF). The harmonized schedule includes a minimum of two doses of IPV (full dose or fractional dose) with the first dose administered at age 4 months and the second dose at least 4 months later [1]. The schedule should be implemented as soon as is feasible and no later than when all OPV is withdrawn which is anticipated ~2022. It was emphasized that IPV in RI is a risk mitigation strategy to prevent paralytic polio, and not expected to induce intestinal immunity. The WG recognized the trade-offs in the proposed schedule whereby immunity will be induced at 9 or 10 months (e.g. with only two-doses of IPV administered at 4 and 8 or 9 months of age with measles vaccine) rather than at 7 months (with previously recommended GAP-III three-dose schedule at 2, 4 and 6 months of age). And also the slight decrease in seroconversion with fractional-dose IPV (94%, 98%, 93% to PV1, 2, 3 respectively), compared to full dose (100% for all PV types) [2].

The WG reviewed the coverage requirements and proposed to require the same vaccination coverage for PEFs storing or manipulating Sabin/OPV and/or wild poliovirus. The WG further suggested that countries hosting PEFs need to achieve and document high population immunity against polioviruses in the commuting area of a PEF (area to include districts within a 100km commuting distance, and >90% vaccination coverage in this area), and recognized this may require cross-border collaboration. The WG proposed that countries hosting PEFs develop an outbreak plan specifying response to a containment breach, including the opportunity to conduct regular simulation exercises. The WG recognized that these recommendations will result in substantial changes in the secondary safeguards contained in GAP-III [3], and that countries hosting PEFs may require an appropriate transition period for implementation.

Risk Ranking of PEFs

On request from the Containment Working Group the SAGE WG reviewed the current approach to ranking PEFs for the risk to poliovirus eradication, with poliovirus 2 retention as the basis for risk. Key factors incorporated in ranking the risk of PEFs included: 1) Virus type - WPV or VPDV had greater risk than Sabin or OPV; 2) Virus content and volume level - high content and volume poliovirus materials had greater risk than low content and low volume; 3) Population immunity using WUNEIC POL3 coverage at national level - lower population immunity had greater risk 4) Force of infection (R0) - lower access to sanitation facilities as estimated through WASH surveys had greater risk; and, under discussion 5) Containment safeguards in place.

Each PEF will be assigned a risk rank score [high Rank 1 (≥ 15), med>Rank 2 (>5 to <15), low Rank 3 (≤ 5)] with a higher rank score indicating higher risk to poliovirus eradication. The applicability of this risk ranking scheme will be to assist the programme in informing discussions of relative risk of one PEF compared to other PEFs. In addition, the risk rank will be incorporated into containment targets to be met by the time of certification of WPV

eradication. Lastly where necessary, the risk rank will be used to target country-specific advocacy efforts aimed at reducing the number of PEFs.

In addition, the SAGE WG was updated on development of a whole-cell pertussis Hexavalent vaccine containing IPV currently licensed for use in India. The available stock of this vaccine in the near future will be low for larger programmatic implementation and will likely be used predominantly in the private sector.

WG decision/recommendations

- The WG endorsed the proposal to harmonize the GAPIII and post-certification IPV schedules for countries hosting PEFs, and recommended the same schedule, coverage targets and geographical scope for vaccination target for PEFs storing or manipulating Sabin/OPV or WPV
- The WG recommended a routine schedule of 2 IPV doses (full or fractional dose) with the 1st dose administered at 4 months and the 2nd dose at an interval of at least 4 months after the 1st dose, and recommended achieving and maintaining high population immunity with at least $\geq 90\%$ IPV2 coverage in infants in the area surrounding the PEF defined as within a 100km commutable distance from the PEF
- The WG recommended that beyond the immediate zone of 100km, the GVAP childhood vaccination target should be achieved and maintained ($\geq 90\%$ national coverage and $\geq 80\%$ in every district or equivalent administrative unit with all vaccines in national programs, unless otherwise recommended)
- The WG endorsed the proposed change of the geographic scope of vaccination coverage target in the PEF area from nationwide to subnational level, or multi-national level for facilities near international borders
 - Recommended that vaccination coverage target be achieved in all districts within a minimum radius of 100km from the PEF, with acknowledgement this may require cross-border collaboration (particularly in Europe)
- The WG strongly urged that countries hosting PEFs have in place an outbreak plan specifying response to a containment breach and strongly urged simulation exercises be undertaken regularly (periodicity – annually) in the PEF hosting countries and their immediate neighbours
- The WG endorsed the risk ranking proposal proposed by the CWG to assign a risk score to each PEF, categorizing relative risk to polio eradication
- The WG understands that the decisions on implementation timeframes and alignment of these secondary safeguards in countries hosting PEFs with the application processes for CP, ICC, CC, will be decided by the containment oversight groups (i.e., GCC and CAG)
- The WG will review the status of hexavalent vaccine in 2018 which will be brought to SAGE WG discussions in September 2018, with affordable Hexavalent vaccine use anticipated in 2022-2025.

Polio Vaccine Supply Status

The WG reviewed the IPV supply situation presented by UNICEF Supply Division (SD). The WG was updated on the ongoing critical constraints in global IPV supply with availability for

the period 2014-2018 projected to be only 48% of contracted supply. In addition recent notification was received that 80% of IPV supply from one manufacturer will only be available in the 2nd half of 2018. Clarification was provided that of the reserve stock of 2M IPV doses set aside for outbreak response, only 1.1M doses will be available after factoring in planned SIAs administering IPV in Syria and Somalia. By April 2018, IPV will be available for the remaining 35 countries that are procuring the vaccine through UNICEF and that had been affected by the supply shortage (either they were not able to introduce the vaccine or they had to stop using it because of shortages). The UNICEF IPV tender for 2019-2022 has been concluded, with supply for catch up most likely to be available from 2020 onwards.

The WG reviewed the bOPV projections which based on supply offers received will be sufficient to meet demand through 2022. For 2018, additional awards were required to maintain a minimum buffer stock of +100M doses in April. Currently, no awards have been made for 2022 and additional awards will be made in April 2018 through to 2022 based on SIA plans for 2020 and beyond. The uncertainty of bOPV demand was highlighted which is due to the timing of interruption of WPV1 transmission. It was highlighted that an 18 month lead time will likely be required if there is a change in current plans which do not have pre-cessation campaigns, and therefore timely notification of additional bOPV SIAs prior to cessation will be imperative to secure sufficient supply.

WG decisions/recommendations

- The WG strongly recommended that countries receiving IPV should introduce it in a timely manner without delay
- The WG noted the efforts of UNICEF SD to manage the IPV supply, given the significant constraints
- The WG noted that the presented forecast may not take sufficiently into account IPV demands for outbreak response campaigns and from endemic countries for accelerating eradication
- In line with previous recommendations, the WG strongly endorsed the use of fIPV for catch up vaccinations of cohorts that had not received IPV because of supply shortages
- The WG discussed the role of IPV in outbreak response and agreed that its use should be determined on a case-by-case basis, and where IPV is deemed to be of benefit, fractional-dose IPV should be implemented
- The WG requested an update from PAHO countries. The WG noted the commitment of PAHO to introduce fractional-dose IPV, however due to supply constraints and limited availability of ID syringes in the context of large scale use in Brazil to fight a YF outbreak, intradermal IPV introduction may have to be delayed

Update from Cessation Risk Task Team (CRTT)

The WG reviewed the outcome of the CRTT meeting that was held in Geneva on February 1-2, 2018. As part of this update, epidemiological analysis of VDPV2 events and outbreaks since the switch from tOPV to bOPV was presented and compared with the modelling projections that had been carried out prior to the switch. There were 7 cVDPV2 outbreaks, 27 aVDPV events and 9 iVDPV cases reported in the 2 years following the switch. Although more outbreaks and events occurred in the first year post switch than was forecasted, the

WG noted that the forecast was made in advance of ES expansion and did not encompass post-switch VDPVs, particularly aVDPVs following mOPV2 use.

It was highlighted that all VDPV2 outbreaks have been in high risk areas with known low RI coverage and insufficient quality of pre-cessation tOPV use; furthermore only one outbreak had spread beyond the initial area of response (Haut Lomami to Tanganyika, DRC). The CRTT advised that the GPEI remain vigilant for new emergencies particularly in areas of poor surveillance performance, and that although the risk of emergence would decrease, the risk for spread would increase over time due to declining mucosal immunity.

The CRTT proposed consideration for nation-wide mOPV2 SIA in Syria, due to the risk of ongoing cVDPV2 circulation outweighing concerns over mOPV2 exposure. The role of the mOPV Advisory Group to undertake ongoing qualitative assessment for new emergencies on a case-by-case basis was supported by the CRTT. Lastly the CRTT presented analysis on the benefit of an IPV strategy for cVDPV outbreak control. The group did not change its position on regarding the role of IPV use in cVDPV2 outbreak response. mOPV2 should be the primary response tool. The scope and number of mOPV2 campaigns should be appropriate for the outbreak, and should not be influenced by IPV use. IPV may prevent paralysis and, among OPV2 recipients, boost mucosal immunity. There was no consensus on whether these benefits could justify IPV use. However, IPV is not effective for outbreak control when used outside of the mOPV2 response region or as a supplement to mOPV2 SIAs that are either low quality or of insufficient scope. The EOMG should not approve requests for IPV unless well-justified by epidemiologic or contextual need.

The CRTT supported a similar approach for bOPV cessation to the strategy implemented for the switch from tOPV to bOPV, with critical aspects being global synchronization, high population immunity prior to bOPV withdrawal, and intensification of surveillance to rapidly detect and respond to emerging VDPVs. The suggestion was made for SIAs to maintain high population immunity to types 1 and 3 (rather than intensification of SIAs prior to withdrawal).

The WG noted the conclusions from the CRTT meeting.

Update on cVDPV2 outbreaks and Outbreak Response Protocol Standard Operating Procedures (SOPs)

The WG was updated on the incidence of VDPV2 events and outbreaks as well as detection of Sabin-Like 2 post switch. The types of mOPV2 response were presented including the use of mOPV2 as a preventive measure (Lake Chad) versus response to an event (Mozambique) versus for outbreak response (DRC, Syria).

In the majority of outbreaks, mOPV2 was received in-country within the recommended 7 days (the exception being Syria where complex logistical challenges were faced due to active conflict). In ~50% of outbreaks, the 1st SIA was implemented within the recommended timeframe of 14 days from outbreak confirmation (the exceptions being DRC, Syria, and Somalia). The WG noted that mop-up activities were carried out in DRC, with no subsequent breakthrough VDPV event to date. The use of IPV in outbreak response has been limited

with implementation in Quetta, Borno, Sokoto, Syria; (and approval for use in Somalia). The WG noted that so far there was no evidence to support the emergence of new cVPDV2 outbreaks following mOPV2 use although aVPDV2 have been detected in ES after mOPV2 SIA.

Guidance was requested from the WG on future revisions to the Outbreak Response Protocol Standard Operating Procedures (SoPs); the revisions will be incorporated in the next version of the SoPs.

WG decisions/recommendations

- The WG suggested outlining the definition for high SIA quality/coverage in the protocol or annexes
- The WG recommended implementation of a high quality timely outbreak response within 14 days of notification. The geographic scope may be of smaller scale encompassing the epicenter of the outbreak zone; this immediate response will be in addition to, and followed by the timely implementation of high quality SIAs as recommended in the current outbreak response protocol (round 1 within 28 days; round 2 within 6 weeks; mop-up in poorly performing areas within 3 months after date of notification)
- The WG recommended the inclusion of the concept of “*sentinel event*” as part of the broader risk assessment for any event or outbreak:
 - A “sentinel event” may be any event in an outbreak or contiguous area, suggesting the presence of lower population immunity or increased polio risk for related or unrelated reasons. Examples include: 1. Appearance of vaccine-preventable disease cases or outbreak (e.g. measles, diphtheria, VDPV of any vaccine type) which suggests low routine immunization performance 2. Ongoing or rapid movement of under immunized populations 3. Detection of Sabin-like (SL) virus in the absence of related OPV use (eg. SL 2 in absence of mOPV2 use).
 - The WG strongly recommended that every sentinel event should be investigated and assessed, and included in the risk assessment of any emergent event or outbreak, with consideration for implementation of a timely high quality polio immunization response (strengthening of routine immunization or campaign, where relevant and appropriate)
- The WG supported the information gathering exercise undertaken in AFRO to assess country feasibility for implementation of fractional-dose IPV and anticipated the sharing of this information

New OPV (nOPV2) update

The WG was updated on development of novel live OPV vaccine (nOPV) which would retain its mucosal immunogenicity but would not be able to revert to neurovirulent form. Two nOPV2 candidate strains are in Phase I human clinical study, and nOPV1 and nOPV3 candidate strains are in pre-clinical development. Preliminary results from the Phase I nOPV2 study were discussed including serology, viral shedding, assessment of phenotypic stability and genetic stability. The next steps and the clinical development timeline were outlined.

The WG reviewed the data and welcomed the progress in nOPV development.

Surveillance in security compromised areas

The importance of innovations, approaches and strategies to strengthen surveillance in security compromised areas was emphasized. It was highlighted that recent outbreaks occurred in security compromised areas of Nigeria, DRC, Syria, Somalia and Laos. The challenges in conducting surveillance in security compromised areas were presented including accuracy of data source, unknown population numerators and denominators.

The WG noted and welcomed the efforts made by the GPEI to maintain poliovirus surveillance in the security compromised areas.

Polio Post-Certification Strategy Document Review (PCS)

The WG reviewed the PCS and acknowledged its objective as a high level working document which aims to sensitize and guide member states and key stakeholders on the polio-essential functions required to sustain a polio-free world after global certification of WPV eradication and subsequent dissolution of GPEI. It was emphasized that as a high level document the PCS will not provide specific or detailed country level guidance. The aim of the PCS is to serve as a roadmap to ensure that the oversight, infrastructure and funding is in place to 1) contain polioviruses, 2) protect populations from polio, and 3) retain capacity to detect and respond to any poliovirus event, in the post certification era.

The importance of engaging future stakeholders to develop the governance, implementation and resource mobilization plans, in order to take ownership of the PCS and carry it forward from the time of certification of WPV eradication was emphasized. Engaging key stakeholders occurred in 2017, during two rounds of extensive consultations which were undertaken, incorporating input from polio partners groups, major donors, GCC; SAGE, disease modelling groups, GAVI, smallpox focal point, and global groups including IHR, GVAP, non-polio donors, core NGO focal points and member states and other immunization stakeholders. Thereafter the PCS was endorsed by the Polio Oversight Board in January 2018.

The assumptions for the timeline of the PCS were presented, as were the specific goals, activities and expectations relating to each goal of the PCS. It was highlighted that the implementation elements (including governance, management and financial costs) are not included in the PCS as these will be developed, owned and updated by the stakeholders who will take over the responsibility for implementation of the essential functions post certification.

Further consultation with SAGE is planned for April 2018. After incorporating feedback from all stakeholders it is proposed that the PCS be submitted to the World Health Assembly (WHA) in May 2018.

WG decisions/recommendations

- The WG agreed in principle on the content and approach of the PCS document as a high level working document which aims to alert member states and other key stakeholders to the essential functions required to sustain a polio free world after certification of eradication
- The WG suggested that the PCS include a foreword, with a statement from high level stakeholders (signed by heads of agencies); emphasizing that the PCS remains a dynamic document; with a timeframe given for specific comments to be submitted within 2 weeks
- The WG agreed to have the document shared with SAGE in April 2018 for endorsement with a view to bring the PCS to the WHA in May 2018

Poliovirus certification

The role and responsibilities charged to the Global Commission for the Certification (GCC) of Polio Eradication by the DG of WHO were presented. Since its establishment the GCC has defined global polio eradication as the eradication of all WPV and specified that cases caused by vaccine viruses do not invalidate the achievement of the eradication of WPV. However the GCC recognized the full benefits of polio eradication would only be realized in the absence of VDPVs and therefore GCC will be discussing at its next meeting a proposal to update the criteria for certification of Wild Poliovirus Eradication which will also include pre-conditions related to VDPVs. Specifically, these preconditions are proposed to include absence of persistent polio disease due to cVDPV defined as:

- Detection of cVDPV2 from any population source in the previous 18 months; or
- Detection of cVDPV1 or 3 from any population source in the previous six months

In addition to pre-conditions relating to VDPVs, requirements for poliovirus containment will have to be met and linkage to the PCS will need to be maintained. The GCC meeting in February 2018 will further discuss and endorse this approach.

The WG was briefed that, at the request of GCC, there will be a discussion on how to maintain full understanding of groups other than GCC on certification.

Overview of scientific data and programmatic experience with intradermal fractional IPV (fIPV)

At a request of SAGE WG, this additional agenda item was added in order to potentially strengthen the recommendation on use of fIPV in routine immunizations, catch-up campaigns and outbreak response.

Data comparing humoral and intestinal immunogenicity of full and fractional IPV were presented with a conclusion that two doses of fIPV are superior to one full IPV dose; and that no safety signals were detected in relation to fIPV use. Different intradermal (ID) administration methods were presented with the conclusion that successful ID injection can be achieved with BCG needle as syringe as well as with needle-free injectors or needle adaptors; the latter two methods being preferred by the vaccinators.

Routine immunization and/or campaign experience from Pakistan, India and Sri Lanka with fIPV was generally positive.

Past SAGE recommendations were presented and the WG noted that SAGE has recommended fIPV on several occasions.

WG decisions/recommendations

- The WG emphasized that in principle, and given the continuing IPV supply constraints, the WG does not endorse use of IPV for outbreak response. However in specific instances, such as co-circulation of VDPV2 and WPV1 or in area with past mOPV2 use, IPV may be beneficial for outbreak response through boosting response (humoral and mucosal immunity) in individuals who are OPV vaccinated. In these cases, the WG strongly recommends to only use fractional-dose IPV. In this context high quality training of health workers for standard ID injection (using BCG needle and syringe [NS]) will be a priority; ID injection delivery using needle-free device or needle adaptors, when the device is WHO prequalified and available will be preferred
- The WG recommended that those countries that were willing to use fIPV in RI should be encouraged to do so given the global shortage of IPV.

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3. Organization WH. WHO Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use. WHO Publication **2015**. DOI: http://polioeradication.org/wp-content/uploads/2016/12/GAPIII_2014.pdf



World Health Organization

15th Meeting of the SAGE Polio Working Group (WG)

M505, WHO, Geneva

February 20-21, 2018

AGENDA

Expected outcomes of the meeting:

1. To review and provide recommendation/endorsement on proposed Polio Post-Certification Strategy
2. To review and provide recommendation on VDPV outbreak response protocol
3. To initiate development of recommendations on criteria for certification of poliovirus eradication and clarify, in this context, how vaccine derived polioviruses will be treated
4. To harmonize recommendations between SAGE and GAP III on post-eradication polio immunization schedule

Day 1 (February 20)

| | | |
|---------------|--|---------------------------------------|
| 09:00 - 09:15 | Welcome and opening remarks | I. Jani & P. Figueroa WG co-Chairs |
| 09:15 - 10:20 | Programme update <ul style="list-style-type: none">• Progress toward interruption of WPV and cVDPV2• Progress with the other objectives of the Polio Eradication and Endgame strategic plan | M. Zaffran, WHO |
| 10:20 - 10:40 | Coffee break | |
| 10:40 - 11:50 | Update on poliovirus containment & harmonization of vaccination requirements | J. Fournier-Caruana, WHO |
| | Poliovirus-essential facility (PEF) risk-ranking | R. Sutter, WHO |
| | | J. Partridge, BMGF |
| 11:50 - 12:00 | IPV/OPV supply situation (Q&As on hand out) | I. Lewis, UNICEF |
| 12:00 - 13:00 | Lunch | |

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|----------------------|---|-----------------|
| 13:00 – 13:20 | Update from Cessation Risk Task Team (CRTT) | J. Modlin |
| 13:20 – 13:45 | Update on cVDPV2 outbreaks & revisions of VDPV outbreak protocol | R. Lewis, WHO |
| 13:45 – 14:45 | Discussion | All |
| 14:45 – 15:00 | Update on new OPV development (brief update) | J. Modlin, BMGF |
| 15:00 - 15:30 | Coffee Break | |
| 15:30 – 16:00 | Addressing the challenges of surveillance in security-compromised areas | A. Anand, CDC |
| 16:00 - 17:00 | Discussion | All |
| 19:00 - | Working dinner (Restaurant: Cafe du Soleil, Topic: Switch from bOPV to mOPV1: pros and cons) | |

Day 2 (February 21)

| | | |
|----------------------|---|--------------------------|
| 9:00 – 9:30 | Post-Certification Strategy | M. Zaffran, WHO |
| 9:30 - 10:20 | Poliovirus Certification – what we mean by it | D. Salisbury, Chair GCC |
| 10:20 - 10:40 | Coffee break | |
| 10:40 -12:30 | Discussion | |
| 12:30 - 13:30 | Lunch break | |
| 13:00 - 16:00 | Closed session: Finalizing WG recommendations (Continued; Coffee break at 2pm) | WG members WHO/UNICEF |
| | secretariat | |

Background materials that will be shared with WG members at least 2 weeks prior to the meeting:

- Latest draft of the Post-Certification Strategy
- Revised protocol on response to VDPVs

ANNEX 2: List of Participants

List of Participants
15th Meeting of the SAGE Polio Working Group
20-21 February 2018
WHO-HQ, Salle M505

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BACKGROUND PAPER ON DENGUE VACCINES

REVISION TO THE BACKGROUND PAPER
FROM 17 MARCH 2016

PREPARED BY THE SAGE WORKING GROUP ON DENGUE
VACCINES AND WHO SECRETARIAT

23 MARCH 2018

TABLE OF CONTENTS

| | |
|---|----|
| 1. Executive Summary | 3 |
| 2. Introduction and Rationale for the SAGE Recommendations in April 2016 | 8 |
| 3. Study design to retrospectively identify serostatus at baseline | 12 |
| 4. Efficacy against virologically-confirmed dengue stratified by serostatus | 13 |
| 5. Long-term safety results stratified by serostatus | 18 |
| 6. Non-dengue serious adverse events stratified by serostatus | 27 |
| 7. Immunogenicity by serostatus | 29 |
| 8. Population benefit versus individual risk | 32 |
| 9. Ethical considerations | 34 |
| 10. Programmatic considerations | 35 |
| 11. Planned post-approval evaluation by the manufacturer | 44 |
| 12. Summary of critical assessments | 47 |
| 13. Key recommendations | 55 |
| 14. Research priorities | 59 |
| 15. Acknowledgements | 60 |
| 16. References | 61 |

1. EXECUTIVE SUMMARY

Dengue is the most frequent mosquito-borne virus diseases, with 30-fold increase in annual reported cases over the past 50 years and continued geographic expansion. Infection with any of the four dengue viruses (serotypes 1-4) may result in clinical manifestations ranging from relatively mild febrile illness to severe dengue manifested by plasma leakage, haemorrhagic tendencies, organ failure, shock, and possibly death. Dengue occurs in epidemics of unpredictable timing and often requires hospitalization, thereby challenging fragile health care systems. Fatality rates are around 0.1% to 1% in hospitalized cases. Patients with a second dengue infection with a different dengue serotype to the first are at increased risk for severe dengue. Thus, dengue vaccines must be tetravalent, protecting against all 4 virus serotypes. This document only refers to the first licensed dengue vaccine CYD-TDV.

CYD-TDV (Dengvaxia®) was licensed in December 2015 and as of writing has now been approved by regulatory authorities in 20 countries in Asia, Latin America, and in Australia. WHO issued its position on the use of CYD-TDV in July 2016, based on recommendations provided by SAGE in April 2016. These recommendations by SAGE were based on a review of the following key observations from two large clinical trials in 10 dengue endemic countries involving over 30,000 participants aged 2 to 16 years:

- Efficacy varied by age, dengue serotype, disease severity, and whether or not individuals had a previous natural dengue infection at vaccination.
- Vaccine efficacy against virologically confirmed dengue, over 25 month period from the first dose of a three dose immunization regimen among 9-16 year-olds was 65.6% and in this age-group severe dengue was reduced by 93% and hospitalizations with dengue by 82%.
- Two or more years after the first dose, an increased risk of hospitalized dengue was seen in the 2-5 year age group, with the largest excess in Year 3 (12-24 months after the last vaccine dose). During the 4+ years of trial follow up after the first dose, there was a non-statistical significant overall excess risk of hospitalized dengue in 2-5 year-olds (Relative risk 1.26, 95%CI: 0.76 to 2.13).
- This increased risk was not observed in those aged 9 years and above.

Because of the higher efficacy of the vaccine against dengue and the absence of an increased risk of hospitalized dengue observed in older compared to younger children, licensure of the vaccine was sought with an indication of 9 years and above. A working hypothesis for the increase in severe dengue during the longer term follow up among the 2-5 year olds was that the vaccine acted like a silent primary infection, priming individuals who had not been exposed to dengue previously (seronegatives) to more serious infections. It was unclear at the time whether the poorer performance of the vaccine in younger age groups compared to those over 9 years of age was attributable to a higher proportion of seronegative individuals, or a specific age effect, or to some combination of age and serostatus. Because blood samples before vaccination were collected from only about 2,000 children in the trials, there were limited data available to evaluate these possible vaccine effects by preceding serostatus. SAGE recognized that an increased risk of severe and hospitalized dengue also in older age groups was a theoretical possibility, but this was not substantiated by the available empiric data at the time.

Mathematical modelling suggested that the public health benefits of vaccination could be maximized if seroprevalence in the age group targeted for vaccination was high. In April 2016, SAGE recommended that countries interested in introducing the vaccine consider the use of the vaccine only in areas with a seroprevalence of $\geq 70\%$, but not in those below 50%. Although serosurveys to determine seroprevalence were recognized to be challenging due to cost, logistics, and spatial heterogeneity of dengue transmission, vaccination was proposed as a path forward for countries to reduce the burden of dengue in areas that met the seroprevalence criteria.

SAGE further noted that the evidence of the absence of a safety issue in seronegatives aged 9 and above was based on the limited data set of 10%-20% of the trial population from whom pre-vaccination blood samples were taken, further compounded by the fact that severe dengue is a relative rare event. This important evidence gap was highlighted, as was the need to better describe the benefit-risk ratio of CYD-TDV in seronegative individuals 9 years of age and older.

On 29 November 2017, Sanofi Pasteur announced the results of additional studies they had conducted to better describe the benefit-risk in seronegative individuals. A newly developed NS1 based antibody assay, which was designed to distinguish prior infection from prior vaccination, was applied to serum samples taken 13 months after vaccination (which had been stored for all participants). The assay results, combined with statistical imputation methods, enabled the serostatus of trial participants prior to vaccination to be inferred retrospectively. Though this new method has limitations with respect to sensitivity and specificity, the assays enabled the company to estimate the efficacy and long-term safety of the vaccine by serostatus prior to vaccination.

The new analyses from the long-term safety follow up indicate the following:

CYD-TDV has a differential performance based on serostatus at the time of vaccination

- Overall population level benefit is favourable
- Vaccine efficacy (VE) was high among inferred baseline seropositive participants 9 years of age or older: 76% (95%CI: 63.9, to 84.0), but much lower among baseline seronegative participants: 38.8% (95%CI: -0.9 to 62.9%) in the first 25 months after the first dose of vaccine
- In the approximate 5 year follow-up period after the first dose of vaccine, an overall higher risk of severe dengue and hospitalizations from dengue was observed in vaccinated seronegative trial participants of all ages compared to unvaccinated seronegative trial participants
- For the entire trial population aged 2-16 years, these results were statistically significant: Hazard Ratio (HR) in seronegative subjects aged 2-16 over an observation period of 60-72 months for severe dengue was 2.997 (CI95% 1.102-8.148; p=0.032)
- The excess risk in those aged 9 to 16 was apparent from year 3 and persisted through the 5 years of follow up time point but, over the whole follow-up period, was not statistically significant
- Clinical manifestations and relative risk of severe dengue were similar in vaccinated seronegative persons compared to unvaccinated seropositive persons, consistent with the working hypothesis that CYD-TDV mimics a primary-like infection

Following the release of the new findings, Sanofi Pasteur has stated its intention to change the label so that individuals who have not been previously infected by dengue virus (those who are seronegative) should not be vaccinated. WHO's Global Advisory Committee on Vaccine Safety (GACVS) and the WHO Secretariat published interim statements on December 7, 2007 (1), and December 22, 2017 (2), respectively. WHO's interim recommendation posted on 22 December 2017 was to vaccinate seropositive individuals only.

It is important to understand the extent of risk at a population level. Based on the incidence in the epidemiological settings of the trials, for those aged 9 years and above, the new analysis indicates that the risk of severe dengue over 5 years stratified by serostatus was as follows:

- In those seropositive prior to vaccination, the incidence of severe dengue was 1.0 per 1,000 in those vaccinated and 4.8 per 1,000 in those not vaccinated (benefit).
- In those seronegative prior to vaccination, the incidence of severe dengue was 4.0 per 1,000 in those vaccinated and 1.7 per 1,000 in those not vaccinated (harm)

Overall, in the trial populations, the number of severe cases prevented in those who were seropositive was substantially greater than the excess number induced in seronegatives. The extent of the population benefit depends on the dengue seroprevalence and the annual dengue incidence in any given setting:

- In areas of 70% dengue seroprevalence, over a 5 year follow up, based on the epidemiological settings of the trials, every 1 excess case of hospitalized dengue in vaccinated seronegatives would be offset by 13 hospitalized cases prevented in vaccinated seropositives, and 1 excess severe dengue in vaccinated seronegatives by 4 severe cases prevented in vaccinated seropositives.
- In areas of 85% dengue seroprevalence, the overall benefit would be predicted to be higher. Every 1 excess case within a 5- year period of hospitalized dengue in vaccinated seronegatives would be offset by 18 cases prevented in vaccinated seropositive persons, and 1 excess severe dengue in vaccinated seronegatives by 10 prevented severe cases in vaccinated seropositives.

Taking into consideration the now demonstrated evidence of increased risk in vaccinated seronegatives in the licensed age group of 9 years and above, the SAGE Working Group on Dengue Vaccines (WG) was re-established to consider the new evidence and propose revised recommendations for SAGE consideration.

Deliberations of the SAGE Working group on Dengue Vaccines, December 2017-March 2018

The WG came to the overall conclusion that CYD-TDV has a potential public health role, in the absence of currently available alternative solutions to combat the expanding problem of the global dengue burden. The challenge is how best to use CYD-TDV to maximize the public health impact, and minimize harm, and restore public confidence in dengue vaccines. In these deliberations, two main approaches were considered if the vaccine were to be further used in public programs:

- (1) Subnational or national mass vaccination strategy based on population seroprevalence criteria, and
- (2) Pre-vaccination screening and vaccinating only those testing seropositive.

Population Seroprevalence Criteria:

The rationale for this strategy is that vaccination based on a high seroprevalence criterion would result in a substantially larger number of severe and hospitalized dengue cases prevented in seropositive individuals than the number of excess cases resulting from priming seronegatives through vaccination. In this strategy, first a population survey would be undertaken to identify areas where seroprevalence thresholds are high enough to maximize public impact and minimize harm, followed by implementation of mass vaccination in the eligible area. With currently available data, harm to seronegatives would be minimized by not vaccinating them, but mathematical modelling, based on plausible assumptions on the immunity induced by the vaccine, predicts that the excess cases in seronegative individuals following vaccination will eventually be offset by a reduction in cases among these seronegatives at later time periods, compared to unvaccinated, when they experience their second natural dengue infection (in areas of high transmission where nearly all individuals will be infected with dengue at least twice). The seroprevalence threshold at which this overall benefit to seronegatives accrues depends on the timescale over which cumulative risk and benefit in seronegatives is evaluated. The shorter the time frame, the higher the threshold to accrue overall vaccine benefit. Furthermore, age at which vaccination would be introduced is an important factor. At age 9 years, the seroprevalence required for predicted benefit in seronegative recipients within 10 years is 80%. At age 16 years, the seroprevalence required is 86%. However, it is important to note that, although eventual reductions in the excess risk of severe and hospitalized disease in seronegative vaccinees are predicted by modelling, there are no available data on the risk in seronegative individuals beyond 5-6 years after vaccination against which this prediction can be tested.

Several major challenges of a seroprevalence-based strategy warrant consideration:

- (1) To minimize harm in seronegatives, high seroprevalence thresholds of 80% and above in 9-year olds would be required.

- (2) Very few locations have seroprevalence > 80% in 9 year olds, and even fewer have locations with seroprevalence >90% in 9 year olds.
- (3) The spatiotemporal heterogeneity of dengue transmission combined with the need for high seroprevalence thresholds would necessitate large scale serosurveys to identify suitable areas at micro scale, thus adding complexity and cost to any public vaccination programme.
- (4) Given the limited areas with such high seroprevalence rates, national coverage rates would be low and hence the overall public health impact limited.
- (5) A technically identifiable subpopulation of seronegative persons would be put at increased risk of severe dengue, at least for a period of time.
- (6) Communication around a strategy where a subset of individuals are put risk for the sake of overall population level benefit would be challenging, and may undermine vaccine confidence in general.

Recognizing the hurdles of individual testing, combined with the documented overall population benefit of CYD-TDV in very high transmission settings, the use of CYD-TDV without individual pre-vaccination testing could be considered by countries with subnational areas with very high transmission intensity, as defined by seroprevalence in 9-year olds of 80% and above. It is expected that only a very small proportion of (if any) subnational areas in most endemic countries will meet this criterion. Local, recent, age-stratified seroprevalence studies would have to be used to guide decision-making and introduction at subnational levels. Such programmes would need to take into account the feasibility and cost of seroprevalence studies, public confidence in national vaccination programmes, and perceptions of ethical considerations with regard to population level benefit versus individual level risk. Communication would have to ensure due regard for appropriate and full disclosure of risks of vaccination with regards to unknown serostatus.

Pre-vaccination Screening

With this strategy, only persons with evidence of a past dengue infection would be vaccinated (based on a screening test, or in some cases based on a documented laboratory confirmed dengue infection in the past). This approach would maximize the benefit from the vaccine by targeting seropositives, and minimize the risk associated with vaccinating seronegatives. The pre-test probability of an individual being seropositive will be higher in settings with high endemic transmission and thus a “pre-vaccination screening” strategy would likely be more cost effective in such settings than in areas of lower endemicity. The advantage of the “pre-vaccination screening strategy” over “population seroprevalence criteria” is that this strategy may also be considered in low to moderate transmission settings. Preliminary mathematical modelling shows that the population level coverage rates achieved by the “screen and vaccinate” strategy would be higher than the seroprevalence based strategy. Individuals who only had one past dengue infection (monotypic past infection) will benefit most from CYD-TDV. The likelihood of having had two or more dengue infections increases with age and with the transmission intensity in any given country. Therefore, the optimal age to target for vaccination varies significantly with transmission intensity. With high transmission intensity optimal ages are lower, while with low transmission intensity optimal ages are higher. The age group in which the highest dengue hospitalizations occur in a given area, based on surveillance, would be the modelled optimum age target for vaccination.

Despite the advantages of the “pre-vaccination screening” strategy, major challenges remain:

- (1) Screening tests would need to be highly specific to minimize harm in seronegative persons and would need to have high sensitivity to ensure that a high proportion of seropositive persons would benefit
- (2) Such tests would preferentially need to be deliverable at point-of-care as rapid diagnostic tests (RDT).

- (3) To date, no RDTs have been validated and licensed for the indication of screening for past dengue infection (seropositivity)
- (4) Pre-vaccination screening may pose significant hurdles in large-scale vaccination programmes

Therefore, both “Population Seroprevalence Criteria” and “Pre-vaccination screening” are imperfect approaches for achieving high population protection from dengue because they are each programmatically difficult, for different reasons and with different consequences.

Proposed Recommendations

For countries considering vaccination as part of their dengue control program, a “pre-vaccination screening strategy” would be the preferred option, in which only dengue-seropositive persons are vaccinated.

Conventional serological testing for dengue virus IgG (dengue IgG ELISA) could be used to identify persons who have had previous dengue infections. Sensitivity and specificity of dengue IgG ELISA should be assessed in a local context, and will depend on the prevalence of other flaviviruses, and past use of other flavivirus vaccines (Japanese encephalitis and yellow fever).

Currently available RDTs, despite their lower sensitivity and specificity to detect past dengue infection compared with conventional dengue IgG ELISA, could be considered in high transmission settings until better tests are available. In settings with high numbers of seropositives and relatively low numbers of seronegatives, even an imperfect test with lower specificity might be acceptable.

The pre-test probability of an individual being seropositive will be higher in settings with high transmission. However, a pre-vaccination screening strategy may also be considered in low to moderate transmission settings. In settings with low transmission (high numbers of seronegatives) a test with high specificity is needed.

Given that no assay will be 100% specific, some truly seronegative individuals may be vaccinated due to a false positive test result. Furthermore, although the efficacy against dengue infections in seropositive individuals is high, it is still not complete. Hence, the limitations of CYD-TDV will need to be clearly communicated to populations offered vaccination.

There is a continued need to adhere to other disease preventive measures and to seek prompt medical care in the event of dengue-like symptoms, regardless of whether vaccinated or not. Vaccination should be considered as part of an integrated dengue prevention and control strategy together with well-executed and sustained vector control and the best evidence-based clinical care for all patients with dengue.

Decisions about implementing a “pre-vaccination screening” strategy with the currently available tests will require careful assessment at the country level, including consideration of the sensitivity and specificity of available tests and of local priorities, dengue epidemiology, country-specific dengue hospitalization rates, and affordability of both CYD-TDV and screening tests.

Age

Whether there are age-specific effects, independent of serostatus, is the subject of ongoing research. Currently, the vaccine should be used within the indicated age range, which is typically 9 to 45 years of age. The age to target for vaccination depends on the dengue transmission intensity in a given country, and will be lower in countries with high transmission, and higher in countries with low transmission. The optimal age group to be targeted is the age at which severe dengue disease incidence is highest, and this can be ascertained from national and subnational routine hospital surveillance data.

Schedule

In the absence of data on vaccine efficacy and safety with fewer than three doses, CYD-TDV is recommended as a three dose series given 6 months apart. Should a vaccine dose be delayed for any reason, it is not necessary to restart the course and the next dose in the series should be administered.

Booster

There are currently no data on the use of booster doses. Additional studies to determine the utility of a booster dose and its best timing are under way. Accordingly, there is no current recommendation for a booster dose.

Research priorities

Development of a highly sensitive and specific RDT, simplified immunization schedules, and assessment of booster needs should be prioritized.

2. INTRODUCTION AND RATIONALE FOR THE SAGE RECOMMENDATIONS IN APRIL 2016

There are several dengue vaccine candidates in development. This document only refers to the first licensed dengue vaccine, CYD-TDV (Dengvaxia®), developed by Sanofi Pasteur.

Dengue is the most extensively spread mosquito-borne virus. In the last 50 years the incidence of dengue reported to WHO has increased 30-fold, with outbreaks of increasing frequency and magnitude, and continuing geographic expansion. Vector control is an important component of a comprehensive dengue control strategy; however, as a single strategy, it has been difficult to demonstrate its effectiveness in reducing the human dengue burden. As such, a vaccine is critical and must protect against the four different dengue viruses (i.e. be tetravalent).

Dengue is caused by any one of four viruses (serotypes 1-4). Infection by one serotype is thought to provide lifelong immunity against that particular serotype, but susceptibility remains to the other 3 and hence a person can be infected by up to four serotypes during his or her lifetime. After infection with one serotype, cross-immunity provides temporary partial protection against the other serotypes. There is a small risk of severe disease after any dengue infection, but the second infection by a different serotype to the first is associated with the highest risk of severe dengue, while the third and fourth infections are usually associated with a milder clinical course. Fatality rates are around 0.1% to 1% in hospitalized cases. Dengue often requires hospitalization, thereby challenging already fragile health care systems.

The first dengue vaccine, CYD-TDV (Dengvaxia®) has now been licensed by 20 dengue-endemic countries in Asia, Latin America and Australia, typically for use in persons aged 9-45 years, (exceptions are: Singapore (12-45 year-olds), Indonesia (9-16 year-olds) and Paraguay (9-60 year-olds)). The first public program was launched in the Philippines in April 2016 with the aim to vaccinate almost 750,000 students from 6,000 public schools, in three highly dengue-endemic regions in the Philippines. A community-based dengue vaccination program began in June 2017, in a fourth region in the Philippines, Cebu, with the aim to vaccinate almost 450,000 children and adolescents. The Paraná State in Brazil has also launched the first public dengue immunization program in the Americas, targeting vaccination of 500,000 of the state's residents in 2016. In addition, people living in Brazil, Mexico, El Salvador, the Philippines, Costa Rica, Indonesia, Peru, Paraguay, Guatemala, Thailand and Singapore can also access CYD-TDV through the private market. Various countries have licensed the vaccine, but not launched it (Argentina, Australia, Bolivia, Cambodia, Honduras, Malaysia, Myanmar, Venezuela).

Licensure of CYD-TDV was based on two parallel Phase 3 clinical trials, known as CYD14 and CYD15 (3, 4). CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), with 10,275 participants aged 2-14 years at first vaccination. CYD15 was conducted in 5 countries in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico (US)), with 20,869 participants aged 9-16 years at first vaccination. Furthermore, the Phase 2b study in Thailand (CYD23/57) provided some longer term follow data(5). In these trials the vaccine was evaluated with a 3-dose schedule with doses given 6 months apart. For more details, refer to the WHO background paper on dengue vaccines published in April 2016:

http://www.who.int/immunization/sage/meetings/2016/april/1_Background_Paper_Dengue_Vaccines_2016_03_17.pdf

Because of lower efficacy among children first vaccinated aged 2-5-year-old age group and the safety signal in this age group (see below), licensing for the vaccine was sought for those aged 9 years or older. Pooled data from CYD14 and CYD15 (post-hoc analysis) showed that in the 25 months following the first dose, among 9-16 year-olds, the vaccine efficacy was 65.6% (95%CI 60.7-69.9) against virologically confirmed dengue illness (VCD) due to any serotype(6). Protection was evident in the six months following the first dose and showed little variation up to one year following the third dose. Vaccine efficacy varied by infecting serotype (higher protection against DENV 3 and 4), age (higher protection in the 9-16 year age group than in the 2-8 year group), and severity (higher protection against hospitalized and severe dengue). In the subset of 10-20% of the trial population who were serotested before the first dose, vaccine efficacy was higher among participants 9 years of age or older who were seropositive at baseline (i.e., had previous exposure to dengue) (81.9%, 95%CI 67.2-90.0), than among participants who were seronegative at baseline (52.5%, 95%CI 5.9-76.1). Serostatus and age were highly correlated in the population studied. The seroprevalence among participants 9 years of age or older was approximately 70-80% in both Phase 3 trials, although there was large variation between countries.

After the first 25 months of follow up, participants were monitored by surveillance that only captured hospitalised cases of dengue. In those aged 5 years or above, substantial protection against hospitalised disease was seen through to the 5th year of follow up (which is ongoing). In those first vaccinated at ages 2-5 years (only included in Asia), an increased risk of hospitalized dengue was seen in vaccine recipients in the third year after the first dose. The increased risk diminished in the 4th and 5th years and, overall, in the whole follow-up period from the first dose, although the risk was elevated compared to controls, the increase was not statistically significant. No other safety signals were identified in any age group. Aggregated across both trials, with over 4 years of follow up, there was evidence that CYD-TDV was substantially protective against hospitalized dengue in those aged older than 5 years at first vaccination. These findings led to the current licensed indication, starting at 9 years of age.

In 2015, WHO convened eight independent modelling groups to model the long-term safety, public health impact, and cost-effectiveness of routine vaccination with CYD-TDV in a range of transmission settings, as characterised by seroprevalence levels among 9-year-olds. The models used assumed that the CYD-TDV vaccine acted akin to a silent natural infection, in priming or boosting immunity, since this hypothesis fitted the trial data well (including the potential safety signal in 2-5 year-olds). Thus, models included the potential risk of seronegative individuals being primed by vaccination, leaving them at higher risk of severe disease when infected with the first wild type dengue virus than they would have been had they not been vaccinated. The mathematical modelling indicated that in high¹ transmission settings, the introduction of CYD-TDV in early adolescence through routine immunization could reduce dengue hospitalizations by 10-30% over the period of 30 years, representing a substantial public health benefit(7). However, the modelling predicted that the vaccine would be less beneficial in low transmission settings and might even increase incidence of hospitalised dengue in very low transmission settings.

¹ For the purposes of this document, transmission settings are defined by average seroprevalence at age 9 years: very low ~10%, low ~30%, moderate ~50%, high ~70%, very high ~80-90%.

In all settings, the vaccine was predicted to have high sustained efficacy in seropositive recipients, but to prime seronegative recipients to be at higher risk of hospitalised dengue disease upon their first breakthrough infection. The population impact of vaccination therefore depended upon the proportion of the age group targeted for vaccination who might be expected to be seropositive – which would be high in high transmission settings, but low in low transmission settings. In addition, long-term outcomes of vaccination in seronegative vaccine recipients were predicted to differ by transmission setting. In high transmission settings¹, nearly everyone experiences at least 2 natural infections at some time, so, in the modelling, the priming effect of vaccination in seronegative recipients can be seen as bringing forward the response to the natural second infection they would have eventually experienced. In low transmission settings, not everyone would be expected to experience a natural second infection, so vaccination of seronegative recipients can lead to an absolute increase in the lifetime risk of hospitalised dengue disease. It is important to note that underpinning these conclusions was the assumption that seronegative vaccine recipients who have experienced one breakthrough natural infection gain the high level of immunity associated with two consecutive natural infections in unvaccinated individuals. This assumption is consistent with the “silent natural infection” hypothesis of CYD-TDV action but cannot currently be conclusively tested with the trial data available. Since, in the modelling, vaccination only transiently reduces the risk of infection and the main effect of vaccination is to modify the risk of disease, the modelling findings predicted that the indirect (herd) effect of vaccination on DENV transmission would be limited(8).

Overall, vaccination was predicted to be potentially cost-effective at a threshold of US \$2,000 per DALY saved across all models in moderate- to high-transmission settings, if the costs of vaccinating an individual could be kept well below approximately US\$50 (from a provider perspective) or US\$100 (from a societal perspective). At a threshold cost per DALY averted of US\$2,000, most of the benefit of vaccination in all the models came from averting health care costs rather than DALYs.

The increased risk that vaccination may be ineffective or may even increase the risk for severe dengue in those who are seronegative at the time of first vaccination was considered during the SAGE discussions. However, the available evidence at the time did not show such an increased risk for the licensed age group of 9 years and above, based on the table provided by Sanofi Pasteur, as presented to SAGE on April 14, 2016, available at: http://www.who.int/immunization/sage/meetings/2016/april/2_Smith_Clinical_Trial_Results_SAGE.pdf

Table 1: Number of hospitalized and/or severe virologically confirmed dengue cases by age group and dengue serostatus at baseline. Pooled data from CYD14, CYD15, and CYD57, as presented to SAGE in April 2016.

| Age group | Serostatus at baseline | Active phase cases/N (%) | | Hospital phase- SEP ⁺ cases/N (%) | | Cumulative cases/N (%) | |
|------------|------------------------|--------------------------|---------------|--|---------------|------------------------|---------------|
| | | CYD group | Control group | CYD group | Control group | CYD group | Control group |
| 2-8 years | Seropositive | 2/493 (0.4) | 8/240 (3.3) | 7/476 (1.5) | 3/234 (1.3) | 9/481 (1.9) | 11/236 (4.7) |
| | Seronegative | 2/337 (0.6) | 2/178 (1.1) | 15/326 (4.6) | 3/170 (1.8) | 17/330 (5.2) | 5/173 (2.9) |
| 9-16 years | Seropositive | 0/1605 (0.0) | 6/777 (0.8) | 7/1508 (0.5) | 9/736 (1.2) | 7/1546 (0.5) | 15/752 (2.0) |
| | Seronegative | 0/398 (0.0) | 2/214 (0.9) | 7/372 (1.9) | 3/197 (1.5) | 7/382 (1.8) | 4/204 (2.0) |

SAGE noted that the evidence on the absence of a safety signal in those aged 9 years and above who were seronegative at vaccination was based on the small immunogenicity data set (about 10% of the trial population for which baseline samples were available to enable stratification by dengue serostatus prior to vaccination). Based on the review of the quality of the body of evidence, using GRADE, a final score of 2 was given (meaning that the evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome). It was concluded that while the absence of a safety signal was reassuring, there were insufficient data to determine conclusively an absence of a safety issue in seronegative subjects(9).

Informed by the results shown in Table 1 and by the modelling work, the efficacy results showing higher benefit in seropositives than in seronegatives, the WHO SAGE committee in April 2016 recommended countries consider introduction of CYD-TDV only in national or subnational settings with high endemicity, as defined by seroprevalence of approximately 70% or more in the targeted age group, and recommended against its use in age groups with seroprevalence <50%. In high transmission settings, as defined by seroprevalence above 70%, the population health benefit was estimated to be substantial, and, in the longer term, beyond the follow-up period in the trial, even seronegative vaccine recipients were expected to gain benefit, based on the modelling, for the reasons discussed above.

The possibility that vaccination might be ineffective or might even increase the risk of severe dengue in those who are seronegative (at the time of first vaccination) led to the recommendation that further studies would be needed to address this concern, otherwise it would remain a controversial issue and could compromise public confidence in the vaccine programme. SAGE considered further research into the efficacy and safety of the vaccine in seronegative persons a high priority. Hence, WHO requested that Sanofi Pasteur provide more data on efficacy and safety in seronegative vaccine recipients.

3. STUDY DESIGN TO RETROSPECTIVELY IDENTIFY SEROSTATUS AT BASELINE

Serostatus refers to whether a person has experienced a dengue infection in the past, which is determined by a serological assay. A seronegative individual has not had a previous dengue infection. A seropositive individual has had a previous dengue infection with at least one serotype. A person may not know whether he or she was infected in the past, because many dengue infections are clinically inapparent.

Since only a small subset of participants in the Phase 3 trials had blood samples collected before vaccination, the serostatus of most trial participants was not known (i.e., whether they were seropositive or seronegative at the time of receiving the first vaccine dose). Therefore, there was hitherto very limited statistical power to analyse the efficacy and long-term safety data of CYD-TDV according to serostatus.

3.1 Additional analyses

Sanofi Pasteur utilized a new assay to perform additional serological testing to infer pre-vaccination serostatus based on samples that had been collected from all trial participants at month 13 (M13), one month after the 3rd dose was administered. The assay was based on an NS1 antibody ELISA, developed by the University of Pittsburgh. Participant samples were re-tested using this yet unpublished assay that identifies antibodies against the dengue non-structural protein 1 (NS1). The CYD-TDV encodes yellow fever vaccine non-structural proteins including NS1, rather than those for dengue, and thus the new test was able to distinguish immune responses due to past dengue infection from those due to vaccination.

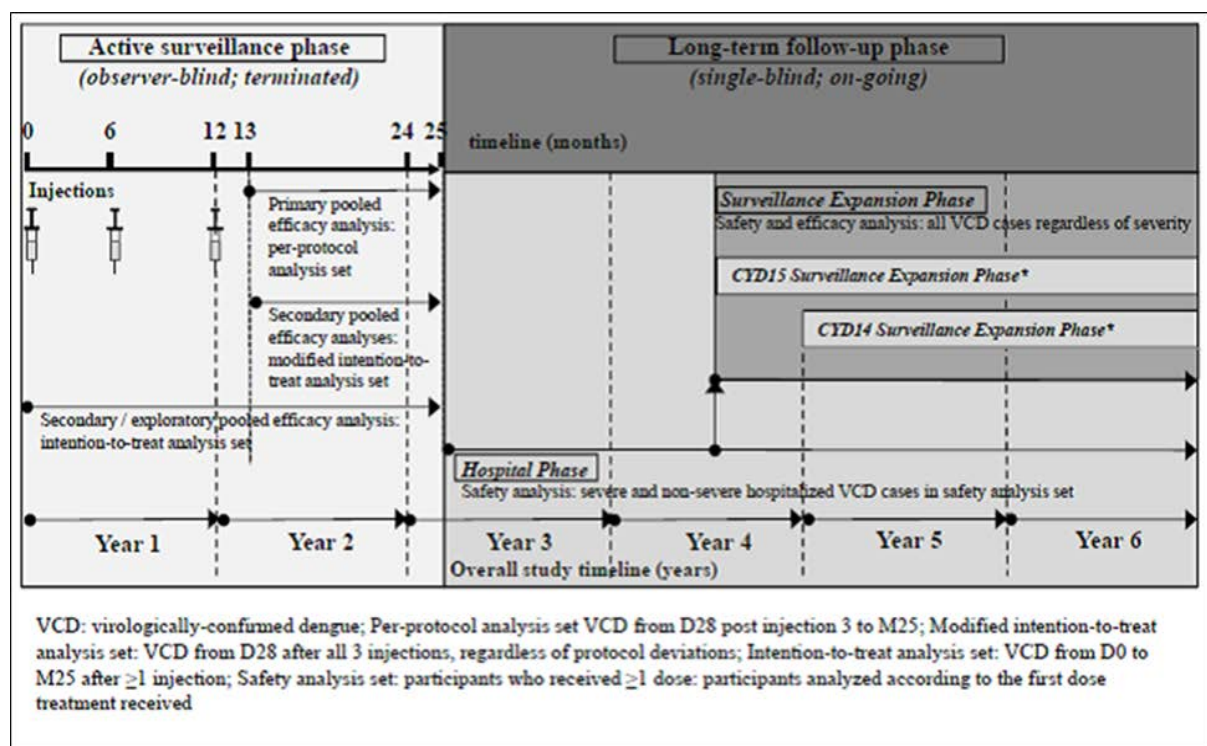


Figure 1. Summary of Phase 3 trial design, including blood sampling at Month 13, and the long-term follow up.

The sensitivity of the NS1 assay (ability to correctly detect “dengue exposed” individuals as seropositive) was estimated to be 95.3%, which means that the false negative rate (“dengue exposed” samples misclassified as seronegative) was 4.7%. The specificity of the assay (ability to correctly identify dengue unexposed individuals as seronegative) subjects was estimated to be 68.6% which means that the false seropositive rate (misclassify “dengue unexposed” samples as seropositive by the assay) was 31.4%. Therefore, among subjects classified as

seropositive by the anti-NS1 assay (Threshold 9), a proportion would be actually seronegative. Thus, it is likely that the efficacy/relative risk estimates obtained for subjects classified as seropositive by the anti-NS1 assay would underestimate benefit to some extent (i.e. disfavour the vaccine), due to the influence of the misclassified seronegative individuals on the estimates. Similarly, those classified as seronegative, would include a small proportion who were truly seropositive.

In addition to the misclassification due to the assay performance, an excess misclassification of about 8% of seronegative subjects as seropositive (anti-NS1 assay threshold of 9 EU/ml) was observed in vaccine recipients compared to placebo recipients due to the impact of CYD vaccination on anti-NS1 titres. To eliminate concerns of biases introduced by the vaccine effect on the dengue anti-NS1 titres and to be consistent with historical assessments based on serostatus, Sanofi Pasteur used PRNT50 to classify serostatus for subjects with pre-vaccination serum samples and used imputation methods to impute baseline PRNT50 titres from M13 anti-NS1 titres and other variables for trial participants for whom baseline PRNT50 measurements had not been made, who constituted the majority of participants. The multiple imputation method is a commonly-used statistical approach to deal with missing data. In addition, a non-parametric statistical method (Targeted Minimal Loss-based Estimator, TMLE) was employed as an alternative to multiple imputation. This approach used machine learning (called “SuperLearner2”) to select among a library of candidate algorithms for estimating the probability that a subject has a given baseline serostatus conditional on M13 anti-NS1 titres, M13 PRNT50 titres (if observed), vaccination status, age, and country. The two key advantages of the multiple imputation and TMLE are: first, it overcomes the limitation of potential bias due to vaccine-effect misclassification of serostatus using a threshold of anti-NS1 titres at M13; second, it enables the estimation of vaccine risk and efficacy from the time of vaccination (M0) onwards.

The primary objective of the analyses was to assess the risk of hospitalization for dengue and of severe dengue (based on the classification of cases of dengue by the Independent Data Monitoring Committee) in vaccinated seronegative participants aged ≥ 9 years at enrolment. Secondary objectives included assessment of the risk of dengue hospitalization and severe dengue for subjects of any age and for those aged < 9 years at enrolment, and evaluation of efficacy against symptomatic VCD up to 25 months in subjects ≥ 9 years, < 9 years of age, and any age. Objectives also included the assessment of vaccine efficacy among vaccinated seropositive subjects. Clinical outcome definitions and assessments methods were the same as previously reported (3-5).

A case-cohort study was undertaken to re-analyse all cases of symptomatic virologically-confirmed dengue (VCD) (n=1258), hospitalized VCD (n=644) and severe VCD (n=142) by serostatus from the three efficacy trials (CYD14, CYD15 and CYD23/57). To represent the population in which cases occurred, a sub-cohort of 10% of all participants from each trial was randomly selected after stratifying by age and trial site. All cases of hospitalized VCD and severe VCD over the follow-up period (60-72 months), and all cases of symptomatic VCD in the first 25 months were included in the analyses.

For more detailed explanations on the three methods employed to infer baseline serostatus retrospectively, refer to Appendix 2 (on WHO website).

4. EFFICACY AGAINST VIROLOGICALLY-CONFIRMED DENGUE STRATIFIED BY SEROSTATUS

4.1 CYD-TDV vaccine efficacy in the active follow-up stratified by serostatus and age group

It was originally planned to evaluate vaccine efficacy (VE) against virologically-confirmed dengue (VCD) of any severity only during the first 25 months after the first dose, and active surveillance was put in place to

detect such cases. In this period there was a total of 1258 cases detected. The per protocol analysis of vaccine efficacy was based on cases arising from one month after the last dose until 12 months later (M13 to M25).

Figure 2 shows vaccine efficacy estimates, measured during the 25 months after the first vaccine dose, against dengue of any severity, using the three different methods of taking account of baseline serostatus. The first row in each age grouping show the estimates based on multiple imputation (MI), the second based on the TMLE method and the third using the NS1 results directly but with efficacy only from month 13 (when blood samples were collected from all participants). The first 2 methods broadly gave very similar findings and results are discussed primarily in relation to the MI method. Using this method, VEs among seropositive participants, were 76% (95%CI: 64;84, $p<0.001$), 60% (95%CI: 31;76, $p=0.002$) and 73% (95%CI: 59;82, $p<0.001$), and for participants aged 9-16 years, 2-8 years, and of any age, respectively.

Figure 3 shows similar estimates for seronegative participants. VEs against symptomatic VCD (up to M25) were 39% (95%CI: -1;63, $p=0.05$), 19% (95%CI: -47;55, $p=0.48$), and 32% (95%CI: -9;58, $p=0.10$) in 9-16-year-olds, 2-8-year-olds and at for all ages, respectively.

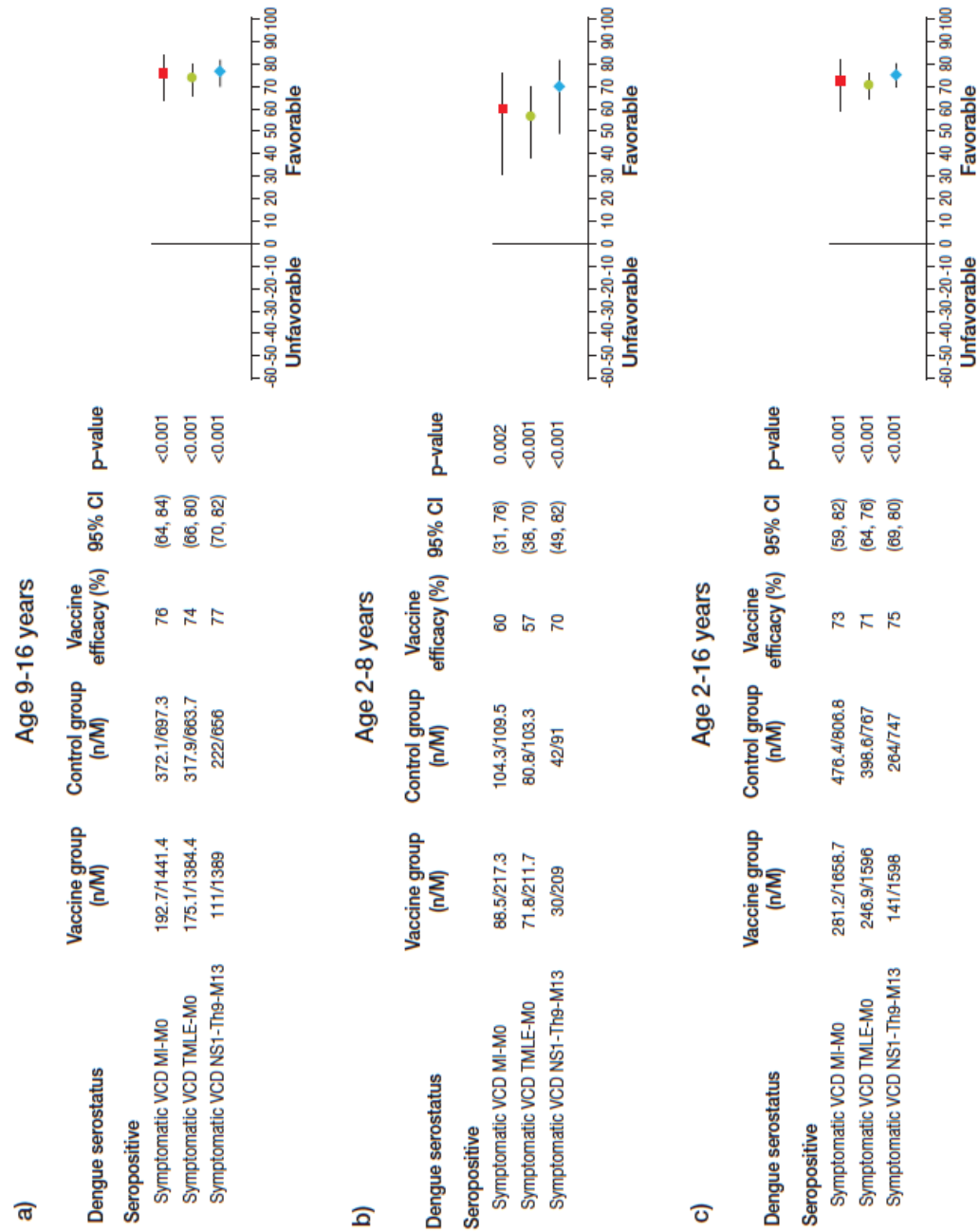


Figure 2. Efficacy against symptomatic VCD up to 25 months after first vaccination in seropositive subjects.

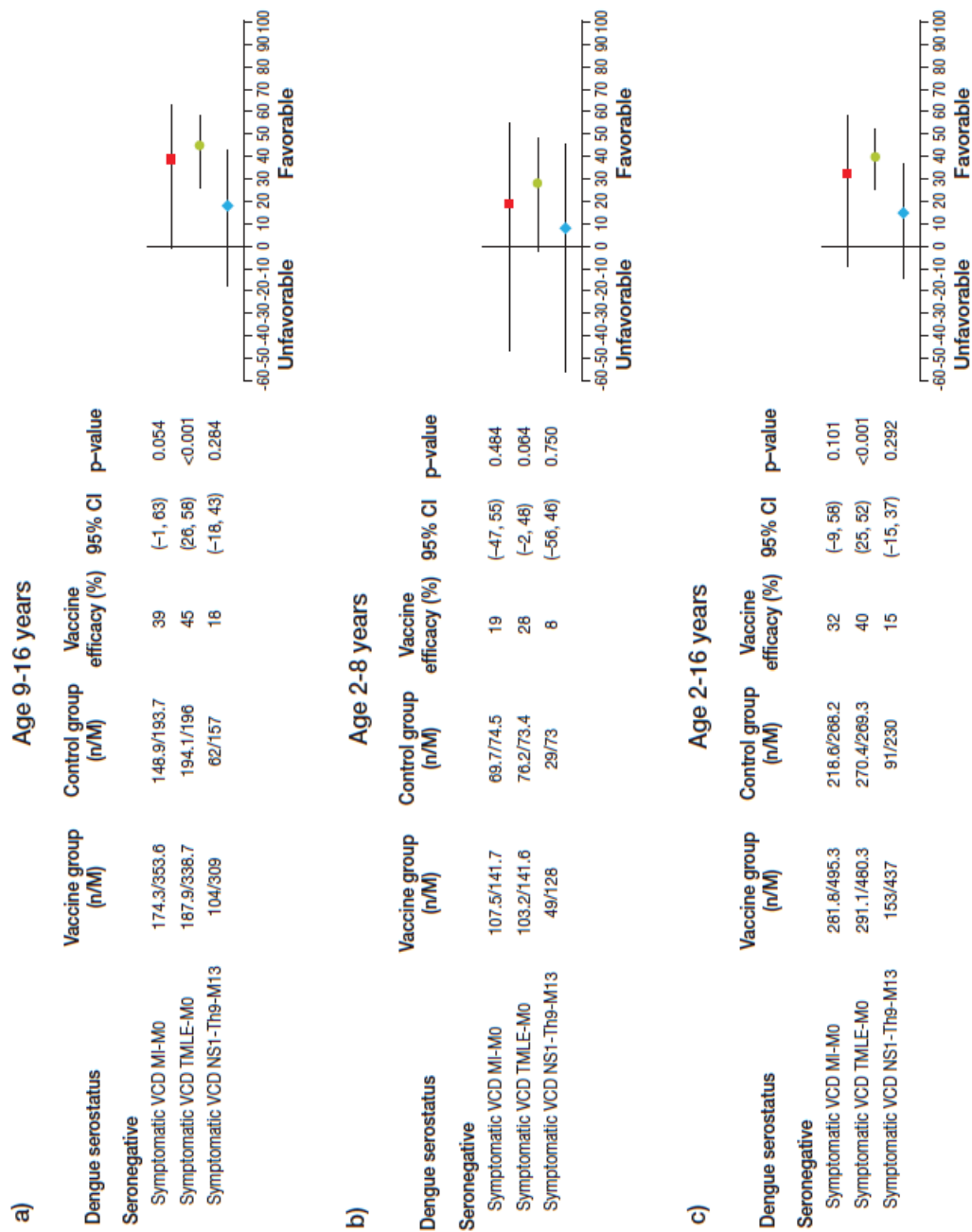


Figure 3. Efficacy against symptomatic VCD up to 25 months after first vaccination in seronegative subjects.

Figures 4 and 5 show efficacy estimates based on the MI method, in finer age strata. In both seropositives and seronegatives efficacy appears to increase with age. Among seronegatives, in no age stratum is the VE estimate formally statistically significant, though it is close to significance in the oldest age group.

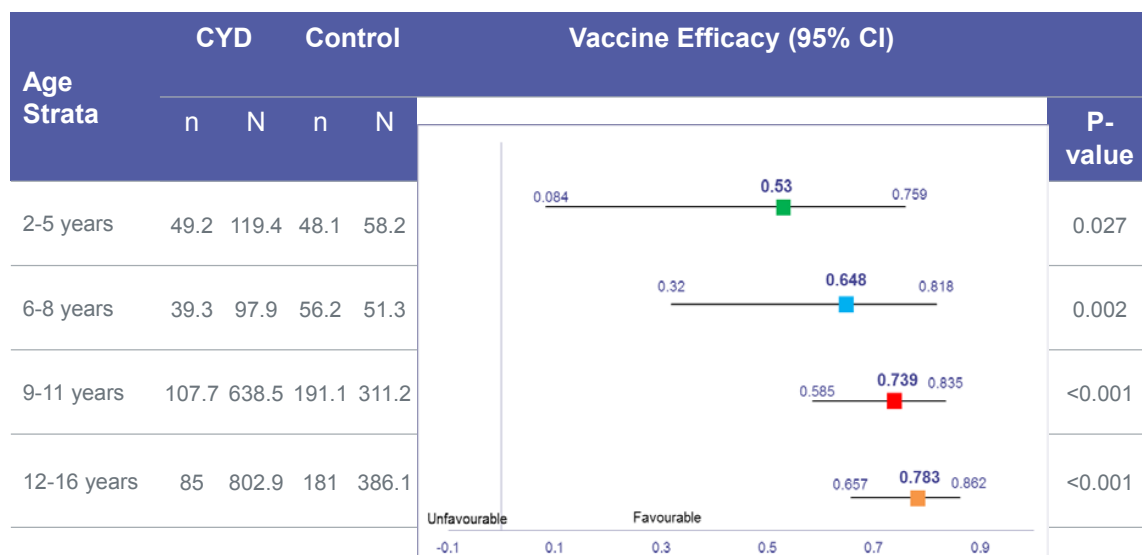


Figure 4. Efficacy against symptomatic VCD in the 25 months after first vaccination in seropositive participants, stratified by age (Multiple Imputation method).

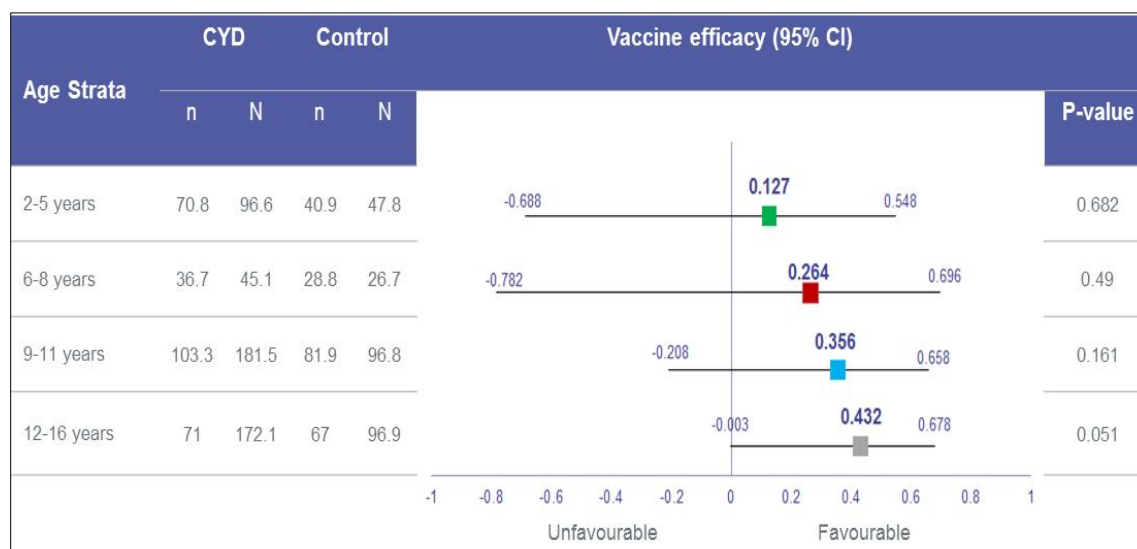


Figure 5. Efficacy against symptomatic VCD in the 25 months after first vaccination in seronegative participants, stratified by age (Multiple Imputation method).

4.2 Duration of efficacy against symptomatic VCD beyond 2 years

Vaccine efficacy against symptomatic VCD of any severity was evaluated in Years 1-2 (active phase). Active surveillance for cases of virologically-confirmed dengue of any severity was reinstituted in year 4 after first vaccination (called the Surveillance Expansion Phase (SEP)) and will continue until the end of 6 years after first vaccination. Thus, there was a gap in active surveillance after the first 2 years and the ability to make inferences about duration of protection against dengue of any severity are therefore limited. Data for cases arising during the SEP period will be available later, likely in Q4 2018. Knowledge on duration protection against VCD beyond 25 months constitutes an important data gap.

5. LONG-TERM SAFETY RESULTS STRATIFIED BY SEROSTATUS

The case-cohort included 644 hospitalized VCD cases, and 142 severe VCD cases, arising during the follow-up time up to 66 months after first vaccination.

5.1 Risk of hospitalized and severe dengue by serostatus

Participants aged 9-16 years

In seropositive participants aged 9-16 years, Hazard Ratios (HRs) were calculated, that is, the ratio of incidence rates in vaccinated and control participants (HRs for hospitalized VCD and severe VCD were 0.21 (95%CI: 0.14;0.31, $p<0.001$) and 0.16 (95%CI: 0.07;0.37, $p<0.001$), respectively (Figure 6, MI method). Cumulative incidences of hospitalized VCD and severe VCD through to M60 in vaccine recipients were 0.38% (95%CI: 0.26;0.54) and 0.08% (95%CI: 0.03;0.17), respectively, and 1.88% (95%CI: 1.54;2.31) and 0.48% (95%CI: 0.34;0.69) in controls.

The HRs for hospitalized VCD and severe VCD in seronegative participants were 1.41 (95%CI: 0.74;2.68, $p=0.29$) and 2.44 (95%CI: 0.47;12.56, $p=0.28$), respectively. Cumulative incidences of hospitalized VCD and severe VCD through to M60 in vaccine recipients were 1.57% (95%CI: 1.13;2.19) and 0.40% (95%CI: 0.22; 0.75) in vaccine recipients, respectively, and 1.09% (95%CI: 0.53;2.27) and 0.17% (95%CI: 0.04;0.83) in controls.

Participants aged 2-8 years

In seropositive participants aged 2-8 years, the HRs for hospitalized VCD and severe VCD were 0.50 (95%CI: 0.33;0.77, $p=0.002$) and 0.58 (95%CI: 0.26;1.30, $p=0.183$), respectively.

The HRs for hospitalized VCD and severe VCD in seronegative participants aged 2-8 were 1.95 (95%CI: 1.19;3.19, $p=0.008$) and 3.31 (95%CI: 0.87;12.54, $p=0.077$), respectively.

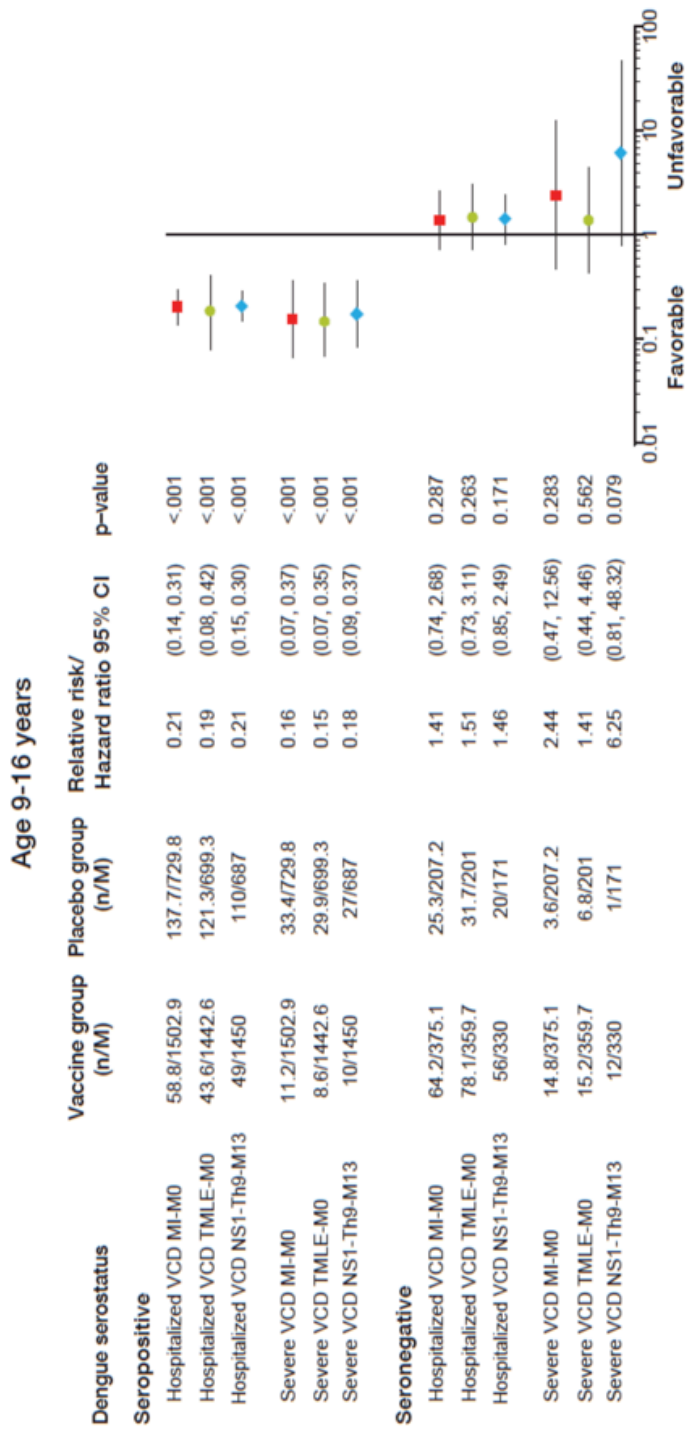


Figure 6. Risk of hospitalized and severe VCD by serostatus in trial participants aged 9–16 years, M0-M66.

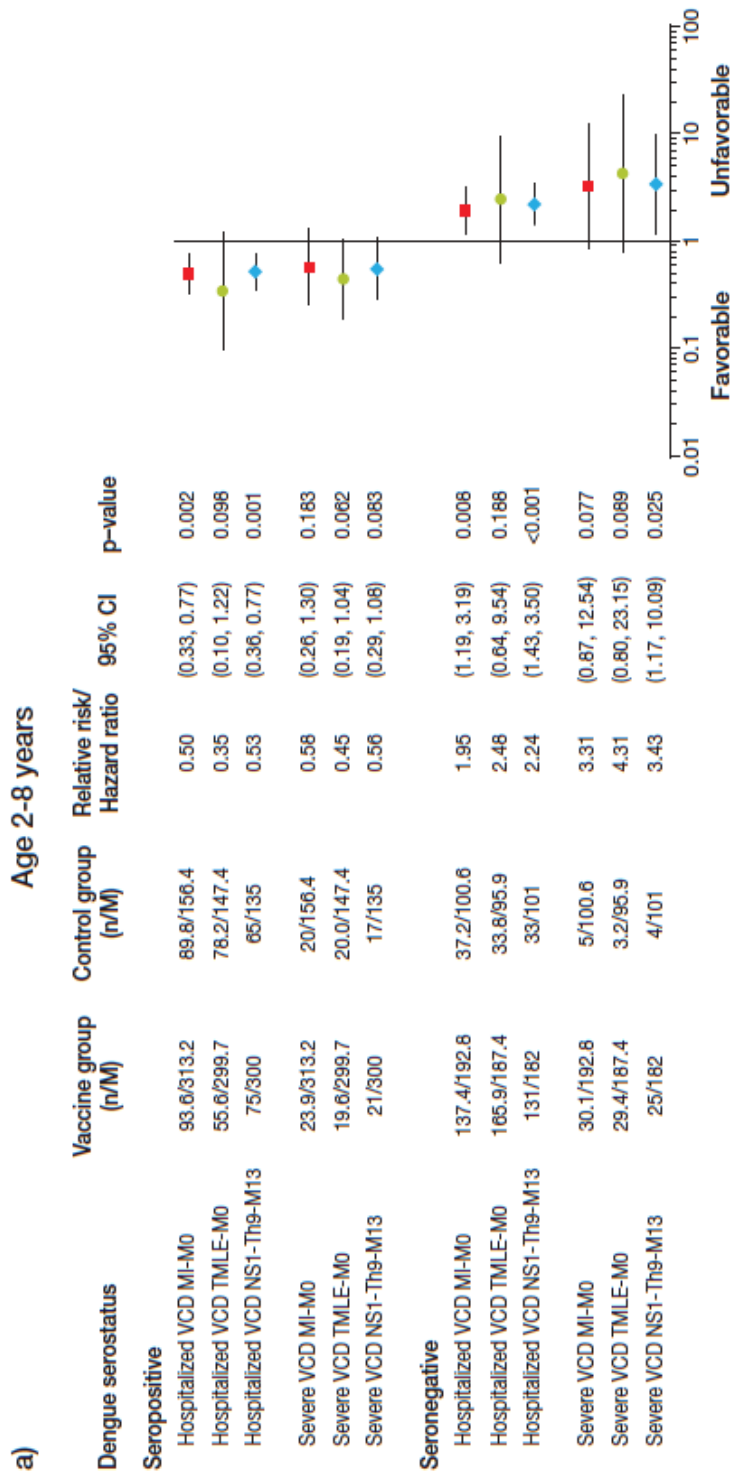


Figure 7. Risk of hospitalized and severe VCD by serostatus in trial participants aged 2-8 years, M0-M66.

Figure 8 shows the estimates for hospitalised dengue among seronegative participants in finer age strata.

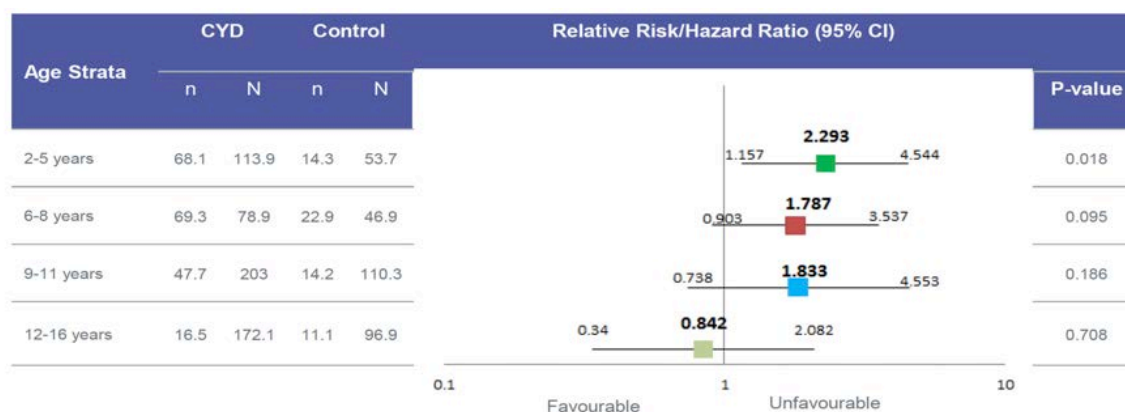


Figure 8. Risk of hospitalized VCD in seronegative participants in CYD14, CYD15, and CYD57 by age-strata by Multiple Imputation (M0 onwards).

5.2 Cumulative incidence of hospitalized VCD by time since first dose (0-66 months after first dose)

Figure 9 shows the cumulative risk of hospitalized dengue by time since the first dose, in different age groups and for seronegative and seropositive participants, according to vaccination status.

In seropositive participants, the cumulative risk of hospitalized VCD over 60 months was lower among vaccine recipients than controls throughout the observation period of 60 months in all age groups.

In seronegative participants, there was an excess risk of hospitalized VCD in vaccine recipients compared to controls from M30 in 9–16-year-olds, and from M18 in 2–8-year-olds. In seronegative participants aged 9-16 years, the cumulative risk of hospitalized VCD was similar to that in seropositive unvaccinated participants. In seronegative participants aged 2-8 years, the cumulative risk of hospitalized VCD approached that for seropositive unvaccinated subjects over the follow-up period.

5.3 Hazard Ratio (HR) by year after first vaccination, in seronegative trial participants

Based on multiple imputation methods, HRs of hospitalized VCD per year of study were calculated, for the active follow-up phase (first two years), Year 1 and 2 of hospitalization phase, and >Year 2 of hospitalization phase for participants aged 9-16 years (Figure 10) and aged 2-8 years (Figure 11). The HR of hospitalized VCD in seronegative subjects was highest in Year 3 after first vaccination, eg in the first year of the hospital phase.

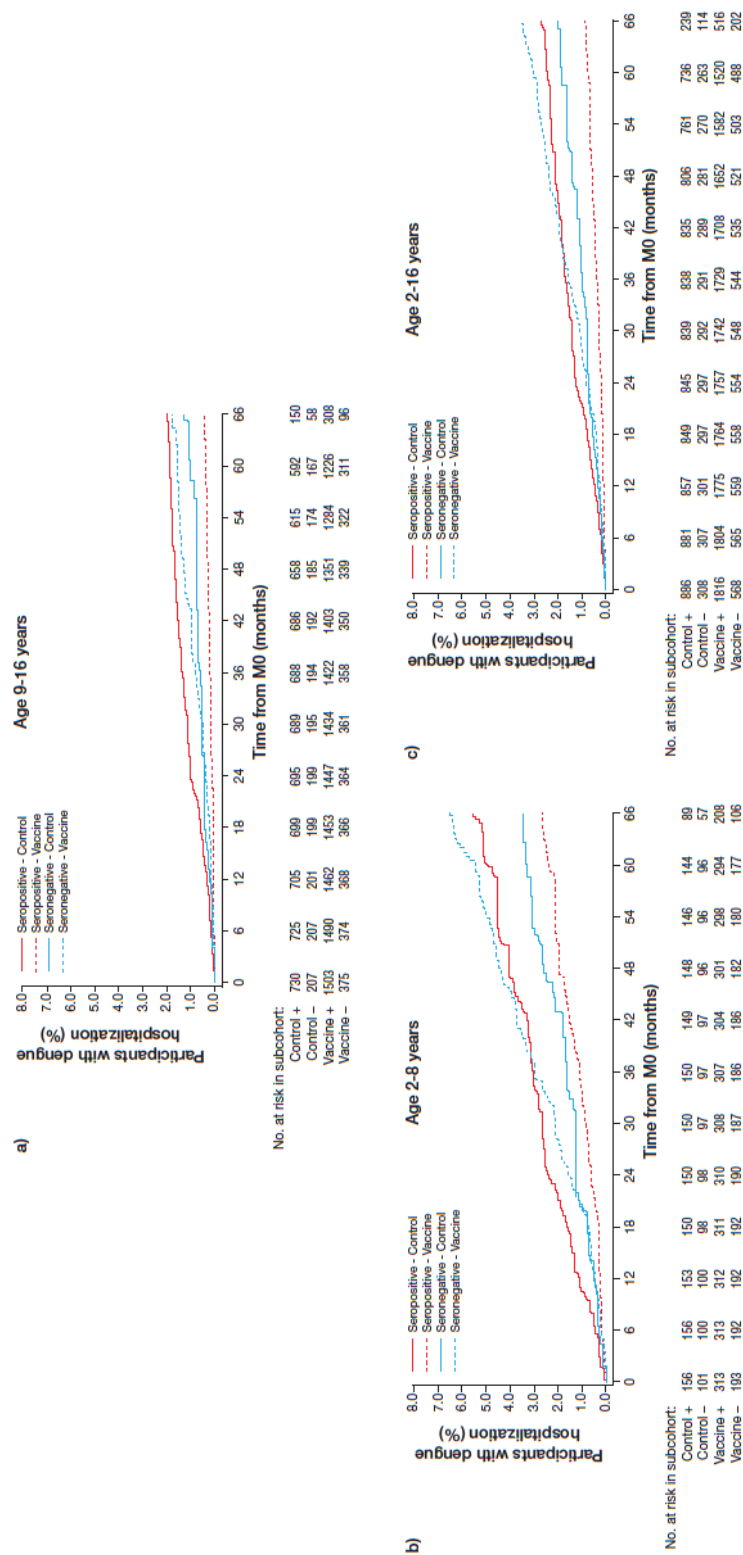


Figure 9. Cumulative incidence of dengue hospitalizations from M0 by baseline serostatus (MI method) and vaccination status, in participants aged 9-16 years (a), 2-8 years (b) and 2-16 years (c). Data represents pooled analysis of CYD14, CYD15 and CYD23/57 trials. The cumulative incidence curves are curtailed at M66 to ensure at least 20% of subjects remaining at risk in each sub-cohort.

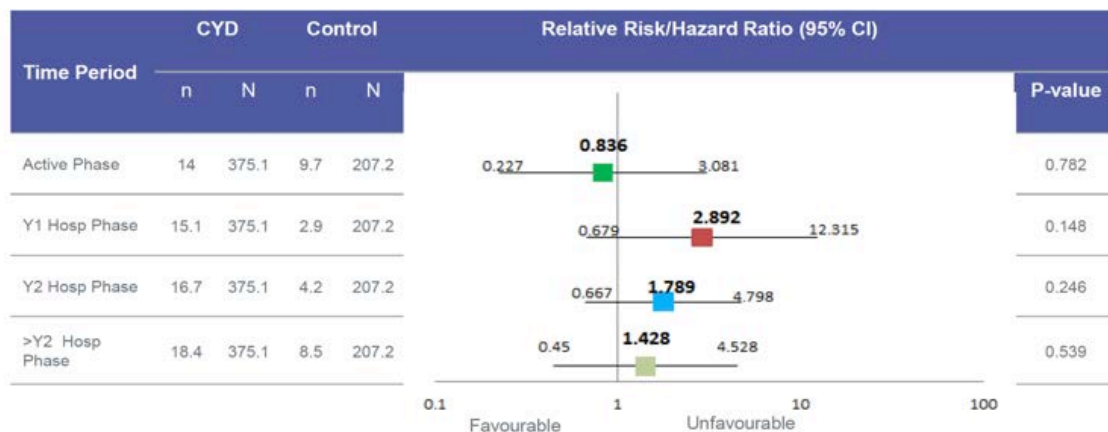


Figure 10. Hospitalized VCD in seronegative participants in CYD14, CYD15, and CYD57, age 9-16 years, by year of study by multiple imputation (M0 onwards).

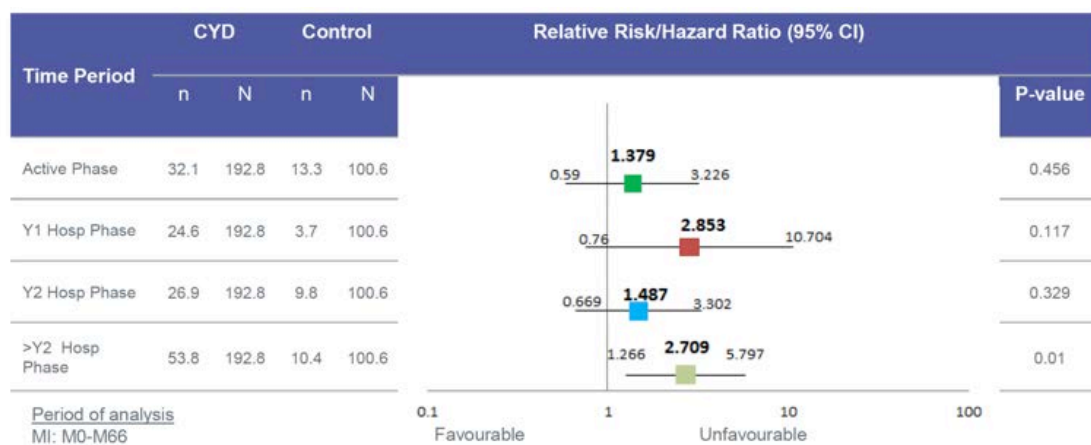


Figure 11. Hospitalized VCD in seronegative participants in CYD14, CYD15, and CYD57, age 2-8 years, by year of study by Multiple Imputation (M0 onwards).

5.4 Attributable risk (AR) and cumulative incidence estimates

The AR is calculated as the difference in the cumulative incidence rates of hospitalised dengue in vaccinated and control participants. Over five-years of follow-up, the AR for seronegative vaccine recipients 9-16Y of age was 4.78 (95%CI: -13.99, 24) for hospitalized VCD and 2.30 (95%CI: -7.0, 10.67) for severe VCD per 1,000 subjects. The corresponding ARs for seropositive vaccinees were -15.08 (95%CI: -25.44, -4.97) and -4.05 (95%CI: -9.59, 0.63) per 1,000 subjects, respectively. In other words, based on the average seroprevalence and annual incidence as observed in the trial settings, during the 5-year follow-up after vaccination, there was a reduction of about 15 cases of hospitalized dengue and 4 cases of severe dengue per 1,000 seropositive persons 9-16Y of age vaccinated.

For 1,000 seronegative persons 9-16Y of age vaccinated, there was an increase of about 5 cases of hospitalized dengue and 2 cases of severe dengue.

Table 2. Attributable risk and cumulative incidence estimates in subjects aged 9–16 years according to baseline serostatus (Multiple Imputation Methods)

| Endpoint | Incidence in non-vaccinated (per 1,000) | 95% CI | Incidence in vaccinated (per 1,000) | 95% CI | Attributable risk (per 1,000) | 95% CI |
|---------------------------------|---|----------------|-------------------------------------|----------------|-------------------------------|-----------------|
| Seropositive at baseline | | | | | | |
| Dengue Hospitalization | 18.83 | (15.36, 23.07) | 3.75 | (2.63, 5.35) | -15.08 | (-25.44, -4.97) |
| Severe Dengue | 4.80 | (3.35, 6.88) | 0.75 | (0.34, 1.65) | -4.05 | (-9.59, 0.63) |
| Seronegative at baseline | | | | | | |
| Dengue Hospitalization | 10.93 | (5.26, 22.65) | 15.71 | (11.25, 21.93) | 4.78 | (-13.99, 24.00) |
| Severe Dengue | 1.74 | (0.36, 8.34) | 4.04 | (2.18, 7.49) | 2.30 | (-7.00, 10.67) |

Data pooled from the CYD14, CYD15 and CYD23/57 studies. Subjects are categorized as seropositive or seronegative by Multiple Imputation approach (M0 onwards to M60).

5.5 Absolute risk of hospitalized VCD and severe VCD by serostatus and vaccination status

The risk depends on the yearly incidence of dengue. Based on the incidence in the epidemiological settings of the trials, for persons aged 9 years and above, the new analysis indicates that the 5-year risk of severe dengue in vaccinated seronegative persons (4 per 1,000 seronegative persons vaccinated) approaches the risk of severe dengue in unvaccinated seropositive subjects (4.8 per 1,000 seropositive persons unvaccinated). The risk of severe dengue is lower in unvaccinated seronegative persons (1.7 per 1,000 unvaccinated seronegative subjects). The risk of severe dengue in vaccinated seropositive participants is the lowest (less than 1 per 1,000 vaccinated seropositive subjects).

5.6 Comparison of clinical severity of hospitalized VCD in seropositive vaccinated and unvaccinated, and seronegative vaccinated and unvaccinated trial participants

The clinical manifestations and laboratory parameters in all hospitalized VCD cases occurring after M13 up to March 2017 in the case-cohort study from CYD14, CYD15 and CYD23/57 are presented below categorized by serostatus defined by anti-NS1 (threshold 9) and intervention group, eg there were four groups: vaccinated and unvaccinated (control) seronegative subjects, vaccinated and unvaccinated (control) seropositive subjects. The data are presented for subjects 2-16 years of age, 9-16 years of age and 2-8 years of age.

Table 3. Summary of clinical signs and symptoms of all hospitalized VCD episodes occurring after M13 in seronegative (NS1 Th9) subjects ≥ 9 years of age classified as seropositive and seronegative by NS1 at M13 (threshold 9) - CYD14/CYD15/CYD23/57.

| | Seronegative Vaccine group | Seronegative Control group | Risk Ratio of seronegative CYD vs placebo (95% CI) | Seropositive Vaccine group | Seropositive Control group | Risk Ratio of seropositive CYD vs placebo (95% CI) |
|--|----------------------------------|----------------------------------|---|----------------------------------|----------------------------------|---|
| Number VCD episodes, n | 56 | 20 | | 49 | 110 | |
| Duration of clinical symptoms, days Median (min-max) | 8 (3-29) | 7.5 (4-14) | | 8 (2-13) | 8 (4-18) | |
| Duration of fever, days Median (min-max) | 5 (1-10) | 5 (2-8) | | 4 (1-9) | 5 (1-17) | |
| Hospitalized VCD episodes | | | | | | |
| Serotype 1, n | 24 | 9 | | 14 | 32 | |
| Serotype 2, n | 19 | 5 | | 18 | 42 | |
| Serotype 3, n | 11 | 6 | | 13 | 16 | |
| Serotype 4, n | 3 | 2 | | 4 | 21 | |
| Median duration of hospitalization, days (min- max) | 4 (1-8) | 4 (2-6) | | 4 (1-10) | 5 (2-12) | |
| Any haemorrhage | 22/56 (39.3%) | 9/20 (45.0%) | 0.873 (0.39; 2.15) | 15/49 (30.6%) | 46/110 (41.8%) | 0.732 (0.38; 1.34) |
| Any visceral manifestation | 0/56 (0.0%) | 1/20 (5.0%) | 0.000 (0.00; 13.93) | 2/49 (4.1%) | 7/110 (6.4%) | 0.641 (0.07; 3.37) |
| Plasma Leakage | | | | | | |
| Any | 20/56 (35.7%) | 2/20 (10.0%) | 3.571 (0.87; 31.51) | 17/49 (34.7%) | 46/110 (41.8%) | 0.830 (0.45; 1.47) |
| With clinical signs | 2/56 (3.6%) | 0/20 (0.0%) | | 4/49 (8.2%) | 17/110 (15.5%) | 0.528 (0.13; 1.62) |
| Hematocrit increase \geq 20% | 20/56 (35.7%) | 2/20 (10.0%) | 3.571 (0.87; 31.51) | 14/49 (28.6%) | 39/110 (35.5%) | 0.806 (0.40; 1.52) |
| Thrombocytopenia | | | | | | |
| Platelet count \leq 50x10 ⁹ /L | 23/56 (41.1%) | 3/20 (15.0%) | 2.738 (0.83; 14.25) | 23/49 (46.9%) | 60/110 (54.5%) | 0.861 (0.51; 1.41) |
| Platelet count \leq 100x10 ⁹ /L | 43/56 (76.8%) | 14/20 (70.0%) | 1.097 (0.59; 2.17) | 39/49 (79.6%) | 94/110 (85.5%) | 0.931 (0.62; 1.37) |
| Shock | 0/56 (0.0%) | 0/20 (0.0%) | | 2/49 (4.1%) | 2/109 (1.8%) | 2.224 (0.16; 0.69) |

Table 4. Summary of clinical signs and symptoms of all severe VCD episodes occurring after M13 in seronegative (NS1 Th9) subjects of any age classified as seropositive and seronegative by NS1 at M13 (threshold 9) - CYD14/CYD15/CYD23/57.

| | Seronegative Vaccine group | Seronegative Control group | Risk Ratio of seronegative CYD vs placebo (95% CI) | Seropositive Vaccine group | Seropositive Control group | Risk Ratio of seropositive CYD vs placebo (95% CI) |
|--|----------------------------------|----------------------------------|---|----------------------------------|----------------------------------|---|
| Number VCD episodes, n | 37 | 5 | | 31 | 44 | |
| Duration of clinical symptoms, days Median (min-max) | 10 (5-29) | 7 (6-10) | | 9 (4-15) | 10 (5-18) | |
| Duration of fever, days Median (min-max) | 4 (2-10) | 5 (3-7) | | 4 (2-7) | 5 (2-17) | |
| Hospitalized VCD episodes | | | | | | |
| Serotype 1, n | 14 | 4 | | 10 | 11 | |
| Serotype 2, n | 16 | 2 | | 8 | 17 | |
| Serotype 3, n | 6 | 0 | | 12 | 8 | |
| Serotype 4, n | 1 | 0 | | 1 | 8 | |
| Median duration of hospitalization, days (min- max) | 5 (1-8) | 4 (3-6) | | 5 (2-10) | 5 (3-11) | |
| Any haemorrhage | 29/37 (78.4%) | 4/5 (80.0%) | 0.980 (0.34; 3.84) | 22/31 (71.0%) | 34/44 (77.3%) | 0.918 (0.51; 1.62) |
| Any visceral manifestation | 1/37 (2.7%) | 0/5 (0.0%) | | 3/31 (9.7%) | 9/44 (20.5%) | 0.473 (0.08; 1.90) |
| Plasma Leakage | | | | | | |
| Any | 37/37 (100.0%) | 5/5 (100.0%) | 1.000 (0.39; 3.26) | 29/31 (93.5%) | 44/44 (100.0%) | 0.935 (0.56; 1.53) |
| With clinical signs | 6/37 (16.2%) | 0/5 (0.0%) | | 6/31 (19.4%) | 19/44 (43.2%) | 0.448 (0.15; 1.17) |
| Hematocrit increase \geq 20% | 37/37 (100.0%) | 5/5 (100.0%) | 1.000 (0.39; 3.26) | 27/31 (87.1%) | 38/44 (86.4%) | 1.008 (0.59; 1.70) |
| Thrombocytopenia | | | | | | |
| Platelet count \leq 50x10 ⁹ /L | 25/37 (67.6%) | 1/5 (20.0%) | 3.378 (0.55; 138.71) | 17/31 (54.8%) | 31/44 (70.5%) | 0.778 (0.40; 1.45) |
| Platelet count \leq 100x10 ⁹ /L | 37/37 (100.0%) | 5/5 (100.0%) | 1.000 (0.39; 3.26) | 29/31 (93.5%) | 44/44 (100.0%) | 0.935 (0.56; 1.53) |
| Shock | 3/37 (8.1%) | 0/5 (0.0%) | | 4/31 (12.9%) | 1/44 (2.3%) | 5.677 (0.56; 279.60) |

Among hospitalized VCD cases in subjects 9-16 and 2-8 years of age, the median duration of fever, symptoms and hospitalization were comparable between cases in the seronegative vaccine and seronegative control groups. A pattern of increased frequency of plasma leakage and severe thrombocytopenia (platelet count $<50 \times 10^9/L$) was observed in the seronegative vaccine group compared to the seronegative control group, with the seronegative vaccine group exhibiting similar features as the unvaccinated seropositive group.

5.7 Possible Reasons for the excess cases of severe dengue in the vaccinated seronegative population

It is clear, from the analyses summarised above, that the vaccine causes seronegative recipients to be at higher risk of hospitalised and severe dengue than unvaccinated controls. A plausible hypothesis is that the vaccine acts as a silent infection, so that the first breakthrough natural infection in seronegative recipients is then “secondary-like”, with an associated higher chance of severe disease. This hypothesis is illustrated in the Figure 12 below and is what was assumed in the mathematical modelling undertaken for the original SAGE consideration of CYD-TDV. However, other mechanisms of action are possible, and there is no definitive explanation of the excess risk as yet. Of note, it is not the vaccine itself that causes excess cases, but rather that the vaccine induces an immune status that increases the risk that subsequent infections be more severe.

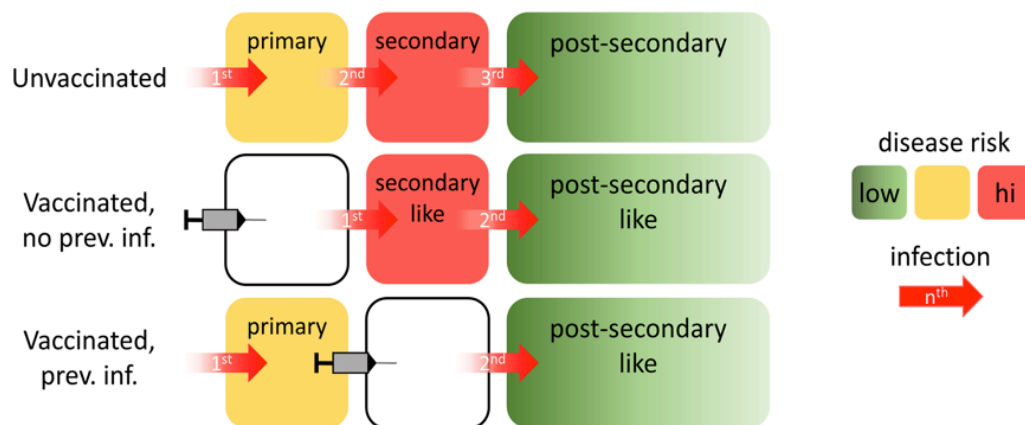


Figure 12. Plausible explanation for the excess cases of severe dengue in vaccinated seronegative individuals.

Image from: Flasche S, Jit M, Rodriguez-Barraquer I, Coudeville L, Recker M, Koelle K, et al. The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. *PLoS Med.* 2016;13:1–19. doi:10.1371/journal.pmed.1002181.

An excess risk of severe dengue in seronegative recipients was seen in all age groups, but was more pronounced in trial participants below the age of 9 years. Vaccine efficacy was higher in the older age groups, and the onset of the increased relative risk for hospitalized dengue in seronegatives started later in older children. Previous studies of the natural history of dengue suggest that younger children are more susceptible to more severe infection, perhaps due to higher capillary fragility in younger age groups(10). The relative risk of severe dengue was most pronounced in year 3 after the first dose of vaccine. The fact that vaccination of seronegative individuals may represent an attenuated subclinical primary infection means that in the efficacy trials, such a primary infection has been temporally clustered in vaccinated individuals due to the condensed enrolment periods of the trials, whereas subjects who received the placebo are exposed to a primary wild-type infection over a longer period of time(11).

6. NON-DENGUE SERIOUS ADVERSE EVENTS STRATIFIED BY SEROSTATUS

An overview on safety data was published in 2016(12). In the pooled analysis of safety that included subjects aged 9-60 years, the serious adverse events (SAEs) reported mostly corresponded to common medical conditions expected in each age group. There was no evidence of any excess of any SAEs attributable to vaccination.

Non-dengue SAE were re-analyzed stratified by serostatus, and are presented in Table 5. There is no evidence of an excess risk in either seronegative or seropositive vaccinated participants.

Table 5. Non-dengue SAEs in CYD14 (2-14Y) and CYD15 (9-16Y) from day 0 to year 5 by baseline dengue serostatus defined by measured PRNT₅₀ in immunogenicity subset.

| Baseline serostatus | Adverse event | CYD14 % (95%CI) | | CYD15 % (95%CI) | |
|---------------------|---------------|---------------------|---------------------|---------------------|----------------------|
| | | CYD | Control | CYD | Control |
| Seronegative | SAE | 11.5% (8.7,15.0) | 14% (9.6,19.3) | 11.2% (7.7,15.7) | 10.7% (6.3,16.9) |
| | Fatal SAE | 0% (0.0,0.9) | 0% (0.0,1.7) | 0% (0.0,1.4) | 0% (0.0,2.4) |
| Seropositive | SAE | 11.7% (9.6,13.9) | 10.1% (7.5,13.3) | 11.4% (9.5,13.4) | 12.9% (10.1,16.1) |
| | Fatal SAE | 0.1% (0.0,0.6) | 0.0% (0.0,0.8) | 0.5% (0.2,1.1) | 0.6% (0.1,1.7) |

Virologically confirmed dengue reported as dengue fever SAE are removed from the analysis.

The Clopper-Pearson method is used for the 95% CI for a single proportion.

Dengue non-immune subjects at baseline are defined as subjects with titers < 10 (I/dil) against all four serotypes at baseline.

Dengue immune subjects at baseline are defined as subjects with titers ≥ 10 (I/dil) against at least one dengue serotype at baseline.

6.1 Adverse events of special interest

The following adverse events of special interest (AESIs) have been defined by the manufacturer for CYD: allergic reactions within 7 days after vaccination, acute viscerotropic or neurotropic disease (AVD, AND) with 30 days after vaccination, and serious dengue disease at any time during the study.

No immediate anaphylactic shock has been reported post-vaccination. Five subjects receiving CYD have experienced a serious potential allergic reaction: 4 subjects with asthma/asthmatic crisis (all had medical history), and 1 urticaria (with history of allergic rhinitis). In the placebo group, there was one serious adverse event suggestive for allergic reaction (asthma in a subject with a history of asthma).

As CYD-TDV is based on YF vaccine backbone, the risk of very rare severe reactions associated with YF vaccine was monitored during its clinical development for YF vaccine-associated viscerotropic disease (YFV-AVD) and YFV vaccine-associated neurotropic disease (YFV-AND).

YFV-AVD: clinical signs and symptoms resemble those of wild-type yellow fever infection and disease and include a rapid onset, within 2-5 days of vaccination after first vaccination after yellow fever vaccine. Laboratory confirmation is usually required to fulfill the case definition of AVD. Large amounts of yellow fever viral antigen are found in the liver, the heart and other affected organs(13).

YFV-AND: three categories of YEL-AND can be distinguished: 1 - encephalitis, 2 - neurotropic auto-immune disease with central nervous system involvement, 3 - neurotropic auto-immune disease with peripheral nervous system involvement. The median of onset is 11 days (range from 2 to 23 days) after yellow fever vaccination.

There have been no confirmed AVD or AND cases in any of the >30,000 trial participants to date.

6.2 Pregnancy

In the licensed indication, pregnancy and lactation are contraindications. A total of 615 pregnancies (404 in the CYD group and 211 in the placebo group) were reported from all CYD dengue vaccine trials (SP personal communication). They were mainly reported during CYD15. Among the 404 pregnancies reported in the CYD group, 22 pregnant women were inadvertently exposed to CYD-TDV (i.e. vaccinated 7 days after LMP or 7 days before estimation of conception or later during pregnancy). Of these, 17 resulted in a live birth, 1 resulted in an abortion (spontaneous and unspecified), 1 resulted in elective termination, 1 still birth, 1 death in utero, and 1 unknown. Of 211 pregnancies reported in the placebo group, 12 pregnant women were exposed, of which all 12 resulted in a live birth. An update of pregnancy analyses will be performed at the end of the hospital phase.

7. IMMUNOGENICITY BY SEROSTATUS

In vaccinees seropositive before vaccination, neutralizing antibodies titres were higher following vaccination compared to the seronegative vaccinees. The Geometric Mean Titres (GMTs) measured by the PRNT₅₀ assay increased mainly after the first dose among participants who were seropositive at baseline; however, a more gradual increase after each dose was observed for serotypes 1–3 among those who were seronegative (14). The GMTs post-dose 3 for serotypes 1–4, respectively, were 580, 741, 827 and 341 for participants who were seropositive at baseline and 34.6, 101, 174 and 119 for those who were seronegative (Figure 13). After the third injection, serotype-specific seropositivity rates were 94.2% or higher, and 100%, 98.6% and 93.4% of participants were baseline seropositive for at least 2, at least 3 and all 4 serotypes, respectively. A lower seropositivity rate for all 4 serotypes was observed in seronegative participants (77.9%) compared with those who were seropositive (97.6%).

The PRNT₅₀ assay does not allow for reliable differentiation between monotypic and heterotypic (temporarily cross-protective) antibodies, hence all the GMT titres may be a mixture of long-lasting monotypic and transient heterotypic antibodies, neutralizing and non-neutralizing antibodies. Statistical analysis suggested that dengue serotype 4 (DENV4) was immunodominant after the first dose (15). No correlate of protection for dengue has been established to date, although some correlation has been described between vaccine-induced neutralizing antibody titres and protection from VCD for a given serotype (16, 17).

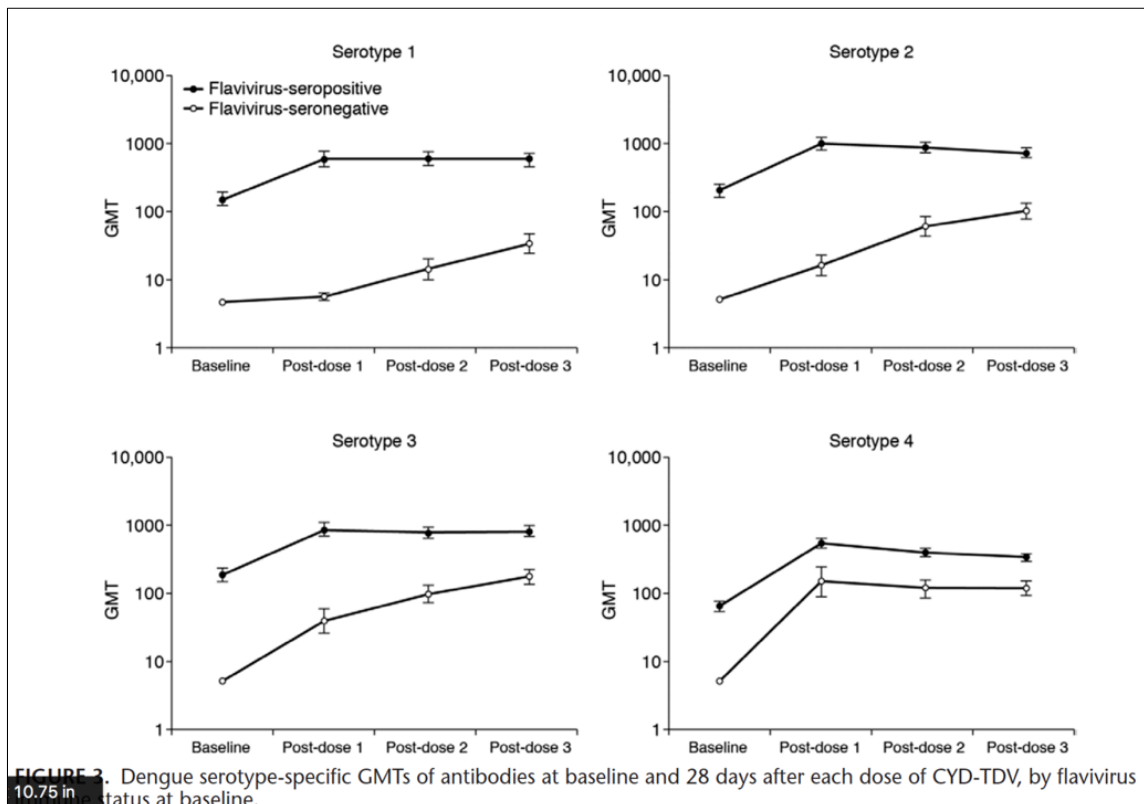


Figure 13. GMTs after one, two and three doses by serotype and serostatus in subjects 9-16Y in Latin America (extracted from (14)).

7.1 Persistence of Immunogenicity by serostatus

GMTs remained higher in seropositive participants aged ≥ 9 y than those aged <9 y throughout follow-up of 3 years as reported by Vigne et al (18). Dengue neutralizing antibody persistence data in 2 studies (CYD22 and CYD28) with longer follow-up to 4 y post-dose 3 (Year 4 of follow-up) also show that GMTs remain 1.2–3.2-fold higher than baseline.

In summary, in seropositive subjects immunogenicity appears to be as high after one dose as after 3 doses. This fits with findings in the Phase III trials that VE between the first and second dose, and second and third doses, was similar to VE after the third dose, in the overall trial population. However, no long-term efficacy data for one or two dose schedules exist because the compliance rates (e.g. completion rate of 3 doses) was very high in the trials. There is an urgent need to study one or two dose vaccination schedules in order to enhance the programmatic use of CYD-TDV.

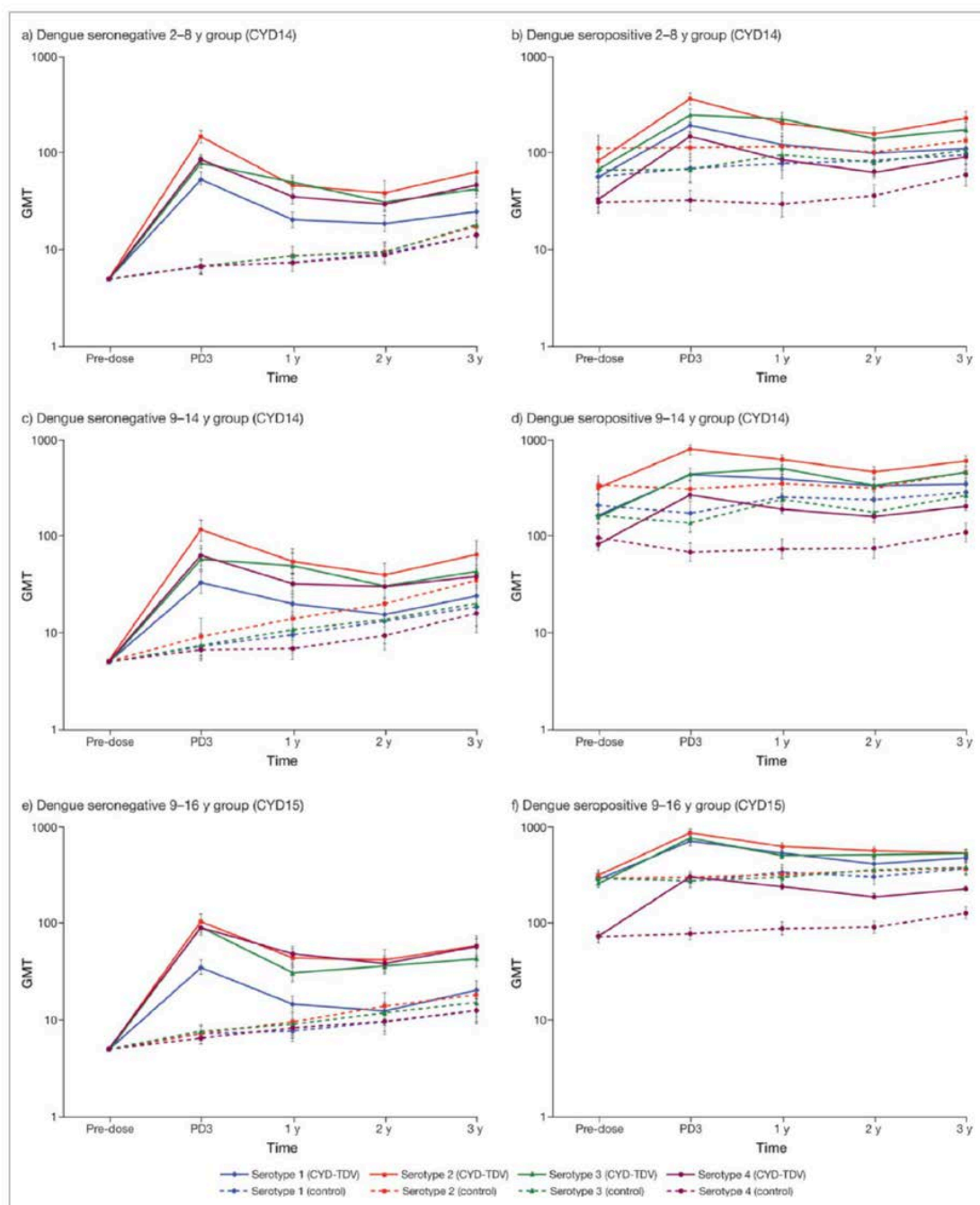


Figure 14. GMTs (95% CI) for each dengue serotype over time (years after the last dose) in children aged 2–8 y or ≥ 9 y in the CYD14 and CYD15 studies, as extracted from (18).

8. POPULATION BENEFIT VERSUS INDIVIDUAL RISK

The new NS1 assay-based data confirms previous findings that, overall, vaccinated trial participants had a reduced risk of virologically-confirmed dengue disease, hospitalizations due to dengue, and severe dengue. Trial participants who were inferred to be seropositive at the time of first vaccination had a durable protection against hospitalized and severe dengue during the 5-year observation period. However, trial participants who were inferred to be seronegative at time of first vaccination had, overall, a significantly higher risk of hospitalized and severe dengue compared with unvaccinated participants, regardless of age at time of vaccination, although some age effect was still observed. The risk persisted over the trial follow up period of about 5 years after the first dose.

The cases of hospitalised and severe disease in seropositive subjects substantially outnumbered those precipitated in seronegative participants. A trade-off therefore exists between the population benefit conferred by vaccination, and the enhanced risk experienced by a subset of seronegative vaccine recipients.

The population and individual impacts of a dengue vaccination programme – on the expected incidence of hospitalized/severe dengue cases – depends primarily on three factors:

- (1) The level of dengue seroprevalence in the target age group for vaccination: this determines the proportion of vaccine recipients who will be seropositive when they receive vaccine, but is also an indicator of the level of dengue exposure in the population.
- (2) The level of dengue incidence that can vary significantly from year-to-year.
- (3) The time horizon considered for assessing the impact of vaccination.

Based on the incidence in the epidemiological settings of the trials (which spanned a range of moderate to high transmissions settings), for persons aged 9 years and above, the new analysis indicates that the 5-year risk of severe dengue in vaccinated seronegative persons (4.04 per 1,000 seronegative persons vaccinated) is similar to the risk of severe dengue in unvaccinated seropositive persons (4.8 per 1,000 seropositive persons unvaccinated). The risk of severe dengue is lower in unvaccinated seronegative persons (1.7 per 1,000 seronegative persons unvaccinated). The risk of severe dengue in vaccinated seropositive persons is the lowest (less than 1 per 1,000 seropositive persons vaccinated). Thus over 5 years, there was a reduction of about 15 cases of hospitalized dengue and 4 cases of severe dengue per 1,000 seropositive persons vaccinated (Table 2 above). For 1,000 seronegative persons vaccinated, there was an increase of about 5 cases of hospitalized dengue and 2 cases of severe dengue.

The similar incidence of hospitalized and severe dengue in vaccinated seronegative trial participants and unvaccinated seropositive participants is consistent with the hypothesis that vaccination in seronegative individuals causes a primary-like infection.

Since dengue incidence varies substantially by geographic setting and over time, it is difficult to translate these absolute estimates of incidence reduction into predictions of programmatic impact in particular settings without using mathematical models. However, given that approximately 80% of trial participants were seropositive, we can estimate the averted numbers if 1,000,000 children over 9 years of age were vaccinated with the same distribution of ages (>9) in the settings as seen in the trials.

If 1,000,000 children were vaccinated under such settings:

- 11,000 hospitalized dengue cases would be averted (12,000 averted in seropositives, 1,000 excess cases in seronegatives)
- 2,800 severe dengue cases would be averted (3,200 averted in seropositives, 460 excess cases in seronegatives).

Dynamic transmission models are required to predict the potential population and individual impacts of vaccination programmes in a wider range of transmission settings, or for a period longer than 5 years. The NS1 antibody assay study provided the opportunity to revisit modelling analyses originally undertaken by eight WHO-coordinated modelling groups in 2015. These models were fitted to the phase III trial data and all models made the assumption that the vaccine acts as a 'silent' first infection, leaving seronegative vaccinated individuals at increased risk of severe dengue when they experience their first natural dengue infection, but at very low risk thereafter (having effectively had two infections). In contrast, unvaccinated seronegatives are at low risk of severe dengue disease when they experience their first natural infection, then have an increased risk of severe dengue when they experience a second infection, and at very low risk thereafter. Thus, vaccination brings forward the risk period for severe dengue (associated with a natural second infection) but does not increase the lifetime risk of severe dengue except in low transmission settings where not everyone is likely to experience two natural dengue infections in their lifetime.

However, from an individual perspective, an important consideration is that the period of risk experienced by seronegative vaccine recipients precedes the hypothesised period of eventual benefit. This ordering has the consequence that the rare individual who experiences fatal severe dengue infection during the period of risk has, mathematically speaking, no opportunity to benefit later. 'Bringing forward' a period of enhanced risk of severe dengue disease therefore may potentially increase overall life-years lost from dengue disease, even if overall numbers of deaths stay constant or even decline.

Whether seronegative vaccine recipients eventually benefit from vaccination depends on the transmission intensity of dengue in their residence location. In high transmission settings, the great majority of people experience two natural dengue infections, and furthermore, mass vaccination in such settings is predicted to cause small reductions in dengue transmission (due to the large impact of vaccination in seropositive recipients) which will benefit seronegative recipients. In addition, the time-period between infections reduces as transmission intensity increases, so the expected long-term benefit of vaccination in seronegatives will be seen sooner in very high transmission settings than in lower (but still high) transmission settings. However, it should be emphasised that the new data still do not validate the assumption that seronegative vaccinees who experience a first natural infection are thereafter at very low risk of severe dengue (akin to an unvaccinated individual who has experienced two natural infections); we have only seen the period of enhanced risk so far in trial data up to 66 months.

Preliminary and still unpublished work independently undertaken by the modelling groups at Sanofi Pasteur and Imperial College indicate that the new data provides new evidence of age-specific effects of vaccination, independent of serostatus. Fitting models to the new data, risk enhancement in seronegative recipients is estimated to be higher in younger age groups (particularly those below the age of 5) than in older age groups (though is present in all age groups), while vaccine efficacy in seropositive recipients is estimated to be higher in older age groups (>9 years) than in younger groups. However, this age-dependence makes relatively little difference to predicted impacts of vaccination in 9 year-old or older children, or to conclusions about population versus individual benefits of mass vaccination.

9. ETHICAL CONSIDERATIONS

The ethical tension between personal and population benefit in vaccination programmes is not new. Vaccines are given to healthy members of society to prevent illness, and thus the tolerance for vaccine adverse events is very low. Vaccines, like all medical products, are associated with some individual risk, even if generally extremely low, and greatly outweighed by the benefits to both individuals and communities. In the case of conflict between the goal to promote societal benefit and the goal to promote individuals' interests/wellbeing, neither goal should be thought to supersede, or have absolute priority over the other. It is widely accepted that it might sometimes be ethically appropriate to take actions that compromise the wellbeing or interests of individuals (i.e. put individuals at some level of risk) when necessary to promote the greater good of society; but it is also widely accepted that it would be inappropriate to compromise individuals' interests and wellbeing *whenever* this would be necessary to benefit population health. The relative magnitude of societal benefits and individual risks is an important consideration when evaluating the acceptability of added risk, together with other key considerations such as public acceptance. For example, it is known that rotavirus vaccination is associated with a very small risk of inducing intussusception, but this is greatly outweighed by the protective effective effect of the vaccine against severe rotavirus disease.

Although in high dengue transmission settings both the population and individuals may eventually benefit from vaccination, it is important to note that there are no data from the trials yet showing the long-term benefit to seronegatives. Even if there is such long-term benefit, other issues related to the timing and cause of risk/harm that might make population-based dengue vaccination programmes ethically problematic and have adverse implications for trust and the long-term success of public health programmes. While most vaccinated individuals (and population health in general) might be expected to ultimately benefit from mass vaccination in high transmission settings, it is easy to imagine scenarios where some cases of severe dengue that result would end up (rightly or wrongly) getting attributed to the vaccine—and thus damage the reputation of the vaccine programme.

Furthermore, an important difference from the rotavirus vaccine cited above, is in that situation it is not possible to predict which vaccinated children will develop intussusception (or indeed who will have a case of severe rotavirus disease averted), but with respect to the dengue vaccine, it is possible to identify a subgroup of the those vaccinated (the seronegative) who will be at increased risk of severe dengue (at least the short-term), even though with current diagnostic tests it may be programmatically difficult to vaccinate large populations while at the same time ensuring that seronegatives are not vaccinated.

Testing and vaccinating only seropositive individuals is also not without ethical tensions. This strategy avoids risk of harm to seronegatives and promotes population health. However, questions of feasibility to develop a sensitive and specific rapid test as well as cost-effectiveness may mean that the vaccine cannot be used for several years; thus, there would be a cost in terms of forgone benefits for seropositives, and the entire community in high transmission settings, if vaccination was delayed.

Some ethicists have drawn a distinction between harms resulting from acts (e.g. harms resulting from vaccinating someone—i.e. the harms to seronegatives vaccinated), and those resulting from omission (e.g. harms resulting from not vaccinating someone—i.e., the harms to seropositives not vaccinated). If a medical product causes harm, someone can be sued. There is less obvious liability if someone doesn't get the product. But there is no widely accepted absolute ethical principle according to which harms from acts outweigh harms from omissions, or where the balance between these two harms lies (i.e. how many cases must be prevented for every case induced). It can

be argued that if one can bring about the prevention of a harm and fails to do so, that can arguably be worse than actively bringing about harms of smaller magnitude, but what the ratio of those harms should be is uncertain.

Much depends on whether the harms in question are avoidable—and thus, in context of dengue vaccine, whether a suitable serological test exists. If it is not feasible and cost effective to test, then would mass vaccination necessarily be wrong (in high prevalence settings) given that no individuals/groups who are (in practice) identifiable would be harmed as a result? As present, most doubt that testing would be feasible in the short-term. At some point in the future, it is hoped that better tests will become available—and relevant research and development appears to be in progress. Thus, perhaps a key question is whether testing is practical logistically and economically in the context of immunization programs.

10. PROGRAMMATIC CONSIDERATIONS

To maximize the public health benefit and minimize harm to individuals, the WG considered two strategies – the population seroprevalence criteria without individual screening and pre-vaccination screening. The WG considered the advantages and disadvantages of each strategy, including programmatic considerations and achievable vaccine coverage.

10.1 Population seroprevalence criteria

The rationale for this strategy is that vaccination based on high seroprevalence criteria would result in a substantially larger number of severe and hospitalized dengue cases prevented in seropositive individuals than the number of excess cases resulting from priming seronegatives through vaccination. In this strategy, first a population survey would be undertaken to identify areas where seroprevalence thresholds are high enough to maximize public impact and minimize harm, followed by a mass vaccination targeted towards an optimal age.

10.1.1 Population serosurveys to determine seroprevalence

There are multiple sources of epidemiologic data that could be used as evidence of high pre-existing immunity to dengue, such as nationally representative surveillance data. However, surveillance data alone can be unreliable, as clinically apparent cases represent a variable fraction of all dengue infections, typically estimated to be around 25%, healthcare seeking for dengue can vary greatly based on access to care, and outbreaks may occur in low seroprevalence areas. Because surveillance data can be unreliable, population-based seroprevalence studies are the only way to reliably measure the proportion of seropositive individuals in a population.

Serosurveys are needed to determine seroprevalence rates. A serosurvey involves collecting and testing blood specimens from a defined population to estimate the proportion positive for DENV immunoglobulin G (IgG) antibodies as a measure of population immunity. Age-stratified serosurveys should be recent (within the last 3–5 years) in a geographically relevant location and capturing the likely vaccine target age range.

WHO has provided recommendations on designing and implementing cross-sectional serosurveys to estimate age-specific dengue seroprevalence: “Informing vaccination programs: a guide to the design and conduct of dengue serosurveys” (http://www.who.int/immunization/research/development/Dengue_Serosurveys_020617.pdf). This guidance document includes recommendations for methods for planning and conducting serosurveys, including

survey design, specimen collection, laboratory testing, data analysis, and the interpretation and reporting of results.

10.1.2 Considerations for serosurveys to determine population seroprevalence

Introducing CYD-TDV in high seroprevalence settings could maximize the public health and follows other models for subnational vaccinations programs based on incidence (e.g. TBE, cholera). However, a potentially identifiable subpopulation of seronegatives will experience harm, despite the overall significant population level benefit. The decision on the cut-off of such seroprevalence thresholds will depend not only on the optimal seroprevalence for public health impact, but also on the risk perceptions, public confidence and communication strategies. Higher seroprevalence thresholds, e.g. 85%, may be considered more acceptable to policy makers and the public. However, with higher seroprevalence thresholds, the parts of the country suitable for vaccination becomes smaller, and the effort required to conduct serosurveys to identify these populations, becomes larger.

Mathematical modelling predicts that even seronegative individuals would benefit from vaccination in as little as 6 years in very high transmission settings where >90% of 9 year-olds would be expected to be seropositive. However, dengue transmission intensity maps (<https://mrcdata.dide.ic.ac.uk/dengue/dengue.php>) derived from serological and age-specific reported dengue incidence data suggest that no country would meet such a high threshold for transmission intensity by the age of 9. Eventual positive benefits of vaccination in seronegatives are still expected, based on the modelling, in slightly lower transmission settings but such benefit takes longer to be seen. However, even if a 10-year timescale for evaluating benefits is used, modelling indicates that vaccine should only be used in settings where seroprevalence in 9 year-olds exceeds 80%. Such a high threshold would effectively exclude the great majority of dengue endemic countries from vaccine introduction. Table 6 shows how the seroprevalence threshold varies with the target age for vaccination. If one chooses 80% for 9 year olds, then conservatively one would want to pick ~90% for 16 year olds in order to be fairly confident that seronegative recipients would benefit within 10 years.

Table 6. Optimal target age in relation to seroprevalence thresholds for predicted benefit in seronegative recipients within 10 years (Table provided by Neil Ferguson, Imperial College)

| Target age for vaccination (years) | Seroprevalence in target age group required (model incorporating best-fit age-specific vaccine effects) | Seroprevalence in target age group required (model with more limited age-specific vaccine effects) |
|------------------------------------|---|--|
| 9 | 80 | 80 |
| 10 | 81 | 83 |
| 11 | 82 | 86 |
| 12 | 82 | 88 |
| 13 | 83 | 90 |
| 14 | 85 | 92 |
| 15 | 87 | 93 |
| 16 | 88 | 94 |
| 17 | 90 | 95 |
| 18 | 91 | 96 |

Dengue transmission intensity shows marked geographic heterogeneity even over relatively small distances (a few km) driven by environmental and socioeconomic factors(19). Hence, decisions to introduce vaccination based on transmission intensity exceeding a fixed threshold need to be made at subnational level. Seroprevalence data are not currently available in any country at the relatively fine level of geographic resolution that is required to ensure that we minimize harm to seronegative individuals. Large-scale serosurveys with relatively complex sampling designs would be needed characterize transmission intensity (e.g. seroprevalence in 9 year-olds above 80%) at fine geographic scales. It is therefore possible that the cost of implementing rigorous population serosurveys may exceed that of a “screen and vaccinate “ strategy. Limiting vaccination introduction to small-scale areas within a country that meet the a seroprevalence cut-off (in 9 year-olds) of between 80% and 90% will also likely result in very low overall vaccine coverage, and hence a low population impact of vaccination.

Figure 15 shows some seroprevalence settings in different countries to illustrate the wide variation between countries by age stratification.

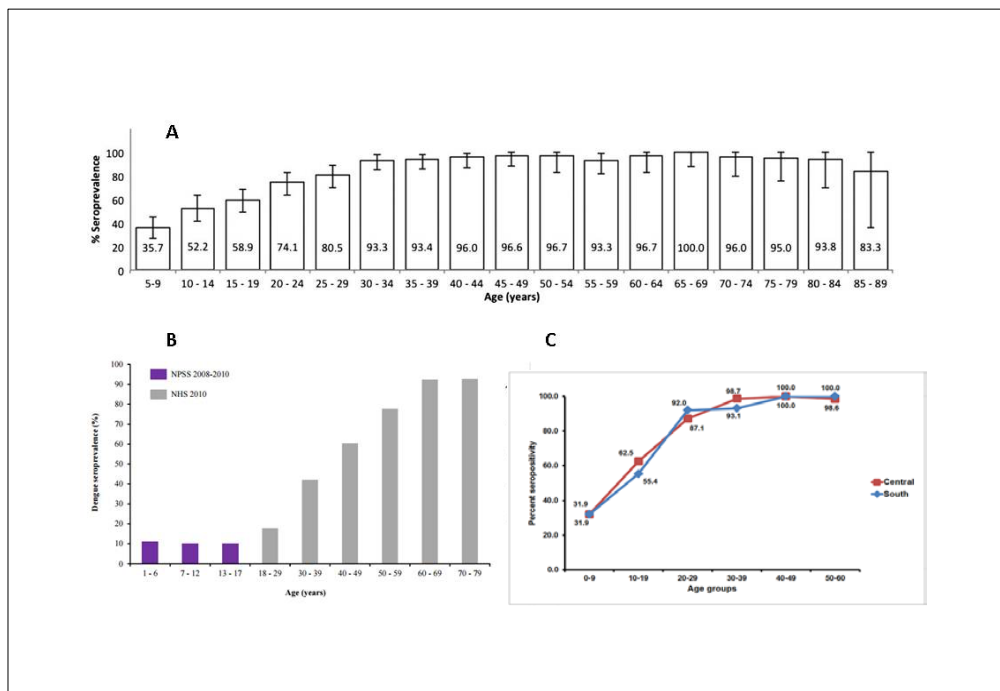


Figure 15. Examples of seroprevalence by age from localities in A) Mexico (20), B) Singapore (21), and C) Thailand (22).

Figure 16 illustrates the extent of spatial heterogeneity within a country, with Brazil as example.

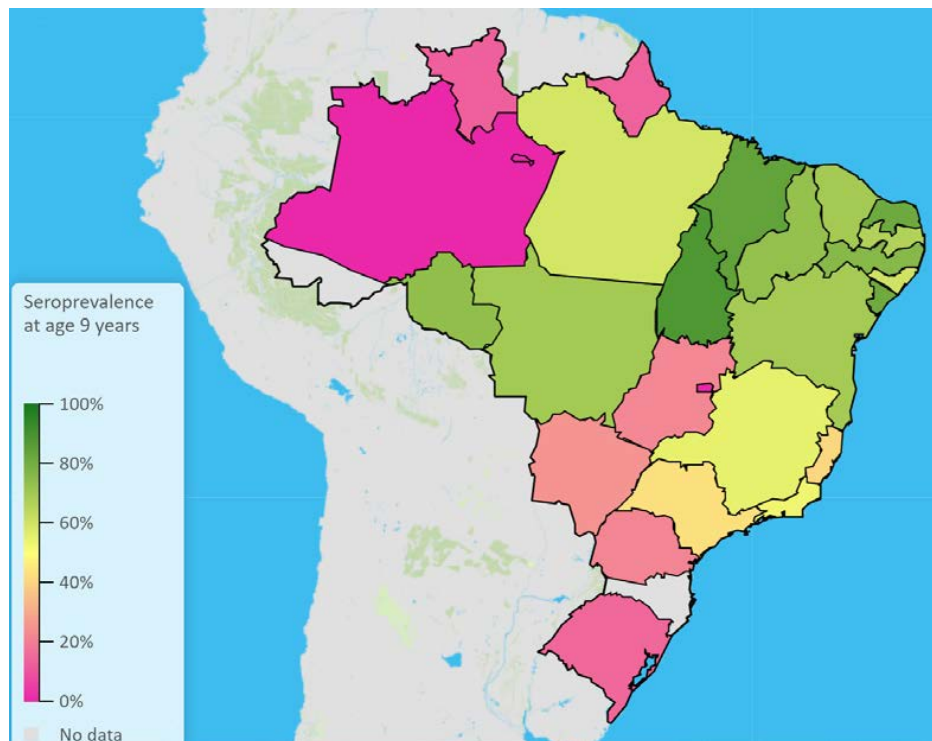


Figure 16. Spatial heterogeneity of seroprevalence at age 9 years in Brazil (Source: <https://mrcdata.dide.ic.ac.uk/dengue/dengue.php>)

For countries where sufficient surveillance data were available, a preliminary assessment was made of the likely proportion of the population that would be eligible for vaccination using seroprevalence criteria (>80%) versus a “pre-vaccination screening” strategy. This assumed that seroprevalence thresholds and consequent mass vaccination decisions would be made at the first administrative unit level (admin 1) within individual countries. From Table 7, it can be seen that no level 1 administrative unit in a selected list of dengue endemic countries listed would be expected to reach a threshold of 90% seroprevalence in 9 year-olds, and that even with 85% or 80% thresholds, expected vaccine coverage would be much lower than might be achieved with an individual test-and-vaccinate policy.

Table 7. Preliminary assessment of predicted coverage of mass-vaccination with seroprevalence threshold versus screen-and-vaccinate policies for countries with dengue force of infection estimates for 5 or more admin 1 units, based on unpublished data. Seroprevalence estimated from force of infection estimates derived from routinely reported age-specific dengue case incidence data. Denominator is total population of admin 1 units for which data were available to estimate force of infection (provided by Neil Ferguson, Imperial College, UK)

| Country | Number of admin1 units | Proportion of admin 1 units with data available to allow estimation of force of infection | Predicted coverage* with 80% seroprevalence threshold in 9 year-olds applied at admin 1 level | Predicted coverage* with 85% seroprevalence threshold in 9 year-olds applied at admin 1 level | Predicted coverage* with 90% seroprevalence threshold in 9 year-olds applied at admin 1 level | Predicted coverage* with screen and vaccinate policy |
|--------------------|------------------------|---|---|---|---|--|
| Brazil | 27 | 93% | 7% | 1% | 0% | 50% |
| Colombia | 32 | 88% | 4% | 0% | 0% | 64% |
| India | 36 | 19% | 44% | 17% | 0% | 64% |
| Mexico | 32 | 84% | 0% | 0% | 0% | 24% |
| Philippines | 81 | 69% | 17% | 1% | 0% | 67% |
| Thailand | 77 | 94% | 0% | 0% | 0% | 57% |
| Venezuela | 25 | 96% | 59% | 24% | 0% | 79% |

* proportion of 9 year-olds receiving vaccine

10. 2. Pre-vaccination screening strategy

Screening and vaccinating those tested seropositive offers the potential of retaining much of the benefits of vaccination for seropositive individuals while largely eliminating the risks experienced by seronegative recipients. Such “screen and vaccinate” strategies are not entirely new, with test-based targeting having also been undertaken in some populations for Hepatitis B, BCG and other vaccines. A pre-vaccination screening strategy involves the use of a rapid diagnostic (or screening) test to determine dengue serostatus. Those with a documented history of laboratory confirmed dengue would not need to be screened.

10.2.1 Screening tests

Various tests that can be used to determine serostatus; each test has its advantages and disadvantages. The test with the highest sensitivity and specificity to diagnose seropositivity would be the desirable option. Low sensitivity would result in missing truly seropositive persons; while low specificity would lead to falsely classifying seronegative as seropositive persons. Hence, low sensitivity would decrease the benefit of the vaccine in truly seropositives, low specificity would increase the potential harm. To facilitate programmatic use, the test should be simple and at point of care, and should be affordable.

Table 8. Overview of diagnostic tests that could be used for screening for serostatus

| Diagnostic Test | Advantage | Disadvantage |
|--|---|--|
| Plaque reduction neutralisation test (PRNT) | <ul style="list-style-type: none">• PRNT is specific for detecting dengue specific seropositivity | <ul style="list-style-type: none">• Time-consuming• Expensive• Requires high level of expertise and for these reasons, it has remained a research tool |
| Dengue immunoglobulin G (IgG) enzyme-linked immunoassay (ELISA) | <ul style="list-style-type: none">• Anti-DENV IgG ELISA is relatively fast (2-3 hours)• inexpensive (\$4-10 USD/test). | <ul style="list-style-type: none">• Lab-based assay, so screen and vaccinate policy would require separate visits for testing and vaccination• Cross-reactivity |
| Rapid diagnostic tests (RDT) for point-of-care tests (POCT) | <ul style="list-style-type: none">• Results within half an hour | <ul style="list-style-type: none">• Suboptimal sensitivity and/or specificity currently less than PRNT or ELISA |

Dengue IgG ELISA

Although PRNT assays were used in the Sanofi Pasteur clinical trials and are viewed as the current gold standard for dengue serological testing, they are time-consuming, expensive and require expertise, and are therefore limited to research settings. IgG ELISA is comparable to PRNT with high sensitivity and specificity of 91% and 98% respectively(23) (study done prior to the emergence of Zika as a public health problem in dengue endemic countries in Latin America). Dengue IgG ELISA requires taking a venous blood sample to obtain serum, about 2.5 hours of laboratory time, excluding the time for sample transportation to the laboratory and reporting results to

the clinician. ELISAs are formatted such that multiple specimens are tested simultaneously thus laboratories often batch samples before starting an ELISA. Hence, the lag time between the availability of IgG ELISA result to the clinician (and the individual) is usually at least a day, more often a week. Therefore, dengue IgG ELISA would require two visits before deciding whether or not to administer the first vaccine dose, thereby adding a level of inconvenience to the potential vaccinee and additional burden to the health care system.

Rapid diagnostic tests

Point-of care testing (POCT) using rapid diagnostic tests (RDT) provides the vaccine recipient a result within 15-30 minutes and can be done in an outpatient or outreach setting such as schools and care facilities using a finger prick sample. Thus a decision on vaccination eligibility can be determined during the same visit. POCT is the most feasible option to ensure a reasonable vaccine uptake, reduces outpatient visits and hence costs to the vaccinee and the health care system. Current POCTs generally have lower sensitivity and specificity than dengue IgG ELISA. However, this needs to be weighed up against the speed of testing, lower cost and accessibility outside specialized laboratories.

Cross-reactivity with available tests

Dengue IgG tests, both RDT or ELISA, could cross-react (i.e. give a false positive test result) with other flaviviruses, acquired through natural infection or vaccination(24). If a dengue IgG ELISA is to be used in areas where JEV or YFV vaccination occur, individual-level vaccine history should be collected and analyses should be stratified to assess for cross-reactivity in the assay. All comparisons of commercial diagnostic assays and evaluations of sensitivity and specificity for dengue IgG were done before Zika became a widespread problem. Hence, the extent of IgG cross reactivity in Zika endemic countries will need to be assessed in prospective studies. Dengue IgG will also be falsely positive in individuals that have already received a dengue vaccine.

Future prospects for RDTs

A number of RDTs were tested by Sanofi Pasteur, some of which exhibited favourable performance characteristics, but as of now, all have limitations due to either cross reactivity with other flaviviruses or due to modest sensitivity. The company is engaging with diagnostic test manufacturers to expeditiously develop, test and register one or more new tests for this indication.

To increase the sensitivity of dengue RDTs in detecting past dengue infection, several modifications could be contemplated, one of which would be 'recalibration' by changing the concentration of the IgG capture antigen and/or detection reagent to lower the limit anti-dengue IgG detection. For tests that also exhibit cross-reactivity with other flaviviruses, particularly Zika, other modifications must be considered to improve specificity.

Possibly 2 years might be required to develop, register, manufacture and deploy a suitable dengue RDT.

10.2.2 Optimizing the impact of a "pre-vaccination screening" strategy

If only a single round of screen and vaccinate is to be offered to each birth cohort, it will be optimal to target the age at which monotypic seroprevalence (the proportion of people who have experienced only one infection) peaks. Routine hospital surveillance data should be able to be used to identify this age group, since the secondary dengue infections are thought to be responsible for the great majority of severe dengue disease. Thus the age at which severe dengue disease incidence is highest will be approximately equal to the age at which monotypic

seroprevalence peaks. For maximal impact, vaccination age should be tuned at a subnational level, given the high level of spatiotemporal variation in dengue transmission intensity.

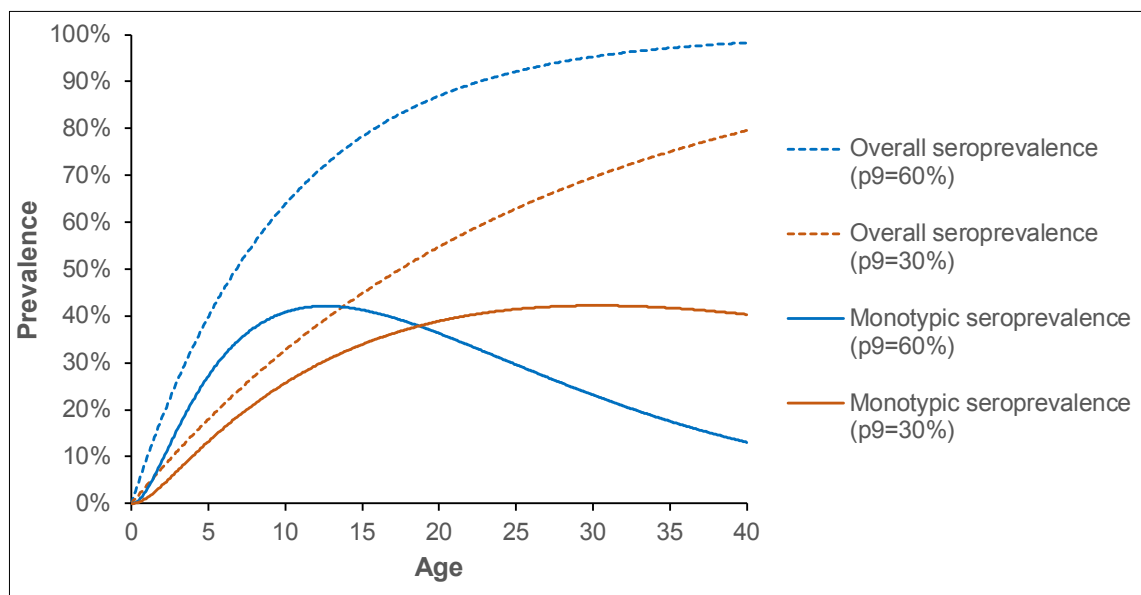


Figure 17. Illustrative profiles of overall seroprevalence (1 or more past dengue infection) by age (dashed lines) and monotypic seroprevalence (only one prior dengue infection) by age (solid lined) for two transmission settings, corresponding to seroprevalence in 9 year-olds of 60% (blue) and 30% (orange). Single round screen and vaccinated policies need to target the age of peak monotypic seroprevalence for maximal impact (Figure prepared by Neil Ferguson).

If multiple rounds of screen-and-vaccinate campaigns are envisaged to target single cohorts at multiple ages, the coverage will increase but so will the complexity of the programme. However, preliminary (unpublished) modelling suggests that a single round of screen-and-vaccinate per annual birth cohort can achieve similar levels of population impact in moderate or high transmission settings as mass vaccination might achieve in high transmission settings, if test sensitivity is high.

10.2.3. Communication with regards to pre-vaccination screening

Given that no assay will be 100% specific, occasionally truly seronegative individuals may be unintentionally vaccinated based on a false positive test result. Furthermore, although the efficacy against dengue infections in seropositive individuals is high, it is still not complete. Therefore transparent communication is needed to inform vaccinees that they may still be at risk of dengue and the need of adhering to other disease preventive measures.

10.2.4 Cost-effectiveness

Implementing individual level testing to determine past dengue infection with the objective to only vaccinate seropositive individuals is associated with added costs related to the diagnostic assay itself, the need for blood taking, waiting for the POCT result, or even adding a second visit to obtain the IgG ELISA result. Cost-effectiveness studies are needed to support countries' decisions to adopt a "screen and vaccinate" strategy.

10.2.5 Implementing the “pre-vaccination screening” strategy

Various settings could potentially be targeted.

Schools

Schools have a clear potential for population-based delivery and provide an opportunity to “screen and vaccinate” to increase coverage. School-based delivery strategies will likely lead to high vaccination coverage when there is high school attendance and either a strong school health system or a strong collaboration between the ministries of health and education. In general, countries need to be aware that school-based programmes tend to be more costly than health-facility based strategies and require significant preparation and coordination with school authorities. WHO has produced a School Vaccination Readiness Assessment Tool in relation to HPV vaccination: http://www.who.int/immunization/hpv/plan/school_readiness_assessment_tool_who_2013.pdf.

The current schedule of the CYD-TDV candidate vaccine (0/6/12 months) may necessitate (an) additional vaccination contact(s) in most programmes. While HPV or TT-containing vaccines could be co-administered based on age indication, there are currently no co-administration data. Thus, countries may elect to stagger HPV and CYD-TDV, either requiring new vaccination visits or targeting different age groups during the same campaigns. Experiences with new visits/school-based campaigns suggest substantial programmatic costs, unless integrated with existing school-based programs (<http://amp-vaccinology.org/activity/dengue-vaccination-program-toolkit>)

Health facility-based delivery

Health facility based HPV vaccine delivery to school age adolescents has been successful in several countries and could be considered for dengue vaccine. In general, health facility-based delivery in this age group has worked best in countries with fairly strong health systems.

Campaigns

Where the target age for the CYD-TDV vaccine is outside the school-age group, a possible option may be to deliver the vaccines through campaigns. Although many EPI programmes have significant experience with conducting large-scale and wide-age range campaigns with injectable vaccines (e.g. measles and Men A vaccines), there is limited experience with repeating such campaigns every six months. Other considerations for a campaign mode delivery include the added cost of *per diems* and other logistics, the additional trained manpower that may be needed, and the need to pay attention to how doses are recorded for individual vaccinees (especially those who may have missed the first or second waves of vaccination campaigns). Although the initial coverage may be high, with the build-up of new unvaccinated cohorts, issues of sustainability of the campaign approach will need to be addressed.

Outpatient settings

As all seropositive individuals with a reasonable likelihood of only having had one primary infection in the past will benefit from vaccination with CYD-TDV to reduce the risk of severe dengue during any subsequent wild type infection, private clinics, government clinics or any outpatient setting would provide opportunities for the individual use of CYD-TDV. Furthermore, patients with documented lab-confirmed past dengue infection could benefit from the opportunity to be vaccinated at outpatient settings.

Whether given at the health centre or through school-based campaigns or through campaigns, a three-dose vaccine given six months apart will require use of a vaccine registry maintained by the MOH and vaccination record for each vaccinee to ensure vaccinees receive all three doses. The majority of countries with dengue endemicity may need to build or strengthen such a tracking system.

Hospital settings

For patients hospitalized with laboratory confirmed dengue, vaccination with CYD-TDV could be offered at time of discharge. However, further studies may be needed to document that a very recent dengue illness (resulting in homotypic and heterotypic antibodies) does not suppress the immunogenicity of CYD-TDV.

Travel medicine settings

With increasing global travel including repeated travel to dengue endemic countries, travellers from dengue non-endemic countries may also increasingly have had a past exposure to a dengue infection. Such seropositive travellers may be concerned about repeat travel to a dengue endemic country for fear of severe dengue. However, the current 3-dose schedule renders the use of CYD-TDV in a travel medicine setting difficult, and the results of studies on alternative schedules would need to be available before this approach becomes more widely available. Furthermore, CYD-TDV is currently only registered in dengue endemic countries.

11. PLANNED POST-APPROVAL EVALUATION BY THE MANUFACTURER

The manufacturer has identified important areas for post-approval evaluation: YF vaccine-associated viscerotropic disease (AVD) and YF vaccine-associated neurotropic disease (AND), allergic reactions (including anaphylactic reactions), waning efficacy over time, co-administration with other vaccines, amongst others. Table 9 provides an update of the current status of studies to address these identified risks and research questions.

Table 9. Summary of Risk Management Plan (RMP) proposed by the manufacturer.

| Type of Activity | Description | Status | Planned date for final report submission |
|---|---|---|--|
| Post-marketing pharmacovigilance (PV) activities | Routine PV monitoring | Ongoing | N/A |
| | Evaluate capacity building/Expand AE reporting awareness /Training | | |
| | Enhanced safety surveillance | Ongoing | N/A |
| | Reinforce AE/safety information Exchange between MoH/MAH and independent review by WHO | | |
| Long Term Monitoring of Efficacy studies | Surveillance expansion CYD 14&CYD 15 5year FU post dose 3 for CYD14 & CYD 15 | Studies ongoing Yearly interim reports | Final reports: Q4 2018 (CYD 14) Q1 2019 (CYD 15) |
| | 5 year-FU post dose 3 for CYD 57 (follow-up of CYD23) | Study completed | Final report released in Q4 2016 |
| Active surveillance | DNG15.PASS-Cohort Event Monitoring | Ongoing | 2025* |
| | DNG16-PASS- Pregnancy registry | Planned to start in 2018* | 2023* |
| | DNG11: Background incidence rate of conditions mimicking viscerotropism and neurotropism | Completed | Final report released in Q4 2017 |
| Effectiveness studies § | CYD52 in Mexico (Yucatan) | Planned condition on mass vaccination campaigns | Dependent on study start |
| | CYD70 in Brazil (Goiana & Sao Paolo) | | |
| | CYD 53 in Malaysia | Planned to start in 2018* | 2023* |
| | CYD 69 in Philippines | | |
| Additional clinical studies | DNG10042 in Brazil (Parana) | Ongoing | 2020 |
| | Booster studies (CYD63, CYD64 and CYD65) | Ongoing | 2019 (CYD63 and CYD64), 2020 (CYD65) |
| | Study in clinically-stable HIV+ subjects in Latin America (CYD50) | Planned to start in 2019 | 2021, if starts in 2019 |
| | Co-administration studies (with HPV vaccines, Tdap) (CYD66, CYD67, CYD71) | Ongoing | 2020 |
| Risk minimization activities | Routine: Product Information Update | Submitted** | N/A |
| | Additional: Direct HealthCare Professional letter | Submitted/implemented | N/A |
| | HealthCare Professional guide | In preparation | |

* Study start and finish date may vary depending on the vaccine availability and introduction through mass vaccination programs, and other external factors

** This labelling update was submitted through a safety labelling variation (LCR F2017-724546 for CCDS version 4.0 dated 17 November 2017)

§ Effectiveness studies preceded by preparation studies: DNG25 in Mexico, DNG28 in Brazil, DNG13 in Malaysia

Vaccine schedules

A study was initiated to look at immunogenicity and safety in approximately 1,000 participants 9-50 years of age who received either 1, 2, or 3 doses of the vaccine, and a booster dose at 12-24 months after the last dose (NCT02628444). After the start of the study, the protocol was amended according to IDMC recommendations related to the results of additional exploratory analyses (NS1 study) in order to stop any further vaccination of seronegative individuals. Based on these recommendations, booster vaccinations are planned only in seropositive individuals, and the results will be presented only in seropositive subjects.

Co-Administration

Three Phase 3b, open-label, observer-masked co-administration studies have been identified as high priority given the indicated age range: HPV (tetraivalent and bivalent) and Tdap. These studies will assess the impact of co-administration on immunogenicity of each vaccine, as well as safety and reactogenicity. The initial clinical trial protocols of these 3 studies have been amended based on the recommendations from the IDMC after the review of the results of the additional NS1 studies. All subjects included in these trials have received at least one injection of the CYD-TDV. Baseline serostatus will be made available for all subjects included in the trials. Once the protocol amendment is approved, only the subjects assessed as seropositive for dengue before the first injection will proceed with the remaining injections. As a consequence, the number of subjects who will receive the 3 injections will be lower compared to the initial plan and the outcome of the studies could be only descriptive (as the number of subjects needed for statistical testing may not be reached). The three studies are currently on-hold and will resume once the protocol amendments, currently being reviewed by Ethics Committees and Health Authorities, are approved. This will have an impact on the availability of the results of the co-administration studies: the clinical study report describing the results obtained up to 28 days after the first injection in CYD66 (co-administration with Tdap) will be available in Q4 2018. The final clinical study reports of the three studies will be available in Q1 2020.

Booster dose

Two studies that capitalize on vaccinated recipients from previous Phase 1 and Phase 2 trials are mentioned under the RMP, one study in Asia in a low endemic region (CYD 63), and one in Latin America (CYD64) (Mexico, Honduras, Puerto Rico, Colombia and Brazil). Following a gap of 4-5 years after the primary series of CYD-TDV, a single booster dose of CYD-TDV or placebo will be assessed in terms of non-inferiority of the antibody response.

In interim results from the study conducted in Latin America (NCT02623725) among subjects 9-16 years of age, regardless of serostatus, non-inferiority of the immune response measured 28 days after the CYD dengue vaccine booster injection compared to the third injection of the primary series was demonstrated for each serotype and overall in interim results. The superiority of the booster injection compared to the third injection of the primary was demonstrated for serotypes 1, 2 and 4. This study demonstrated that the anti-Dengue neutralizing antibody levels measured 28 days after booster vaccination can reach levels at least as high as or higher than after the 3rd dose through the stimulation of immunological memory with a CYD-TDV dose 4-5 years after the standard 3-dose vaccination schedule.

Safety

In the study conducted in Latin America, the overall safety profile of the CYD dengue vaccine booster injection was comparable to the controls in terms of frequency, duration and severity of AEs (Coronel D, Garcia E, Rivera M, et al. Dengue Vaccine Booster in Healthy Adolescents and Adults 4 to 5 years after a 3-Dose Primary Schedule in Latin America. Poster presented at: XVII Congreso SLIPE; 2017 Nov 8-11; Cancun, Mexico)

12. SUMMARY OF CRITICAL ASSESSMENTS

12.1 Vaccine efficacy and long-term safety

a) Seropositive trial participants

Table 10 summarizes the efficacy against symptomatic VCD in the first 25 months after first vaccination, and the long-term safety follow up to 66 months, expressed as Hazard Ratio (HR) against hospitalized dengue and severe dengue in inferred baseline seropositive subjects 9-16 years of age. Vaccine efficacy based on the NS1 antibody assay likely underestimates the true efficacy (due to misclassification issues as explained under “Study Design”). Based on the PRNT results in the immunogenicity subset, vaccine efficacy was (81.9%, 95%CI 67.2-90.0) among seropositive participants and 52.5% (95%CI 5.9-76.1) among participants who were seronegative at baseline.

No data beyond 25 months are currently available to assess the long-term efficacy of symptomatic VCD, which presents an evidence gap.

Table 10. Vaccine efficacy and cumulative long-term safety in seropositive trial participants. n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; n and N are average numbers from 10 iterations of multiple imputations

| Number of Subjects with Cases | | | | | |
|--|------------------------|------------------------|----------------------|-------------------------|---------|
| | Vaccine Group n (N) | Placebo Group n (N) | Vaccine Efficacy (%) | 95% Confidence Interval | p-value |
| Symptomatic VCD (M0-M25) | 192.7 (1441.4) | 372.1 (697.3) | 76 | (63.9, 84.0) | <0.001 |
| Number of Subjects with Cases | | | | | |
| | Vaccine Group n (N) | Placebo Group n (N) | Hazard Ratio | 95% Confidence Interval | p-value |
| Hospitalized dengue (M0-M60-72) | 58.8 (1502.9) | 137.7 (729.8) | 0.21 | (0.138, 0.307) | <0.001 |
| Severe dengue (M0-M60-72) | 11.2 (1502.9) | 33.4 (729.8) | 0.16 | (0.068, 0.371) | <0.001 |

b) Seronegative trial participants

Table 11 summarizes the efficacy against symptomatic VCD in the first 25 months after first vaccination, and the long-term safety follow up to 66 months, expressed as Hazard Ratio against hospitalized dengue and severe dengue in inferred baseline seronegative subjects 9-16 years of age.

Table 11. Estimates in seronegative subjects 9-16 years of age with Multiple Imputation M0 onwards. n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; n and N are average numbers from 10 iterations of multiple imputations

| Number of Subjects with Cases | | | | | |
|--|------------------------|------------------------|----------------------|-------------------------|---------|
| | Vaccine Group n (N) | Placebo Group n (N) | Vaccine Efficacy (%) | 95% Confidence Interval | p-value |
| Symptomatic VCD (M0-M25) | 174.3 (353.6) | 148.9 (193.7) | 39 | (-1, 63) | 0.054 |
| Number of Subjects with Cases | | | | | |
| | Vaccine Group n (N) | Placebo Group n (N) | Hazard Ratio | 95% Confidence Interval | p-value |
| Hospitalized dengue (M0-M60-72) | 64.2 (375.1) | 25.3 (207.2) | 1.41 | (0.74, 2.68) | 0.287 |
| Severe dengue (M0-M60-72) | 14.8 (375.1) | 3.6 (207.2) | 2.44 | (0.47, 12.56) | 0.283 |

- The HRs for the entire trial population (aged 2-16) for hospitalized VCD and severe VCD in seronegative children were 1.65 (95%CI: 1.047-2.614; p=0.031) and 2.997 (95% CI 1.102-8.148; p=0.032), respectively, over 66 months.
- The excess risk was apparent from month 30 of the trial (17 months after the 3rd dose) in seronegatives aged 9 years and above and persisted throughout the 66 months of available observation time. The excess risk was apparent from month 18 in children <9 years of age.
- The magnitude of risk was higher in younger children. The HRs for hospitalized VCD and severe VCD in seronegative children aged 2-8 were 1.95 (95%CI: 1.19;3.19, p=0.008) and 3.31 (95%CI: 0.87;12.54, p=0.077), respectively, over 66 months.
- Clinical manifestations of severe dengue were similar in vaccinated seronegative persons compared to unvaccinated seropositive persons, consistent with the working hypothesis that CYD-TDV vaccination mimics a primary-like dengue infection.
- The majority of severe cases were classified as DHF I and DHF II and all recovered.

12.2 Assessment of modelled long-term benefit in seronegative subjects

Mathematical modelling, based on plausible assumptions on the mode of action of the vaccine, predicts that the harm in seronegatives following vaccination over time will be balanced by excess cases of severe disease in the unvaccinated seronegatives at later time periods in areas of high incidence where nearly all individuals will be infected with dengue at least twice in their lifetime.

- Risk increase in seronegatives occurs relatively soon after vaccination (from month 30 onwards in those aged 9 years and above)

- Predicted benefit in seronegative (reduction in long-term cumulative risk of hospitalised dengue) takes longer to accumulate and depends on dengue transmission intensity
- Timescale over which cumulative risk excess falls to zero is sensitive to assumptions about vaccine action (and statistical uncertainty)
- Excess risk can take >30 years to reach zero (if ever achieved) in lower seroprevalence settings
- For positive benefit in seronegative 9 year-olds in <10 years, need >80% seropositivity in that age group (>90% for benefit in 6 years)
- Risk in seronegatives is clear from the data; benefit (or at least reduction of relative risk over time) is predicted from modelling, but yet to be proven

12.3 Assessment of 3-dose schedule

A 3-dose schedule given 6 months apart is not optimal from a programmatic perspective. Immunogenicity in seropositives is high after the first dose and does not increase with subsequent doses. Phase 3 trial data suggest protection from the vaccine begins with the first dose. However, due to the high vaccine series completion rate in the trial, there are insufficient data to evaluate efficacy during the 25 follow up period by dose received, other than in the 6 months following each dose. Therefore, until additional data are available on fewer than three doses through vaccine effectiveness studies, or until an immune correlate of protection is available, the protection seen in the trial can only be assured through use of a 3-dose schedule.

12.4 Assessment of population seroprevalence criteria to introduce mass vaccination without individual screening

While it is recognized that targeting vaccination based on high seroprevalence criteria would result in a substantially larger number of severe and hospitalized dengue cases prevented in seropositive individuals than the number of such cases induced by priming seronegatives through vaccination, several major challenges have been highlighted in previous sections of the background paper.

Challenge 1: spatiotemporal heterogeneity of dengue transmission

- Transmission intensity varies over fine geographic scales
- Requires very large scale serosurveys to characterise

Challenge 2: coverage/impact

- Very few locations have seroprevalence > 80% in 9 year olds
- Almost no locations globally where seroprevalence in 9 year olds is >90%

Challenge 3: communication/uncertainties

- Long-term benefit in seronegatives not (yet) demonstrated in trial data
- Risk occurs before benefit, and is quantifiable

The optimal indication would be seroprevalence rates in a population or subpopulation exceeding 80% by the age of 9. In this setting the public health impact would be highest, and the harm to seronegatives lowest. It is important to note that if one increases the target age group, the seroprevalence threshold above which seronegatives see benefit also increases, explained by the fact that a certain average force of infection is being targeted. A setting with an average force of infection of 18% per year would be expected to have 80% seroprevalence in 9 year olds and 94% seroprevalence in 16 year olds. Changing the threshold seroprevalence affects the timescale over which benefit would be expected in seronegatives.

Cost-effectiveness analyses that incorporate the costs of high-resolution serosurveys to identify subnational areas of seroprevalence clearly above 80% have not been undertaken to date. Country-specific analyses will be needed to assess cost-effectiveness with locally relevant parameters.

12.5 Assessment of pre-vaccination screening

The advantages of a “pre-vaccination screening” strategy is that risk associated with vaccinating seronegatives can be minimized, while maximizing benefit from targeting seropositives only. One advantage of the pre-vaccination screening strategy over a “population seroprevalence criteria mass vaccination” is that the former strategy may also be considered in low to moderate transmission settings. Preliminary modelling predicts that more people would be eligible for vaccination using the pre-vaccination screening strategy than the seroprevalence based strategy refer to “programmatic use”). However, there are also some major challenges:

Challenge 1: age-targeting

- Too young: a high proportion of the population is still seronegative
- Too old: high proportion of the population will already have had 2 infections

Challenge 2: test performance

- High specificity required to minimise risk
- But consequence may be low sensitivity – and hence reduced impact

Challenge 3: policy design

- Mass vaccination – single age, or multiple ages?
- Private use – communicating context-specific benefits

The public health impact of the “screen and vaccinate” strategy depends on test sensitivity. High sensitivity ensures that eligible persons receive the vaccine. High specificity ensures that the risk to seronegatives is minimized. High specificity is more important in lower transmission settings. In a high transmission area with high seroprevalence, although high specificity is always desirable, the proportion of misclassified seronegatives will be small even with suboptimal specificity. In Table 12 the reduction in dengue incidence in a vaccinated cohort calculated from the age of vaccination onwards, versus vaccinating without serotesting, is represented. As the impact is dependent on underlying seroprevalence in the population, three scenarios are presented (seroprevalence 70, 80 and 90%).

Table 12. Expected number and proportion of dengue events prevented in a cohort of 100,000 vaccinated individuals over a 5-year follow-up with and without serotesting (Table provided by Sanofi Pasteur)

| Cases prevented * | | | | | | | | | | | | |
|-----------------------|--------------------|-------------------------------|------------------|-----------------|-----------------|---------------|----------------------------------|----------------|---------------|----------------|----------------------------------|--|
| Dengue seroprevalence | Events | Vaccinate without serotesting | | | | | Screen and vaccinate | | | | | |
| | | | | | | | Sensitivity 90%, Specificity 99% | | | | Sensitivity 69%, Specificity 98% | |
| | | Sero+ | Sero- | All | Sero+ | Sero- | All | Sero+ | Sero- | All | | |
| 90% | Hospitalized cases | 1357 (80,1%) | -48 (-43,7%) | 1309 (72,6%) | 1221 (72,1%) | 0 (-0,4%) | 1221 (67,7%) | 936 (55,2%) | -1 (-0,9%) | 935 (51,8%) | | |
| | Severe cases | 364 (84,3%) | -23 (132,2%) | 341 (75,9%) | 328 (75,9%) | 0 (-1,32%) | 328 (72,9%) | 251 (58,2%) | 0 (-2,6%) | 251 (55,8%) | | |
| 80% | Hospitalized cases | 1206 (80,1%) | -96 (-43,7%) | 1110 (64,4%) | 1085 (72,1%) | -1 (-0,4%) | 1084 (62,9%) | 832 (55,2%) | -2 (-0,9%) | 830 (48,1%) | | |
| | Severe cases | 324 (84,3%) | -46 (132,2%) | 278 (66,3%) | 291 (75,9%) | 0 (-1,32%) | 291 (69,5%) | 223 (58,2%) | -1 (-2,6%) | 222 (53,1%) | | |
| 70% | Hospitalized cases | 1055 (80,1%) | -143 (-43,7%) | 912 (55,4%) | 950 (72,1%) | -1 (-0,4%) | 948 (57,6%) | 728 (55,2%) | -3 (-0,9%) | 725 (44,1%) | | |
| | Severe cases | 1357 (80,1%) | -48 (-43,7%) | 1309 (72,6%) | 1221 (72,1%) | 0 (-0,4%) | 1221 (67,7%) | 195 (58,2%) | -1 (-2,6%) | 194 (50%) | | |

*Compared to no vaccination, negative numbers correspond to excess cases.

•Numbers reflect cases prevented compared to no vaccination.

•Percentage in brackets are proportion increase or decrease compared to no vaccination setting

•Incidence is based on cumulative incidence over the first 5 years following dose 1observed in 9-16 years old in clinical trials (pooled studies), Multiple Imputation approach from M0

Age-targeting:

Transmission intensity will determine the most optimal age for the “screen and test” strategy. A good proxy for the optimal target age for a single round vaccination is the age when hospitalizations due to dengue peak.

Table 13 shows the preliminary modeling results on both optimal age and estimated population based long-term reduction in total burden of hospitalised dengue over 30 years based on the “pre-vaccination screening” policy. In contrast to the reduction of burden in the vaccinated cohort (Table 12), the model results in Table 13 estimate the reduction of the overall burden of hospitalised dengue in the population.

Table 13. Preliminary modelling results on both optimal age and estimated population based long-term reduction in total burden of hospitalised dengue over 30 years based on the “pre-vaccination screening” strategy (prepared by Neil Ferguson, Imperial College)

| Transmission setting (seroprevalence in 9 year-olds) | Optimal age for screen and vaccinate | 30yr reduction in total burden of hospitalised dengue with 100% coverage of screen and vaccinate policy, assuming: <ul style="list-style-type: none">• Test sensitivity of 100%• Test specificity of 100%• Targeted at optimal age within range 9-18 | 30yr reduction in total burden of hospitalised dengue with 80% coverage of screen and vaccinate policy, assuming: <ul style="list-style-type: none">• Test sensitivity of 90%• Test specificity of 95%• Targeted at optimal age within range 9-18 |
|--|---|---|--|
| 40 | >18 | 12% | 18% |
| 45 | >18 | 13% | 20% |
| 50 | 18 | 14% | 21% |
| 55 | 17 | 15% | 21% |
| 60 | 16 | 15% | 21% |
| 65 | 15 | 15% | 21% |
| 70 | 13 | 15% | 21% |
| 75 | 11 | 15% | 21% |
| 80 | 9 | 15% | 21% |
| 85 | 8 | 15% | 21% |
| 90 | 7 | 14% | 20% |

If programmatically feasible, repeated RDT testing in vaccination-naïve individuals from early childhood might increase the overall impact of screen and vaccinated policies, albeit at considerable additional cost and diminishing returns after the first round.

12.6 Comparison of “pre-vaccination screening” with “population seroprevalence criteria”

Both the “pre-vaccination screening” and the “population seroprevalence criteria” approach are logistically challenging and associated with additional costs beyond those associated with a more typical blanket vaccination programme. A significant advantage of the “screen and vaccinate” strategy is that it can also be used in moderate transmission settings with similar levels of expected impact, so long as the age of vaccination is tuned for maximal impact. Table 14 summarises the different aspects to be considered in the choice of the population seroprevalence criteria versus pre-vaccination screening.

Table 14. Comparison of the two strategies: population seroprevalence criteria versus individual pre-vaccination screening

| | Population Seroprevalence Criteria without Screening | Pre-Vaccination Screening |
|--|---|---|
| Benefits and harm | <p>Overall substantial population benefit in areas with high seroprevalence predicted.</p> <p>An identifiable subset of the population will be put at increased risk of severe dengue, at least in the short to medium term.</p> | <p>Maximizing the benefit (high efficacy and good safety) in seropositive while avoiding harm in correctly identified seronegatives.</p> <p>Some seronegative individuals will be put at increased risk of severe dengue if vaccinated due to a false positive screening test result.</p> |
| Proportion of vaccinated population that will be put at increased risk of severe dengue | <p>Dependent on seroprevalence criteria chosen: if vaccine is introduced in a setting with 80% seroprevalence, 20% of the vaccinated population will be put at risk.</p> | <p>Dependent on the specificity of the screening test.</p> <p>In a setting with 80% seroprevalence and a test with 80% specificity, 20% of true seronegatives will be unintentionally vaccinated. That is, 4% of the total population would be unintentionally vaccinated.</p> <p>In a setting with 80% seroprevalence and a test with 98% specificity, 0.4% of the population would be unintentionally vaccinated.</p> |
| Population eligible for vaccination | <p>Subnational areas with seroprevalence >80% in 9 year olds are predicted by modelling to be rare, those with seroprevalence >90% by the age of 9 very rare.</p> | <p>Modelling predicts vaccine eligibility will be higher on a population basis compared to the seroprevalence criteria strategy, as all seropositive persons in the population are eligible.</p> <p>Strategy can be used in both high and moderate transmission settings, although pre-test probability will be higher in high transmission settings.</p> |
| Risk perceptions | <p>Loss in vaccine confidence (dengue vaccines and possibly other vaccines).</p> <p>Inability of vaccinees to know own serostatus may lead to increased vaccine hesitancy.</p> | <p>Risk of false positive test: seronegative individuals will be misclassified as seropositive and unintentionally vaccinated as no test will be 100% specific.</p> |
| Challenges for implementation | <p>Dengue transmission exhibits a high spatiotemporal heterogeneity. To identify subnational areas with seroprevalence above 80% by age 9 years, multiple small-scale age stratified seroprevalence studies need to be conducted.</p> <p>Limitations of available tests require additional validation work to estimate seroprevalence.</p> <p>Providing appropriate information to those eligible for vaccination of the potential risks and benefits will be more challenging than for other vaccines.</p> | <p>Pre-vaccination blood sampling may lead to decreased acceptance of the vaccination programme</p> <p>No RDT has been validated or licensed for the indication of screening for past dengue infection.</p> <p>Unlikely that any test will have a 100% specificity, thereby still putting some truly seronegatives at risk.</p> <p>Tests with high sensitivity are needed to ensure that a large proportion of seropositives will benefit from CYD-TDV.</p> |
| Population impact | <p>Given that areas with seroprevalence above 80% by age 9 are predicted to be rare, population impact is likely to be low.</p> | <p>Population impact on reduction of hospitalized dengue modelled at approximately 20% over 30 years</p> |

Continued on next page

| | Population Seroprevalence Criteria without Screening | Pre-Vaccination Screening |
|---------------------------|---|---|
| Age | Seroprevalence threshold in target age group increases for higher target ages. So while 80% seroprevalence required for a target age of 9 years, a seroprevalence threshold of 90% or more is required if 16 year olds are targeted. | Seropositive individuals of any age as indicated in the label can be targeted. As monotypic seropositives would be the target group that will benefit most from CYD-TDV, the optimal age for vaccine introduction will depend on dengue transmission intensity and can be informed by the age at which dengue hospitalisations due to severe dengue peaks. |
| Cost effectiveness | Cost effectiveness studies not done for scenarios of >80% seroprevalence. Cost effectiveness studies done in 2016 for seroprevalence threshold at 70% can be found in(7) Cost-effectiveness studies need to take into account the costs required to conduct population serosurveys to identify sub-national areas with seroprevalence above 80%. | No cost-effectiveness studies have been conducted to date. Cost-effectiveness studies need to take into account cost associated with identifying seropositives. |

12.7 Indirect effect of vaccination with CYD-TDV

Since vaccination only transiently reduces the risk of infection and the main effect of vaccination is to modify the risk of disease, mathematical modelling predicts that the indirect effect of vaccination on DENV transmission will be limited(8). This explains why the predicted impacts of routine vaccination (whether positive or negative) scale almost linearly with vaccine coverage. The only empiric data available to date on the reduction of asymptomatic infections is based on a study between months 13 and 25 after the first dose and was not stratified by serostatus.(25). The efficacy of CYD-TDV against asymptomatic dengue virus infection was assessed using pooled data for 3736 individuals in the phase 3 trials who received either CYD-TDV or placebo and found a vaccine efficacy of 33.5% (95% CI, 17.9%–46.1%) against asymptomatic infection. The annual incidence of asymptomatic dengue virus infection in this age group was 14.8%, which was 4.4 times higher than the incidence for symptomatic dengue (3.4%).

12.8 Non-dengue serious adverse events

Data from Phase 2 and Phase 3 trials have not signalled any safety concern other than the dengue-related signal described above. With regard to traditional safety considerations (reactogenicity, serious adverse events, etc.), CYD-TDV is well-tolerated. Due to the hypothetical risk of viscerotropic (AVD) and neurotropic disease (AND), the sponsor identified these events as adverse events of special interest and has initiated studies to assess background rates of AVD/AND-like disease, followed by post-licensure cohort event monitoring. To date, no cases of viscerotropic or neurotropic disease have been reported. The licensed Japanese encephalitis vaccine using the same ChimeriVax technology, IMOJEV®, is similarly being evaluated, with no signal to date.

12.9 CYD-TDV in the context of the dengue control program

CYD-TDV is a partially efficacious vaccine and vector control must remain a critical component of dengue control programs. Furthermore, the mosquito vectors of dengue transmit other important viruses, including Yellow Fever, Chikungunya, and Zika virus. Vaccination should be viewed as part of an integrated strategy to control dengue(26).

12.10 Second-generation dengue vaccines

CYD-TDV is the only vaccine licensed against dengue at this point in time. Two other candidate vaccines are currently being evaluated in large Phase 3 trials(27, 28). The data obtained from these trials are needed before the vaccines may be licensed by national regulatory authorities. No conclusions can be drawn from the data generated from CYD-TDV onto these two candidate vaccines.

WHO convened a technical consultation in June 2017 to guide dengue vaccine developers on trial design and duration of observation to enable broader public health recommendations for second-generation dengue vaccines(29). The clinical development of second generation vaccines would be greatly facilitated if established correlates of protection were available(30). Both correlates of protection and correlates of enhancement are needed (29, 31).

13. KEY RECOMMENDATIONS

The WG came to the overall conclusion that CYD-TDV still has a potential public health role, in the absence of currently available alternative solutions to combat the expanding problem of the global dengue burden. The challenge is how best to use CYD-TDV to maximize the public health impact, and minimize harm. In these deliberations, two main approaches were considered if the vaccine were to be further used in public programs:

- Subnational or national mass vaccination strategy based on population seroprevalence criteria, and
- Pre-vaccination screening whereby only those tested seropositive will be vaccinated

Population Seroprevalence Criteria

While implementing vaccination based on high seroprevalence criteria would result in a substantially larger number of severe and hospitalized dengue cases prevented in seropositive individuals than the number of excess cases resulting from priming seronegatives through vaccination, several major challenges warrant consideration:

- (1) To minimize harm in seronegatives, high seroprevalence thresholds of 80% and above in 9-year olds would be required.
- (2) Very few locations have seroprevalence > 80% in 9 year olds, and even fewer have locations with seroprevalence >90% in 9 year olds.
- (3) The spatiotemporal heterogeneity of dengue transmission combined with the need for high seroprevalence thresholds would necessitate large scale serosurveys to identify suitable areas at micro scale, thus adding complexity and cost to any public vaccination programme.
- (4) Given the limited areas with such high seroprevalence rates, national coverage rates would be low and hence the overall public health impact potentially limited.
- (5) A potentially identifiable subpopulation of seronegative persons would be put at increased risk of severe dengue, at least for a period of time
- (6) Communication around a strategy where a subpopulation would be put at risk for the sake of overall population level benefit would be challenging, and may undermine vaccine confidence in general.

Recognizing the hurdles of individual testing, combined with the documented overall population benefit of CYD-TDV in very high transmission settings, the use of CYD-TDV without individual pre-vaccination testing could be considered by countries with subnational areas with very high transmission intensity, as defined by

seroprevalence in 9-year olds of 80% and above. It is expected that only a very small proportion of subnational areas in most endemic countries will meet this criterion. Local, recent, age-stratified seroprevalence studies would have to be used to guide decision-making and introduction at subnational levels. Such programmes would need to take into account the feasibility and cost of seroprevalence studies, public confidence in national vaccination programmes, and perceptions of ethical considerations with regard to population level benefit versus individual level risk. Communication would have to ensure due regard for appropriate and full disclosure of risks of vaccination with regards to unknown serostatus.

Pre-vaccination Screening

With this strategy, only persons with evidence of a past dengue infection would be vaccinated (based on a screening test, or in some cases based on a documented laboratory confirmed dengue infection in the past). This approach would maximize the benefit from the vaccine by targeting seropositives, and minimize the risk associated with vaccinating seronegative persons. The pre-test probability of an individual being seropositive will be higher in settings with high endemic transmission and thus a “pre-vaccination screening” strategy would likely be more cost effective in such settings than in areas of lower endemicity. The advantage of the “pre-vaccination screening strategy” over “population seroprevalence criteria” is that this strategy may also be considered in low to moderate transmission settings. Preliminary mathematical modelling shows that the population level coverage rates achieved by the “screen and vaccinate” strategy would be higher than that achieved by the seroprevalence criteria based strategy. Individuals who only had one past dengue infection (monotypic past infection) will benefit most from CYD-TDV. The likelihood of having had two or more dengue infections increases with age and with the transmission intensity in any given country. The age group in which the highest dengue hospitalizations occur in a given area, based on surveillance, would be the modelled optimum age target for vaccination.

Despite the advantages of the “Pre-vaccination screening” strategy, major challenges remain:

- (1) Screening tests would need to be highly specific to avoid harm in seronegative persons, and would need to be highly sensitive to ensure that the vast majority of seropositive persons would benefit.
- (2) Such tests would preferentially need to be deliverable at point-of-care as rapid diagnostic tests (RDT).
- (3) To date, no RDTs has been validated and licensed for the indication of screening for past dengue infection (seropositivity).
- (4) Pre-vaccination screening poses significant hurdles in large-scale vaccination programmes.

The WG concluded that both “Population Seroprevalence Criteria” and “Pre-vaccination screening” are imperfect approaches for achieving high population protection from dengue because they are each programmatically difficult, for different reasons and with different consequences.

Proposed Recommendations

For countries considering vaccination as part of their dengue control program, a “pre-vaccination screening strategy” would be the preferred option, in which only dengue-seropositive persons are vaccinated.

Conventional serological testing for dengue virus IgG (dengue IgG ELISA) could be used to identify persons who have had previous dengue infections. Sensitivity and specificity of dengue IgG ELISA should be assessed in a local context, and will depend on the prevalence of other flaviviruses, and past use of other flavivirus vaccines (Japanese encephalitis and yellow fever).

Currently available RDTs, despite their lower sensitivity and specificity to detect past dengue infection compared with conventional dengue IgG ELISA, could be considered in high transmission settings until better tests are available. In settings with high numbers of seropositives and relatively low numbers of seronegatives, even an imperfect test with low specificity might be acceptable.

The pre-test probability of an individual being seropositive will be higher in settings with high transmission. However, a pre-vaccination screening strategy may also be considered in low to moderate transmission settings. In settings with lower transmission (higher numbers of seronegatives), a test with higher specificity is recommended.

Given that no assay will be 100% specific, some truly seronegative individuals may be vaccinated due to a false positive test result. Furthermore, although the efficacy against dengue infections in seropositive individuals is high, it is still not complete. Hence, the limitations of CYD-TDV will need to be clearly communicated to populations offered vaccination.

There is a continued need to adhere to other disease preventive measures and to seek prompt medical care in the event of dengue-like symptoms, regardless of whether vaccinated or not. Vaccination should be considered as part of an integrated dengue prevention and control strategy together with well-executed and sustained vector control and the best evidence-based clinical care for all patients with dengue.

Decisions about implementing a “pre-vaccination screening” strategy with the currently available tests will require careful assessment at the country level, including consideration of the sensitivity and specificity of available tests and of local priorities, dengue epidemiology, country-specific dengue hospitalization rates, and affordability of both CYD-TDV and screening tests.

Age

Whether there are age-specific effects, independent of serostatus, is the subject of ongoing research. Currently, the vaccine should be used within the indicated age range, which is typically 9 to 45 years of age. The age to target for vaccination depends on the dengue transmission intensity in a given country, and will be lower in countries with high transmission, and higher in countries with low transmission. The optimal age group to be targeted is the age at which severe dengue disease incidence is highest, and this can be ascertained from national and subnational routine hospital surveillance data.

Schedule

In the absence of data on vaccine efficacy and safety with fewer than three doses, CYD-TDV is recommended as a three dose series given 6 months apart. Should a vaccine dose be delayed for any reason, it is not necessary to restart the course and the next dose in the series should be administered.

Booster

There are currently no data on the use of booster doses. Additional studies to determine the utility of a booster dose and its best timing are under way. Accordingly, there is no current recommendation for a booster dose.

Research priorities

Development of a highly sensitive and specific RDT, simplified immunization schedules, and assessment of booster needs should be prioritized.

Special settings and populations:

Outbreak response

CYD-TDV should not be considered as a tool for outbreak response. A dengue outbreak is a signal that an improved dengue control strategy is needed. When an outbreak occurs in an area that meets the criteria for routine introduction in relation to transmission intensity, vaccination with the 3-dose schedule as part of an overall dengue control strategy may be considered.

Special populations

Pregnant women: CYD-TDV is contraindicated in pregnant and lactating women because insufficient data have so far been gathered on its use in pregnancy. However, based on limited data generated from inadvertent pregnancies that occurred during clinical trials, there are no data to warrant termination of an inadvertent pregnancy should the vaccination have occurred anytime during pregnancy. If a woman becomes pregnant before all three doses have been administered, the remaining doses should be administered after lactation.

Immunocompromised: CYD-TDV is contraindicated in immunocompromised individuals. More data will be available from upcoming studies in HIV-infected individuals.

Travellers: CYD-TDV has not formally been licensed for use in travellers. In travellers who have already been previously infected with dengue, vaccination for travel to high transmission settings may be beneficial.

Surveillance

Dengue surveillance should be strengthened, particularly in the context of emerging infections with clinical similarities to dengue. In areas of the world for which there is a paucity of data, further characterization of the burden of dengue, which appears to be growing, is needed. Harmonized case-definitions are encouraged to enhance data sharing and comparisons across regions.

Using surveillance data to monitor population impact of a vaccination program may be challenging as the year-to-year variability in dengue transmission may be greater than the expected vaccine impact. Long-term monitoring for severe dengue in vaccinated subjects to assess long-term effects of vaccination should be done in selected areas.

14. RESEARCH PRIORITIES

Tables 15 and 16 summarize the research priorities for CYD-TDV and beyond.

Table 15. Research questions to be addressed in the Risk Management Programme (RMP) by Sanofi Pasteur and other research questions beyond the RMP.

| Research Question | Priority | Addressed in RMP? | Notes |
|---|-----------------|--|--|
| Improved point of care (POC) tests to identify seropositive/seronegative individuals | Critical | Dedicated studies are needed. Not addressed by RMP, but Sanofi Pasteur has expressed their intent to co-develop rapid diagnostic tests | Improved POC tests to identify past dengue infection |
| Duration of protection / need for booster doses | Critical | CYD14 and CYD15 long-term follow up will inform duration of protection, and booster dose studies are underway by the manufacturer. | Post-licensure monitoring will need to contribute to follow up for time periods beyond the 6 years planned in the clinical trials. |
| Vaccine effectiveness with fewer than three doses | Critical | Vaccine effectiveness studies are included in RMP. | |
| Cost-effectiveness of “screen and vaccinate” strategies | Critical | Out of scope of RMP | Cost-effectiveness based on seroprevalence and heterogeneity of seroprevalence in a given country |
| Novel diagnostic assays to diagnose past or recent dengue infections in vaccinated individuals | High | Out of scope of RMP | |
| Co-administration with age-appropriate vaccines | High | Co-administration studies are planned by the manufacturer. | Of particular interest are co-administration with HPV vaccines and Tdap |
| Health impact assessment of vaccination program | High | Planned as part of RMP | |
| Long-term transmission dynamics (serotype/genotype selection) | High | Out of scope of RMP | As seen for other vaccine preventable diseases, serotype replacement is a real risk and should be monitored. Dedicated studies are needed. |

Table 16. Research priorities for the dengue vaccine field identified by the SAGE Working Group on Dengue Vaccines.

| General Research Areas | Priority | Notes |
|--|-----------------|---|
| Second-generation vaccines that include characteristics such as improved protection against all four dengue serotypes, single-dose, for use in younger age groups | Critical | Two Phase 3 trials are ongoing; results to be expected by Q1 2019 |
| Immune correlate of protection, immune correlates of disease enhancement | High | Broader efforts that could potentially be extrapolated to other/all dengue vaccines are needed. Dedicated studies are needed. |
| Implementation strategies for “screen and vaccinate” policies | High | Operational research |
| Optimal integrated dengue control strategy (vector control strategies together with vaccination for maximum public health impact) | High | Dedicated studies are needed to understand the effectiveness of vector control and optimal integrated strategies. |
| Development of simple mathematical modelling tools for country use in decision-making with consideration of the local context. | High | Dedicated efforts are needed. |
| Research on dengue burden in Africa | High | Dedicated studies are needed. |

15. ACKNOWLEDGEMENTS

The SAGE Working Group on CYD-TDV dengue vaccine (WG) would like to acknowledge the openness and responsiveness of the manufacturer in providing data requested and identified by the WG to be important for global recommendations. The WG had to rely on unpublished data with regards to the new NS1 antibody based analyses and imputation methods, as presented by Sanofi Pasteur. The WG was granted access to draft versions of the manuscript prepared by Sanofi Pasteur submitted for publication.

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BIOLOGICAL STANDARDIZATION

Sixty-eighth report of the Expert Committee on Biological Standardization

Geneva, 17–20 October 2017

The Expert Committee on Biological Standardization reviews developments in the field of biological substances used in human medicine, which include vaccines, biological therapeutics, blood products and related in vitro diagnostic reagents. It coordinates activities leading to the adoption of guidelines and recommendations for assuring the quality, safety and efficacy of such substances and the establishment of international standards and other reference materials.

The use of international reference materials for designating the activity of biological substances used in prophylaxis or therapy, or for ensuring the reliability of quality control or diagnostic procedures, allows comparability of data worldwide.

Main recommendations

Based on the results of international collaborative laboratory studies, the Expert Committee established 25 new or replacement WHO international biological reference preparations (WHO TRS 1011, annex 6). These are the primary standards intended for use as calibrants against which secondary standards (for example, regional or national measurement standards) are benchmarked. Measurement standards of particular importance for regulatory evaluation of vaccines include but are not limited to 1st International Standards (ISs) for monovalent (type 1, 2 and 3), bivalent (type 1+3) oral poliovirus vaccines, 2nd IS for pertussis toxin, 1st IS for Vi polysaccharide of Vi polysaccharide of *S. typhi*, 1st IS for Anti-Typhoid capsular Vi polysaccharide IgG (Human), 1st IS for antiserum to Respiratory Syncytial Virus, 1st IS for EBOV antibodies and 1st International Reference Panel for EBOV antibodies. An up-to-date list of WHO international biological reference preparations is available at <http://www.who.int/bloodproducts/catalogue/en/> (accessed 26 March 2018).

The Expert Committee also adopted new guidance documents on:

- the quality, safety and efficacy of Ebola vaccines
- procedures and data requirements for changes to approved biotherapeutic products
- rapid diagnostic tests for HIV infection for professional use and/or self-testing
- establishing stability of in vitro diagnostic medical devices.

The Expert Committee recommended that WHO urgently establish a small working group of experts to further consider the most appropriate approach and time to develop WHO guidelines for cell therapies and prepare a progress report on this rapidly developing global biologicals field for the Committee's meeting later in 2018. It was also agreed that any WHO standardization activities should include stem cells.

The Expert Committee also provided advice to the Director-General on the written standards and reference preparations under development and on the plans for submission to the Expert Committee in 2018–2020.

New written standard of particular interest for Strategic Advisory Group of Experts (SAGE) on immunization is recently developed document entitled “Guidelines on the quality, safety and efficacy of Ebola vaccines” (WHO TRS 1011, annex 2). It was prepared in response to the request of the Expert Committee at its sixty-fifth meeting in October 2014 when it recognized the importance of providing guiding principles for evaluation of these vaccines. Development of this document started during the Ebola virus disease outbreak in 2014-2015 and it was reviewed by the Expert Committee at its sixty-seventh meeting in October 2016. The Expert Committee noted progress in its elaboration but requested further revision to address the potential use of multivalent Ebola vaccines and innovative clinical trial designs. The latest version of the guidelines, adopted by the Expert Committee at its sixty-eighth meeting, includes this new information and also takes note of the fact that the development of Ebola vaccines had been the subject of discussions by the SAGE on immunization. It is expected that the new written standard for Ebola vaccines will serve as a tool for regulatory preparedness in Member States for future public health emergencies. The adopted text not only provides comprehensive guidance on regulatory expectations for quality, safety and efficacy for full licensure, but also considers which aspects might be accelerated and data sets required during a public health emergency so as to allow rapid vaccine introduction.

Next ECBS meeting is going to take place from 29th October to 2nd November 2018.



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<http://www.who.int/wer>

Contents

- 17 Global Advisory Committee on Vaccine Safety, 6–7 December 2017
- 31 Monthly report on dracunculiasis cases, January–November 2017

Sommaire

- 17 Comité consultatif mondial pour la sécurité des vaccins, 6-7 décembre 2017
- 31 Rapport mensuel des cas de dracunculose, janvier-novembre 2017

Global Advisory Committee on Vaccine Safety, 6–7 December 2017

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides WHO with scientifically rigorous advice on vaccine safety issues of potential global importance.¹ GACVS held its 37th meeting in Geneva, Switzerland, on 6–7 December 2017.² The Committee examined 3 vaccine specific safety issues: progress with pharmacovigilance readiness for the RTS,S malaria vaccine pilot countries, and updates on the safety profiles of both rotavirus and dengue vaccines. It also reviewed 3 generic issues: the interrater reliability of the revised causality assessment algorithm for serious adverse events following immunization (AEFIs); guidance on prevention and management of immunization-triggered stress reactions; and harmonized approaches for the vigilance of vaccine and other interventions during pregnancy.

Vaccine pharmacovigilance readiness for malaria vaccine implementation

The pilot implementation plans for the RTS,S malaria vaccines in Kenya, Malawi and Ghana have continued to develop since the GACVS meeting in June 2017.³ In

Comité consultatif mondial pour la sécurité des vaccins, 6-7 décembre 2017

Le Comité consultatif mondial pour la sécurité des vaccins (GACVS) est un organe consultatif indépendant composé d'experts cliniques et scientifiques qui fournissent à l'OMS des conseils d'une grande rigueur scientifique sur des problèmes de sécurité des vaccins susceptibles d'avoir une portée mondiale.¹ Le GACVS a tenu sa 37^e réunion à Genève (Suisse) les 6 et 7 décembre 2017.² Le Comité a examiné 3 questions de sécurité spécifique: la progression de la préparation à la pharmacovigilance des pays pilotes pour le vaccin antipaludique RTS,S et la mise à jour des profils d'innocuité pour les vaccins contre les rotavirus et contre la dengue. Il a aussi abordé 3 questions génériques: la fiabilité interévaluateurs de l'algorithme révisé d'évaluation des liens de causalité pour les manifestations postvaccinales indésirables (MAPI) graves; des orientations concernant la prévention et la gestion des réactions de stress déclenchées par la vaccination; et des démarches harmonisées pour la vigilance à l'égard des vaccins et autres interventions pendant la grossesse.

Degré de préparation à la pharmacovigilance à l'égard des vaccins en vue de la mise en œuvre du vaccin antipaludique

Le développement des plans de mise en œuvre pilote des vaccins antipaludiques RTS,S au Kenya, au Malawi et au Ghana a été poursuivi depuis la réunion du GACVS de juin 2017.³ En

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¹ See No. 41, 1999, pp. 337–338.

² GACVS invited additional experts to present and discuss evidence related to specific topics. These experts included persons affiliated with: The INCLEN Trust International, New Delhi, India; Centers for Disease Control and Prevention, Atlanta GA, USA; Food and Drugs Authority, Accra, Ghana; Women's and Children's Hospital, Adelaide, Australia; University of the Witwatersrand, Johannesburg, South Africa; University of Guelph, Canada; Pharmacy and Poisons Board, Nairobi, Kenya; Medicines Control Authority, Harare, Zimbabwe; Pharmacy, Medicines and Poisons Board, Lilongwe, Malawi; The Cochrane Collaboration, Oxford, United Kingdom; Sanofi Pasteur, Lyon, France.

³ See No. 8, 2017, pp. 393–396.

¹ Voir N° 41, 1999, pp. 337-338.

² Le GACVS a invité d'autres experts à présenter et à analyser les données relatives à des sujets particuliers. Il s'agissait notamment de personnes affiliées aux organismes suivants: INCLEN Trust International, New Delhi, Inde; Centers for Disease Control and Prevention, Atlanta GA, États-Unis d'Amérique; Food and Drug Authority, Accra, Ghana; Women's and Children's Hospital, Adelaide, Australie; University of the Witwatersrand, Johannesburg, Afrique du Sud; Université de Guelph, Canada; Pharmacie et Poisons Board, Nairobi, Kenya; Médicines Control Authority, Harare, Zimbabwe; Pharmacie, Médicines et Poisons Board, Lilongwe, Malawi; The Cochrane Collaboration, Oxford, Royaume-Uni; Sanofi Pasteur, Lyon, France.

³ Voir N° 8, 2017, pp. 393-396.

particular a tripartite agreement between PATH, GSK and WHO, in terms of roles and responsibilities, and a funding agreement with GAVI, UNITAID and the Global Fund to Fight AIDS, Tuberculosis and Malaria were signed. Plans for a joint regulatory review in the implementing countries for restricted use in pilots have also been devised. In addition, a programme advisory group has been established. It is anticipated that pilot introduction will start mid- to late-2018.

At the June 2017 meeting, GACVS endorsed 6 key indicators of readiness for vaccine pharmacovigilance (PV) for the implementing countries – to be in place 6 months prior to vaccine administration. These were i) a minimum of 10 AEFI reports per 100 000 surviving infants; ii) a functioning AEFI committee that meets regularly; iii) trained and resourced AEFI investigation teams; iv) safety communication plans evaluated and tested; v) an identified person within the Expanded Programme on Immunization (EPI) to oversee and ensure optimal reporting and training; and vi) methods for active surveillance of adverse events of special interest (AESIs) developed and data collection initiated.⁴ GACVS received progress updates from each country on PV readiness, as well as the results of meetings between the countries on establishing the scope and their methodology to monitor.

In Kenya, reporting rates are close to the target, with plans in place for education sessions and guidance for health-care providers to achieve the target. Work is in progress to establish a national AEFI committee and implement training at the national level. One officer in the EPI programme will oversee safety; communication plans are currently being developed.

In Malawi, a national AEFI committee has been constituted and a reporting system developed. Training has led to an increase in reporting of AEFIs, and also covered causality assessment for national experts. Plans are in place to use the VigiFlow reporting software for adverse events developed by the WHO Programme for International Drug Monitoring as the national database and for vaccine safety data sharing in early 2018.

In Ghana, AEFI reporting rates have increased and initiatives are in place to further increase not only the rates, but also timeliness, so that reporting levels will be achieved in all regions of the country. Additional activities include sharing revised reporting forms, educational lectures and the development of job aids. A national AEFI committee is in place, and additional training is being planned for AEFI investigation. A communication plan is also being developed.

particulier, un accord tripartite entre le programme PATH, GSK et l'OMS définissant les rôles et les responsabilités respectives, et un accord de financement entre GAVI, UNITAID et le Fonds mondial de lutte contre le sida, la tuberculose et le paludisme ont été signés. Des plans pour un examen réglementaire conjoint dans les pays de mise en œuvre en vue d'un usage restreint dans les projets pilotes ont été conçus. En outre, un groupe consultatif pour les programmes a été mis en place. On s'attend à ce que l'introduction pilote débute entre le milieu et la fin de l'année 2018.

Lors de sa réunion en juin 2017, le GACVS a approuvé 6 indicateurs clés de la préparation à la pharmacovigilance (PV) pour les pays entreprenant de mettre en œuvre le vaccin – qui devraient être en place 6 mois avant le début de la vaccination. Ces indicateurs étaient les suivants: i) 10 notifications de MAPI au minimum pour 100 000 nourrissons survivants; ii) un comité pour les MAPI opérationnel se réunissant régulièrement; iii) des équipes d'investigations des MAPI formées et disposant des moyens nécessaires; iv) des plans de communication à propos de la sécurité évalués et testés; v) une personne identifiée au sein du Programme élargi de vaccination (PEV) pour superviser et garantir une notification et une formation optimales; et vi) des méthodes de surveillance active des événements présentant un intérêt particulier (EIIP) mises au point et une collecte des données entamée.⁴ Le GACVS a reçu de la part de chaque pays des mises à jour concernant leur degré de préparation à la PV ainsi que les résultats des réunions entre les pays sur la définition de la portée et de la méthodologie à suivre.

Au Kenya, les taux de notification sont proches de la cible, avec des projets en place pour des sessions d'éducation et des orientations à l'intention des prestataires de soins pour atteindre cette cible. Des travaux sont en cours pour établir un comité national pour les MAPI et mettre en œuvre la formation au niveau national. Un responsable du PEV assurera une supervision de la sécurité; des plans de communication sont actuellement en cours de développement.

Au Malawi, un comité national pour les MAPI a été constitué et un système de notification a été mis sur pied. La formation a entraîné une augmentation de la notification de MAPI et a également couvert l'évaluation des liens de causalité par des experts nationaux. Des plans sont en place pour utiliser le logiciel de notification des événements indésirables VigiFlow, élaboré par le Programme OMS de suivi pharmaceutique en tant que base de données nationale et pour partager les données sur la sécurité vaccinale au début de l'année 2018.

Au Ghana, les taux de notification de MAPI ont augmenté et des initiatives sont en place non seulement pour faire progresser ces taux, mais aussi pour améliorer la promptitude des rapports, de manière à ce que les niveaux de notifications visés soient atteints dans toutes les régions du pays. À ces activités s'ajoutent la communication de ces formulaires de notification révisés, l'organisation de conférences éducatives et la mise au point de fascicules d'aide. Un comité national pour les MAPI est en place et une formation supplémentaire est prévue pour l'investigation de ces manifestations indésirables. Un plan de communication est également en cours d'élaboration.

⁴ See No. 28, 2017, pp. 393–396.

⁴ Voir N° 28, 2017, pp. 393-396.

Joint meetings of the 3 countries have occurred through a web-based work group platform to help establish the AESI to be monitored. A total of 10 events have been selected and a surveillance manual is being prepared with appropriate reporting forms and assessment tools. Training will need to be conducted to enable surveillance to begin.

GACVS welcomed the progress achieved, but also recognized the challenges remaining in reaching PV readiness prior to RTS,S introduction, and in AESI surveillance, given how soon vaccinations will begin. GACVS emphasized the importance of each country continuing to rapidly progress PV readiness according to the indicators, in view of target introduction later in 2018. Although the target of AESI reporting starting 6 months prior to vaccine introduction may not be feasible, nonetheless, this should occur as soon as possible to allow comparisons between pilot areas randomized to receive RTS,S and corresponding control areas. Ascertainment of vaccination history of AESIs was also identified as an area that could be challenging. However, GACVS learned that additional resource will be available to register vaccination status in RTS,S pilot areas.

Rotavirus vaccine safety update

In December 2011, GACVS initially reviewed the safety of currently administered rotavirus vaccines.⁵ The Committee noted that both Rotateq® and Rotarix® vaccines had a good safety profile and that although they may be associated with an increased (up to 6-fold) risk of intussusception, the benefit of the vaccines outweighed the potential risk. In December 2013, GACVS reviewed additional data that had become available from Australia and the United States of America (USA).⁶ It noted that both countries confirmed a risk of intussusception following vaccine administration, particularly within the first 7 days after the first dose, although attributable risk estimates varied across studies. The Committee concluded that the benefits of the vaccine outweighed the small potential risk of intussusception (in the range of 1–2 cases per 100 000 first doses).⁷ GACVS also suggested that given possible population differences in the risk of intussusception, active surveillance should be undertaken in countries where rotavirus vaccines are being introduced to ensure that benefits and risks can continue to be assessed.

The GACVS session in December 2017 reviewed recent evidence on the impact of rotavirus vaccine, an updated Cochrane review on rotavirus vaccines and intussusception, and recent data from multicountry studies from sub-Saharan Africa and South Africa.

Les réunions conjointes de ces 3 pays se sont tenues par le biais d'une plateforme de travail sur le Web destinée à aider à déterminer les EIIP à suivre. Dix de ces événements au total ont été sélectionnés et un manuel de surveillance est en cours de préparation avec des formulaires de notification et des outils d'évaluation appropriés. Des formations devront être organisées pour pouvoir mettre en route la surveillance.

Le GACVS s'est félicité des progrès réalisés, mais a également reconnu les difficultés restant à surmonter pour que la PV soit prête à l'introduction du RTS,S et à la surveillance des EIIP, sachant que les vaccinations vont bientôt commencer. Il a souligné l'importance pour chaque pays de progresser rapidement dans la préparation à la PV conformément aux indicateurs, en visant une introduction ultérieure en 2018. Bien que la cible consistant à débiter la notification des EIIP 6 mois avant l'introduction du vaccin puisse se révéler impossible à atteindre, cette notification devra néanmoins débiter dès que possible pour permettre des comparaisons entre des zones pilotes sélectionnées aléatoirement pour recevoir le RTS,S et des zones témoins correspondantes. La détermination des antécédents de vaccination pour les EIIP a aussi été identifiée comme une opération potentiellement difficile. Cependant, le GACVS a appris que des moyens supplémentaires seraient disponibles pour enregistrer le statut vaccinal dans les zones de mise en œuvre pilote du RTS,S.

Le point sur l'innocuité des vaccins contre les rotavirus

En décembre 2011, le GACVS avait réalisé un examen initial de l'innocuité des vaccins antirotavirus actuellement administrés.⁵ Le comité avait noté que le vaccin Rotateq®, comme le Rotarix®, tout en présentant des profils d'innocuité satisfaisants, avaient cependant été associés à une augmentation (d'un facteur pouvant aller jusqu'à 6) du risque d'invagination intestinale, le bénéfice de ces vaccins outrepassant néanmoins le risque potentiel. En décembre 2013, le GACVS a examiné des données supplémentaires en provenance d'Australie et des États-Unis d'Amérique.⁶ Il a noté que ces deux pays confirmaient un risque d'invagination intestinale suite à l'administration du vaccin, en particulier dans les 7 premiers jours suivant la première dose, même si l'estimation du risque attribuable variait entre les études. Le comité a conclu que les bénéfices du vaccin outrepassaient le faible risque potentiel d'invagination (compris entre 1 et 2 cas pour 100 000 premières doses).⁷ Il a aussi suggéré que compte tenu des différences démographiques pouvant influencer sur le risque d'invagination, une surveillance active devait être entreprise dans les pays où des vaccins antirotavirus sont en cours d'introduction pour veiller à ce que l'évaluation des risques et des bénéfices se poursuive.

Lors de la session de décembre 2017, le GACVS a examiné des éléments récents sur l'impact des vaccins antirotavirus, une revue Cochrane actualisée consacrée à ces vaccins et à l'invagination intestinale ainsi que des données récentes provenant d'études menées dans plusieurs pays d'Afrique subsaharienne et d'Afrique du Sud.

⁵ See No. 6, 2012, pp. 54–56.

⁶ See No. 7, 2014, pp. 57–58.

⁷ See http://www.who.int/vaccine_safety/initiative/tools/Rotavirus_vaccine_rates_information_sheet.pdf?ua=1.

⁵ Voir N° 6, 2012, pp. 54–56.

⁶ Voir N° 7, 2014, pp. 57–58.

⁷ Voir http://www.who.int/vaccine_safety/initiative/tools/Rotavirus_vaccine_rates_information_sheet.pdf?ua=1.

As regards vaccine impact, data from randomized controlled clinical trials (RCTs) showed that RV1, RV5, Rotasiil® and Rotavac® vaccines reduced severe rotavirus gastroenteritis by 52–94% after 1 year of follow-up. Overall, weak evidence from observational studies suggested that the introduction of RV1 and RV5 vaccines reduced diarrhoea-related deaths in children. While the effectiveness was lower in some low-income countries, the benefit was still large due to the high disease burden.

A systematic review⁸ was conducted to update a 2012 Cochrane systematic review regarding the efficacy and safety of rotavirus vaccines. This review included RCTs (low power, low bias); historical controls (low power, high risk of bias); case-control studies (high power, high risk of bias); cohort studies (high power, high risk of bias); and self-controlled case series (SCCS) (high power, unclear risk of bias). Data were insufficient to evaluate many of the new vaccine products. For those reviews with sufficient data, evidence from RCTs showed that there was no difference in incidence of serious adverse events in the use of RV1, RV5, Rotasiil®, or Rotavac® compared with placebo, up to 2 years after vaccination. There was conflicting evidence from different sources as to whether RV1 or RV5 was associated with an increased risk of intussusception. While RCTs of RV1 and RV5 found no association between intussusception and vaccination, SCCS studies suggested an increased risk in the weeks following vaccination.

In the African Intussusception Surveillance Network that was formally established in 2014, and included 7 countries using Rotarix® (Ethiopia, Ghana, Kenya, Malawi, United Republic of Tanzania, Zambia and Zimbabwe), surveillance for intussusception (defined using Brighton case definition criteria) was conducted at 28 sentinel paediatric hospitals. Vaccination status was identified via vaccination card or medical/clinic record. The potential association between oral rotavirus vaccine and intussusception was analysed using an SCCS study, in which each of the 717 identified case-patients (aged 28–245 days) served as their own control (risk periods were 1–7 days, 8–21 days, and 1–21 days following each dose, while the control periods were the other time windows). No increased risk of intussusception was identified after either dose 1 or 2.

Post-marketing monitoring is also ongoing in South Africa, where an SCCS study (using the same methods as described above) is being conducted among >300 case-patients aged 28–275 days. Thus far, no risk following the first dose, and a small risk (approx-

S'agissant de l'impact des vaccins, des données provenant d'essais cliniques contrôlés randomisés (ECR) ont montré que les vaccins RV1, RV5, Rotasiil® et Rotavac® réduisaient la fréquence de la gastroentérite à rotavirus sévère de 52 à 94% après un an de suivi. Globalement, des preuves faibles tirées d'études observationnelles laissent à penser que l'introduction des vaccins RV1 et RV5 a fait diminuer la mortalité due à la diarrhée chez les enfants. Si l'efficacité était plus basse dans certains pays à faible revenu, le bénéfice restait important en raison de la forte charge de morbidité concernée.

Une revue systématique⁸ a été réalisée pour actualiser une revue systématique Cochrane de 2012 concernant l'efficacité et l'innocuité des vaccins antirotavirus. Cette revue incluait des ECR (puissance et biais faibles); des témoins historiques (faible puissance, risque de biais important), des études cas-témoin (forte puissance, risque de biais important); des études de cohorte (forte puissance, risque de biais important); et des séries de cas autocontrôlées (SCCS, forte puissance, risque de biais mal déterminé). Les données étaient insuffisantes pour l'évaluation de nombreux nouveaux produits vaccinaux. Pour les évaluations ayant disposé de données suffisantes, les données provenant d'ECR ont montré qu'il n'y avait pas de différence dans l'incidence des manifestations indésirables graves après l'utilisation des vaccins RV1, RV5, Rotasiil® ou Rotavac® par comparaison avec un placebo, jusqu'à 2 ans après la vaccination. Il existait des preuves conflictuelles émanant de sources différentes concernant l'existence d'un lien entre l'administration du RV1 ou du RV5 et une augmentation du risque d'invagination. Alors que les ECR ne mettaient en évidence aucune association entre la vaccination par les vaccins RV1 ou RV5 et l'invagination, des études de type SCCS suggéraient un accroissement de ce risque dans les semaines suivant la vaccination.

Dans le cadre du Réseau africain de surveillance de l'invagination intestinale formellement mis en place en 2014 et comprenant 7 pays utilisant le vaccin Rotarix® (Éthiopie, Ghana, Kenya, Malawi, République-Unie de Tanzanie, Zambie et Zimbabwe), on a exercé une surveillance de ce problème médical (répondant aux critères de la définition de cas de Brighton) dans 28 hôpitaux pédiatriques sentinelles. On a déterminé le statut vaccinal à partir des cartes de vaccination ou des dossiers médicaux/cliniques. On a analysé les possibilités d'association entre le vaccin antirotavirus oral et l'invagination intestinale à l'aide d'une étude SCCS, dans laquelle chacun des 717 cas patients identifiés (âgés de 28 à 245 jours) a constitué son propre témoin (périodes à risque: 1-7 jours, 8-21 jours et 1-21 jours après chaque dose, tandis que les périodes témoins correspondaient aux autres fenêtres temporelles). Aucune augmentation du risque d'invagination n'a été repérée après la 1^{re} ou la 2^e dose.

Une surveillance postcommercialisation est également en cours en Afrique du Sud, où une étude de type SCCS (selon les mêmes méthodes que décrit précédemment) a été entreprise chez >300 cas patients de 28 à 275 jours. Jusqu'à maintenant, aucun risque n'a été identifié après la première dose et un risque faible

⁸ Soares-Wiser et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Available at http://www.cochrane.org/CD008521/INFECTN_vaccines-for-preventing-rotavirus-diarrhoea-vaccines-in-use, accessed December 2017.

⁸ Soares-Wiser et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Disponible à l'adresse: http://www.cochrane.org/CD008521/INFECTN_vaccines-for-preventing-rotavirus-diarrhoea-vaccines-in-use, consulté en décembre 2017.

mately 2-fold) in the first 7 days following the second dose, have been identified, but no overall increased risk 1–21 days following the second dose. Enrolment is ongoing.

While the reason behind the difference in potential risk of intussusception in different countries is not clear, hypotheses include: differences in age at vaccination; differences in effectiveness of vaccine (e.g. lower effectiveness may be associated with lower risk of intussusception); concurrent use of inactivated polio vaccine (IPV) versus oral poliovirus vaccine (OPV) (e.g. concurrent use of OPV may reduce both effectiveness of the rotavirus vaccine and risk of intussusception); and the “trigger” hypothesis (that vaccination could potentially trigger intussusception in a susceptible individual who may have developed intussusception later in the absence of vaccination). The Committee suggested that future follow-up studies continue to assess these variables. In addition, as countries transition from OPV to IPV, studies evaluating both effectiveness and risk of intussusception should be considered. Countries should also continue to assess risk of new vaccines as they are licensed and introduced. Overall, the Committee continues to be reassured that the benefit of rotavirus vaccination in preventing severe diarrhoea is greater than the small potential risk of intussusception identified in most, but not all post-licensure studies.

Dengue vaccine safety update

The GACVS has been following the development of a tetravalent recombinant live dengue virus vaccine for the past 5 years.^{9–12} The most advanced product, CYD-TDV by Sanofi-Pasteur (Dengvaxia®) is a yellow fever vaccine virus backbone vector that expresses envelope proteins of dengue viruses type 1 to 4. During early clinical trials, no serious vaccine-related events had been documented among the recipients, and no excess cases of dengue fever or severe dengue attributable to the vaccine had been observed. Subsequent large-scale phase 3 trials, CYD14 in Asia (among subjects aged 2–14 years) and CYD15 in Latin America (among subjects aged 9–16 years) were conducted in over 20 000 vaccine recipients and 10 000 control subjects and demonstrated partial efficacy of the vaccine.

Dengvaxia® received its first marketing authorizations in late 2015 and is currently available in several Asian and Latin American countries. This report briefly reviews the experience presented to GACVS during clinical trial development (now with >5 years of follow up), and discusses new evidence presented to WHO during the GACVS meeting in December 2017. These

(d'un facteur 2, approximativement) a été décelé au cours des 7 premiers jours suivant la deuxième dose, mais aucune augmentation globale du risque n'a été constatée de 1 à 21 jours après la deuxième dose. Le recrutement est encore en cours.

Les raisons des différences observées pour le risque potentiel d'invagination dans les divers pays n'étant pas claires, un certain nombre d'hypothèses ont été avancées, dont: des variations dans l'âge de vaccination, des différences d'efficacité du vaccin (une plus faible efficacité pouvant, par exemple, être associée à un risque plus réduit d'invagination), l'usage concurrent du vaccin antipoliomyélitique inactivé (VPI) ou du vaccin antipoliomyélitique oral (VPO) (l'usage concurrent du VPO, par exemple, peut réduire à la fois l'efficacité du vaccin antirotavirus et le risque d'invagination intestinale); et l'hypothèse de l'effet déclencheur (selon laquelle vaccination pourrait déclencher l'invagination chez un individu susceptible qui aurait pu présenter une invagination ultérieurement en l'absence de vaccination). Le comité a suggéré que les futures études de suivi continuent d'évaluer ces variables. En outre, les pays passant du VPO au VPI, il faudrait envisager des études évaluant à la fois l'efficacité et le risque d'invagination. Les pays devraient aussi continuer à évaluer les risques des nouveaux vaccins à mesure de leur homologation et de leur introduction. Globalement, le Comité demeure rassuré quant à l'écart entre le bénéfice de la vaccination antirotavirus dans la prévention des diarrhées sévères et le faible risque potentiel d'invagination, identifié par la plupart des études posthomologation, mais non toutes.

Le point sur l'innocuité des vaccins contre la dengue

Le GACVS a suivi la mise au point d'un vaccin vivant recombinant tétravalent contre le virus de la dengue au cours des 5 dernières années.^{9–12} Le produit le plus avancé, le vaccin CYD-TDV de Sanofi-Pasteur (Dengvaxia®) est constitué d'un vecteur dont la colonne vertébrale est un virus vaccinal amaril qui exprime des protéines enveloppes des virus de la dengue de types 1 et 4. Lors des premiers essais cliniques, aucune manifestation postvaccinale grave n'a été enregistrée chez les bénéficiaires de la vaccination et aucun excès de cas de dengue ou de dengue sévère attribuable au vaccin n'a été observé. Des essais de phase III à grande échelle menés ultérieurement, à savoir l'essai CYD14 en Asie (sujets de 2 à 14 ans) et l'essai CYD15 en Amérique latine (sujets de 9 à 16 ans) ont été réalisés >20 000 bénéficiaires de la vaccination et chez 10 000 sujets témoins et ont démontré une efficacité partielle du vaccin.

Le Dengvaxia® a reçu ces premières autorisations de mise sur le marché à la fin de l'année 2015 et se trouve actuellement disponible dans plusieurs pays d'Asie et d'Amérique latine. Le présent rapport examine succinctement les expériences présentées au GACVS et acquises dans le développement des essais cliniques (avec maintenant >5 ans de suivi) et discute des nouveaux éléments présentés à l'OMS lors de la réunion de ce

⁹ See No. 6, 2013, pp. 68–69.

¹⁰ See No. 4, 2015, pp. 17–18.

¹¹ See No. 34, 2015, pp. 421–423.

¹² See No. 28/29, 2016, pp. 346–347.

⁹ Voir N° 6, 2013, pp. 68–69.

¹⁰ Voir N° 4, 2015, pp. 17–18.

¹¹ Voir N° 34, 2015, pp. 421–423.

¹² Voir N° 28/29, 2016, pp. 346–347.

new data are based on the reanalysis of clinical trial data using a new test that retrospectively distinguished subjects with and without prior exposure to wild dengue virus.

Background

Dengue is an increasingly important disease worldwide. As outlined in the WHO position paper on dengue vaccines published in July 2016,¹³ the number of cases reported annually to WHO increased from 0.4 to 1.3 million during the decade 1996–2005, reaching 2.2 million in 2010 and 3.2 million in 2015. Based on mathematical modelling, the global annual incidence has been estimated at approximately 50–100 million symptomatic cases, predominantly in Asia, followed by Latin America and Africa. However clinical cases are likely to represent only about 25% of all dengue virus infections. In 2013 dengue was estimated to be responsible for approximately 3.2 million severe cases and 9000 deaths, the majority occurring in lower middle-income countries. GACVS recognized several challenges for the evaluation of the safety of dengue vaccines, particularly the follow-up time needed to monitor the theoretical risk of increased severe dengue following vaccination. Severe dengue cases represent a small percentage of all dengue infections and are more common on second exposure to wild dengue viruses.

In 2015, the Committee was presented with results from the third year of follow-up in the CYD14 trial conducted in Asia. The trial found that the risk of hospitalized dengue was significantly higher in the vaccinated group compared with the control group of age 2–5 years (relative risk = 7.45, 95% confidence interval: 1.15, 313.80). This risk was not found to be elevated in older age groups. At the time, GACVS highlighted the importance of understanding potential factors, other than age, that may be associated with this increased relative risk of hospitalization and of severe dengue. Among them, understanding if a subject had been exposed to wild dengue virus prior to vaccination was deemed critical given the lower vaccine efficacy in participants who were serologically naïve, and the potential risk of immune enhancement among previously infected subjects.

Based on these results, GACVS noted that the excess cases of hospitalized dengue (in the age group 2–5 years) could be related to age, serostatus, or both. The plausible hypothesis proposed was that vaccination primes the immune system similarly to natural infection, and that after a period of protection following vaccination, immunity wanes. According to this hypothesis, among seronegative individuals, the response to the first natural infection following vaccination (and waning immunity) may act as a second infection, which has typically

comité en décembre 2017. Ces nouveaux éléments proviennent de la réanalyse des données d'essais cliniques à l'aide d'un nouveau test qui distingue rétrospectivement les sujets ayant subi ou non une exposition antérieure au virus sauvage de la dengue.

Contexte général

La dengue est une maladie qui progresse partout dans le monde. Comme indiqué dans la note de synthèse de l'OMS sur le vaccin contre la dengue publiée en juillet 2016,¹³ le nombre de cas notifiés chaque année à l'OMS est passé de 400 000 à 1,3 million entre 1996 et 2005 pour atteindre 2,2 millions en 2010 et 3,2 millions en 2015. Sur la base d'une modélisation mathématique, l'incidence mondiale annuelle a été estimée entre 50 et 100 millions de cas symptomatiques environ, situés principalement en Asie, devant l'Amérique latine et l'Afrique. Cependant, les cas cliniques ne représentent probablement qu'environ 25% de l'ensemble des infections par le virus de la dengue. On estime qu'en 2013, la dengue était responsable d'environ 3,2 millions de cas de maladie sévère et 9000 décès, principalement dans les pays à revenu intermédiaire de la tranche inférieure. Le GACVS a reconnu que l'évaluation de l'innocuité des vaccins contre la dengue posait plusieurs difficultés, s'agissant notamment de la durée nécessaire au suivi du risque théorique d'augmentation de la dengue sévère suite à la vaccination. Les cas de dengue sévère représentent un faible pourcentage de l'ensemble des infections par la dengue et sont plus courants à la deuxième exposition aux virus sauvages de la dengue.

En 2015, le Comité a pris connaissance des résultats de la troisième année de suivi de l'essai CYD14 mené en Asie. Cet essai a révélé que le risque de dengue nécessitant une hospitalisation était nettement plus élevé dans le groupe vacciné que dans le groupe témoin de sujets âgés de 2 à 5 ans (risque relatif = 7,45, intervalle de confiance à 95%: 1,15; 313,80). Ce risque n'est pas apparu élevé dans les groupes plus âgés. Le GACVS a alors souligné l'importance de comprendre les facteurs potentiels, autres que l'âge, qui pourraient être associés à cette augmentation du risque relatif d'hospitalisation et de dengue sévère. Il a notamment été jugé essentiel de déterminer si le sujet avait été exposé au virus de la dengue sauvage avant la vaccination, compte tenu de l'efficacité plus faible du vaccin chez les participants sérologiquement naïfs et du risque potentiel de renforcement de la dengue lié à l'immunité chez les sujets antérieurement infectés.

Se fondant sur ces résultats, le GACVS a noté que l'excédent de cas de dengue hospitalisés (dans la tranche d'âge des 2 à 5 ans) pourrait être lié à l'âge, au statut sérologique, ou à ces 2 facteurs. L'hypothèse plausible proposée était que la vaccination stimule le système immunitaire de la même manière que l'infection naturelle, et qu'après une période de protection consécutive à la vaccination, l'immunité s'estompe. Selon cette hypothèse, chez les sujets séronégatifs, la réaction à la première infection naturelle survenant après la vaccination (et après la diminution de l'immunité) s'apparenterait à une seconde infection, laquelle est géné-

¹³ See No. 30, 2016, pp. 349–364.

¹³ Voir N° 30, 2016, pp. 349–364.

been associated with a higher risk of serious disease. In seropositive individuals, the response to the first natural infection following vaccination is as if it was a third or later infection and not associated with a higher risk of serious disease. As a result of available evidence, licensure was sought for children and adults aged ≥ 9 years. The Strategic Advisory Group of Experts (SAGE) on Immunization issued recommendations in April 2016 to introduce Dengvaxia® in geographical settings (national or subnational) with high endemicity only, as indicated by seroprevalence of $>70\%$ in the age group targeted for vaccination.

In June 2016,⁴ GACVS was presented with the longer-term 4-year follow-up of hospitalized dengue among CYD14 and CYD15 clinical trial participants. While no consistent increase was observed in the risk of hospitalization or severe dengue in vaccinated individuals aged 9–16 years, in the younger age group of 2–8 years, an increased relative risk (not reaching significance) was observed in year 3 of follow-up that persisted during year 4 but was declining. GACVS recommended that existing and planned clinical efficacy trials should be evaluated in depth and include careful assessment of pre-immunization seropositivity in selected cohorts. These data would contribute to a greater understanding of the potential risk factors and underlying immunology of dengue infection and severe dengue post-vaccination.

Current status and new data

To date, the vaccine has been licensed in 19 countries and introduced in public immunization programmes in the Philippines and Brazil. Immunization began in the Philippines in April 2016 and GACVS was presented with the programme's early post-market surveillance experience.⁴ The country had seen dramatic increases in cases since 2010 with $>150\,000$ dengue episodes and approximately 1000 deaths annually. By the time of the meeting in June 2016,⁴ almost 250 000 children aged ≥ 9 years had been vaccinated.

As SAGE identified vaccine safety in the seronegative population as a research priority,⁶ Sanofi Pasteur has undertaken a case-cohort study using a dengue anti-NS1 IgG ELISA assay (NS1) on blood samples available from clinical trial participants at 13 months after the first dose (1 month following the third and last dose of vaccine administered during the clinical trials). The research assay is designed to differentiate between prior natural infection and vaccination. Based on these results, the company reanalysed the safety and efficacy according to this surrogate of serostatus as well as age at the time of vaccination.

Overall, vaccinated trial participants had a reduced risk of virologically-confirmed severe dengue and hospitalizations. The subset of trial participants who had not been exposed to dengue virus infection prior to vacci-

nalement associée à un risque accru de maladie sévère. Chez les sujets séropositifs, au contraire, la réaction à la première infection naturelle après la vaccination s'apparente à celle qui surviendrait avec une troisième infection ou une infection subséquente et n'est pas associée à un risque accru de maladie sévère. Sur la base des données factuelles disponibles, l'homologation du vaccin a été demandée pour les enfants de ≥ 9 ans et les adultes. Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination a présenté en avril 2016 des recommandations selon lesquelles le Dengvaxia® devrait être introduit exclusivement dans les zones géographiques (nationales ou infranationales) de forte endémicité, c'est-à-dire celles où la séroprévalence est $>70\%$ dans la tranche d'âge visée par la vaccination.

En juin 2016,⁴ le GACVS a pris connaissance des résultats du suivi à long terme (sur 4 ans) des cas de dengue hospitalisés parmi les participants aux essais cliniques CYD14 et CYD15. Aucune augmentation systématique n'a été observée dans le risque d'hospitalisation ou de dengue sévère chez les sujets vaccinés âgés de 9 à 16 ans, mais dans la tranche d'âge inférieure (2 à 8 ans), une augmentation du risque relatif (inférieure au seuil de signification) a été observée pendant la troisième année de suivi ainsi que durant la quatrième année (où elle est apparue de moins en moins marquée). Le GACVS a recommandé que les essais cliniques d'efficacité existants et prévus fassent l'objet d'une évaluation approfondie incluant une évaluation rigoureuse de la séropositivité prévacination dans certaines cohortes. Ces données contribueraient à une meilleure compréhension des facteurs de risque potentiels et de l'immunologie de l'infection par la dengue et de la dengue sévère postvaccination.

Situation actuelle et nouvelles données

À ce jour, le vaccin a été homologué dans 19 pays et introduit dans les programmes de vaccination publics des Philippines et du Brésil. La vaccination a commencé en avril 2016 aux Philippines et le GACVS a pris connaissance des premiers résultats de la surveillance postcommercialisation réalisée par le programme.⁴ Une forte hausse des cas avait été observée dans le pays depuis 2010, avec $>150\,000$ épisodes de dengue et environ 1000 décès annuels. Au moment de la réunion en juin 2016,⁴ près de 250 000 enfants âgés de ≥ 9 ans avaient été vaccinés.

Le SAGE ayant déterminé que l'innocuité des vaccins dans la population séronégative est une priorité de la recherche,⁶ Sanofi Pasteur a entrepris une étude cas cohorte utilisant un essai ELISA pour les anticorps IgG anti NS1 de la dengue (NS1) sur des échantillons sanguins prélevés chez les participants à l'essai clinique 13 mois après la première dose (1 mois suivant la troisième et la dernière doses du vaccin administré lors des essais cliniques). L'essai est conçu de manière à distinguer une infection naturelle antérieure et la vaccination. Sur la base de ces résultats, l'entreprise a réalisé une nouvelle analyse de l'innocuité et de l'efficacité en se fondant sur ces données de substitution du statut sérologique et l'âge de la vaccination.

Globalement, les participants à l'essai vaccinés présentaient un risque réduit de dengue sévère confirmée virologiquement et d'hospitalisation. Le sous-ensemble de participants à l'essai qui n'avaient pas été exposés à l'infection par le virus de la dengue

nation (i.e. dengue-naïve, seronegative according to the NS1 assay) had a twice higher risk of more severe dengue and hospitalizations compared with unvaccinated participants, regardless of age. In contrast, those trial subjects, at any age, with evidence of a previous dengue infection (as determined by NS1 assay) experienced a reduced risk of severe dengue for the duration of the observation period.

Based on this new analysis, Sanofi Pasteur estimated the actual risks in the study population. In study subjects aged 2–16 years without prior dengue infection, data suggest modest efficacy (15–32%) of vaccine against symptomatic dengue until the second year of follow-up. Subsequently, starting during year 3, the risk of hospitalized and severe illness becomes higher than among controls. In practical terms, and within the population studied, these data suggest that during a 5-year follow-up, approximately 5 additional hospitalized dengue cases, or 2 additional severe dengue cases, per 1000 vaccinees with no previous dengue infection (i.e. dengue naïve subjects) could occur following vaccination, compared with unvaccinated seronegative children. Importantly, in the clinical trial population, all cases recovered and no deaths were observed. On the other hand, among children who had a prior dengue infection (i.e. seropositive) there was a reduction of 15 cases of hospitalized dengue and 4 cases of severe dengue per 1000 who were vaccinated for the same duration of follow-up.

Implications and assessment by GACVS

GACVS considered these new results as well as the clinical trial data and early post-market data submitted. Key issues included the validity of these findings, the subgroups to which they mostly apply, the magnitude of the risk, and implications, both for those subjects already vaccinated, and those not yet vaccinated. GACVS acknowledged that the vaccine is safe and efficacious in individuals who have had a primary infection with wild dengue preceding immunization, thus preventing a “second” and therefore more severe episode of dengue. GACVS noted that the increased risk of severe dengue among vaccinated individuals who are seronegative to dengue at the time of vaccination became apparent during the third year after receipt of the first vaccine dose irrespective of age. Thus, as post-licensure use started in the second quarter of 2016, an increase in the number of severe dengue cases among seronegative subjects would not occur before 2018 in Brazil and the Philippines – the 2 countries with early introduction of the vaccine.

The new data indicate that the increased risk of hospitalization (and severe disease) from dengue affects vaccinated subjects who are naïve to wild dengue infection prior to vaccination. This provides strong indication that previously identified excess risk among younger vaccine recipients in the Asian study reflected

avant la vaccination (c’est-à-dire naïfs pour la dengue, séronégatifs d’après l’essai NS1) avaient un risque 2 fois plus élevé que les participants non vaccinés de présenter une forme de dengue plus sévère et d’être hospitalisé, indifféremment de l’âge. Au contraire, chez les participants ayant eu une infection antérieure à la dengue (attestée par un essai NS1), le risque de dengue sévère était réduit pour toute la durée de la période d’observation, et ce quel que soit l’âge.

Se fondant sur cette nouvelle analyse, Sanofi Pasteur a estimé les risques effectifs dans la population d’étude. Chez les sujets participants âgés de 2 à 16 ans et non antérieurement infectés par la dengue, les données indiquent une efficacité modeste (15–32%) du vaccin contre la dengue symptomatique jusqu’à la deuxième année de suivi. Ensuite, à partir de la troisième année, le risque d’hospitalisation ou de maladie sévère devient plus élevé que chez les témoins. En pratique, et dans la population étudiée, ces données tendent à indiquer que, sur une durée de suivi de 5 ans, environ 5 cas supplémentaires de dengue avec hospitalisation, ou 2 cas supplémentaires de dengue sévère, pourraient survenir suite à la vaccination pour 1000 sujets vaccinés sans infection antérieure à la dengue (c’est-à-dire des sujets naïfs pour la dengue), par rapport à ce qui serait le cas chez des enfants séronégatifs non vaccinés. Fait important, dans la population ciblée par cet essai clinique, tous les cas sont rétablis et aucun décès n’a été observé. En revanche, chez les enfants antérieurement infectés par la dengue (c’est-à-dire séropositifs), une réduction de 15 cas de dengue entraînant une hospitalisation et de 4 cas de dengue sévère a été enregistrée pour 1000 sujets vaccinés sur la même durée de suivi.

Implications et évaluation par le GACVS

Le GACVS a examiné ces nouveaux résultats ainsi que les données d’essais cliniques et les premières données postcommercialisation. Les principales questions traitées étaient la validité de ces résultats, les sous groupes auxquels ils s’appliquent le mieux, l’ampleur du risque, et les implications pour les sujets déjà vaccinés et ceux qui ne le sont pas encore. Le GACVS a reconnu que le vaccin est sûr et efficace chez les sujets qui ont eu une infection primaire par la dengue sauvage avant la vaccination, empêchant ainsi la survenue d’un deuxième épisode de dengue, plus sévère. Le GACVS a noté que l’augmentation du risque de dengue sévère chez les sujets vaccinés qui étaient séronégatifs pour la dengue au moment de la vaccination est apparue la troisième année suivant l’administration de la première dose du vaccin, indifféremment de l’âge. Par conséquent, l’usage post-homologation ayant débuté au deuxième trimestre 2016, le nombre de cas de dengue sévère chez les sujets séronégatifs ne devrait pas augmenter avant 2018 au Brésil et aux Philippines – les 2 pays où une introduction préliminaire du vaccin a eu lieu.

Les nouvelles données montrent que l’augmentation du risque d’hospitalisation (et de maladie sévère) imputable à la dengue concerne les sujets vaccinés qui étaient naïfs pour l’infection à la dengue sauvage avant la vaccination. Cela indique manifestement que le risque excédentaire que l’étude asiatique avait antérieurement mis en évidence chez les sujets vaccinés de la

a confounding association between age and exposure to wild dengue virus. Thus it appears that history of exposure to wild dengue, rather than age, predicts the risk of severe disease among vaccine recipients. This also corroborates prior hypotheses suggesting that immune priming from natural or other stimulation such as immunization with the dengue vaccine can lead to a higher risk of severe dengue disease on secondary exposure to wild dengue viruses.

GACVS recognizes that the vaccine has, to date, been administered to a large majority of subjects among populations where exposure to dengue virus is high and therefore most vaccine recipients are seropositive to wild dengue. Notable is that the clinical data presented by Sanofi Pasteur also showed that, even among seronegative population, the number that would experience untoward severe dengue is likely to be <1%, and that with proper clinical care, more serious consequences can be prevented in most instances.

As a result, GACVS recommends that Dengvaxia® should not be administered to individuals who have not been previously infected with wild dengue virus. Data are not currently available to allow an analysis of the risk according to the number of vaccine doses received by subjects seronegative at baseline. It is therefore not possible to determine if incomplete vaccination would lead seronegative subjects to a higher or lower risk of severe dengue as compared to seronegative subjects who have received the full 3-dose course.

In order to minimize untoward consequences for dengue-naïve vaccinated subjects, GACVS recommends ensuring the enhancement of measures that reduce exposure to dengue infection among populations where the vaccine has already been administered. For vaccine recipients who present with clinical symptoms compatible with dengue virus infection, access to medical care should be expedited to allow for proper evaluation, identification, and management of severe forms of the disease.

Interrater reliability of causality assessment for serious adverse events following immunization

An AEFI is defined as any untoward medical occurrence following immunization which does not necessarily have a causal relationship to the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. Based on the advice from GACVS to review the causality assessment system, WHO commissioned a group of experts to develop a methodology and tools to assist health-care personnel in the assessment of causality of an adverse event and use of a vaccine. The causality assessment (CA) methodology and tool developed included an eligibility component for the assessment

plus jeune tranche tient à une association porteuse de confusion entre l'âge et l'exposition au virus sauvage de la dengue. Il apparaît par conséquent que ce sont les antécédents d'exposition à la dengue sauvage, plutôt que l'âge, qui permettent d'anticiper un risque de maladie sévère chez les sujets vaccinés. Ces éléments corroborent également des hypothèses antérieures selon lesquelles la stimulation du système immunitaire, naturellement ou par d'autres voies telles que l'administration du vaccin contre la dengue, peut accroître le risque de dengue sévère lors d'une exposition secondaire aux virus de la dengue sauvage.

Le GACVS reconnaît qu'à ce jour, le vaccin a été administré à une grande majorité de sujets appartenant à des populations caractérisées par une forte exposition au virus de la dengue, dans lesquelles la plupart des sujets vaccinés sont donc séropositifs pour la dengue sauvage. Il est notable que les données cliniques présentées par Sanofi Pasteur ont également démontré que, même dans la population séronégative, le nombre de sujets susceptibles de connaître un épisode de dengue sévère devrait être <1%, et que moyennant des soins cliniques adaptés, les conséquences les plus graves peuvent être évitées dans la plupart des cas.

Par conséquent, le GACVS recommande que le Dengvaxia® ne soit administré à des sujets qui n'ont pas été préalablement infectés par le virus sauvage de la dengue. Aucune donnée n'est actuellement disponible pour analyser le risque à la lumière du nombre de doses de vaccin reçues au départ par les sujets séronégatifs. Il est donc impossible de déterminer si une vaccination incomplète entraînerait une augmentation ou une diminution du risque de dengue sévère par rapport aux sujets séronégatifs ayant reçu le schéma complet à 3 doses.

En vue de réduire au minimum les conséquences négatives pour les sujets vaccinés naïfs pour la dengue, le GACVS recommande de renforcer les mesures tendant à réduire l'exposition à l'infection chez les populations déjà vaccinées. Les sujets vaccinés présentant des symptômes cliniques évocateurs de l'infection par ce virus doivent avoir un accès plus rapide aux soins médicaux afin de bénéficier d'une évaluation, d'une identification et d'une prise en charge appropriées des formes sévères de la maladie.

Fiabilité interévaluateurs de l'évaluation de la causalité pour les manifestations postvaccinales indésirables graves

Par MAPI, on entend tout événement médical intempestif qui suit la vaccination, qu'il ait ou non un lien de causalité avec le vaccin. Il peut s'agir d'un signe défavorable ou imprévu, d'un résultat de laboratoire anormal, d'un symptôme ou d'une maladie. Sur les conseils du Comité, qui a préconisé de revoir le système d'évaluation de la causalité, l'OMS a chargé un groupe d'experts de mettre au point une méthodologie et des outils pour aider le personnel de santé dans l'évaluation du lien de causalité entre une manifestation indésirable et l'utilisation d'un vaccin. La méthodologie d'évaluation de la causalité et l'outil mis au point incluaient des critères d'admissibilité à cette évaluation permettant l'examen du diagnostic associé à la

that reviews the diagnosis associated with the event and identifies the administered vaccines; a checklist that systematically guides users to gather available information to feed a decision algorithm; and a decision support algorithm that assists the assessors to arrive at a classification of the individual AEFI (manual classification). This revised methodology was endorsed by GACVS at its meeting in June 2012.¹⁴ A causality assessment manual and AEFI causality assessment software were developed (electronic classification). Final classification generated by the process includes 4 categories in which the event is either: (1) consistent; (2) inconsistent; (3) indeterminate with respect of causal association; or (4) unclassifiable. Feedback obtained from end users of this methodology included the importance of conducting a validation study regarding the interrater agreement of the classification.

To address this concern, an interrater study of causality assessment for serious AEFIs was conducted in April 2017 to evaluate the reliability (i.e. the degree to which an assessment tool produces consistent results between country evaluators) of the methodology and to compare the manual AEFI causality assessment method with the electronic method. The study was conducted using serious AEFI cases from India and Zimbabwe. Each country had 2 assessing teams and each team had 4 persons with expertise in paediatrics, epidemiology, pharmacovigilance and public health.

During the GACVS meeting in December 2017, members were presented with the methods and findings from the interrater study as well as proposed changes to the worksheets and manual. Overall, there was a good concordance of ratings with >80% agreement on cases between experts from both countries and >80% agreement between experts from the same countries using the manual or the electronic methods. Based on the data obtained from this study, it was concluded that the methodology was reliable and the electronic AEFI-CA methodology was a suitable process for CA at country level and for comparison of the CA across countries. The CA appeared to be influenced by the quality of the case report and understanding of country specific processes of AEFI reporting, along with the experience of the assessors. A full scientific report is in preparation.

The results derived from the interrater study, as well as qualitative feedback from study participants, were used to further revise the worksheet and CA methodology by a GACVS working group. The Committee made several recommendations. To further refine the algorithm of the CA tool, GACVS recommended a systemic analysis of unclassifiable events; an analysis of the questions posed as part of the checklist to evaluate interrater agreement regarding the responses provided; the inclusion of addi-

manifestation et l'identification des vaccins administrés; une liste de contrôle qui aide de manière systématique les utilisateurs à rassembler les informations disponibles pour alimenter un algorithme de décision; et un algorithme de soutien à la prise de décision qui aide les évaluateurs à parvenir à une classification des différentes MAPI (classification manuelle). Cette méthodologie révisée a été approuvée par le Comité à sa réunion de juin 2012.¹⁴ Un manuel et un logiciel d'évaluation du lien de causalité pour les MAPI ont été mis au point (classification électronique). Ce processus permet un classement final de la manifestation, en fonction du lien de causalité, dans l'une des 4 catégories suivantes: 1) compatible; 2) incompatible; 3) indéterminée; ou 4) inclassable. Dans les observations obtenues auprès des utilisateurs finaux de cette méthodologie, l'importance de mener une étude validant l'accord interévaluateurs sur la classification a aussi été notée.

Pour répondre à cette préoccupation, une étude interévaluateurs de l'évaluation de la causalité pour les MAPI graves a été menée en avril 2017 pour évaluer la fiabilité (c'est-à-dire le degré de constance des résultats produits par un outil d'évaluation lorsqu'il est utilisé par les évaluateurs dans les pays) de la méthodologie et pour comparer la méthode manuelle d'évaluation de la causalité pour les MAPI et la méthode électronique. L'étude a été menée en utilisant des cas de MAPI graves survenues en Inde et au Zimbabwe. Chaque pays disposait de 2 équipes d'évaluation et chaque équipe était composée de 4 personnes ayant des compétences en pédiatrie, épidémiologie, pharmacovigilance et santé publique.

Au cours de la réunion du Comité tenue en décembre 2017, les méthodes utilisées et conclusions tirées lors de l'étude interévaluateurs, ainsi que les changements proposés à apporter aux feuilles de calcul et au manuel, ont été présentées aux membres. Globalement, la concordance des notations a été satisfaisante, avec un accord >80% sur les cas entre les experts des deux pays et un accord >80% entre experts d'un même pays utilisant la méthode manuelle ou la méthode électronique. Sur la base des données obtenues à partir de cette étude, il a été conclu que la méthodologie était fiable et que la méthodologie électronique était un processus adapté à l'évaluation du lien de causalité pour les MAPI au niveau des pays et à sa comparaison d'un pays à l'autre. L'évaluation de la causalité semble être influencée par la qualité de la notification du cas et la connaissance des processus de notification des MAPI spécifiques au pays, ainsi que par l'expérience des évaluateurs. Un rapport scientifique complet est en cours de préparation.

Les résultats issus de l'étude interévaluateurs, ainsi que les observations qualitatives faites par les participants à l'étude, ont été utilisés pour une nouvelle révision des feuilles de calcul et de la méthodologie de l'évaluation de la causalité par un groupe de travail du Comité. Le Comité a formulé plusieurs recommandations. Pour affiner encore l'algorithme de l'outil d'évaluation de la causalité, le Comité a recommandé une analyse systémique des manifestations inclassables; une analyse des questions posées dans le cadre de la liste de contrôle afin

¹⁴ See No. 30, 2012, pp. 284–286.

¹⁴ Voir N° 30, 2012, pp. 284-286.

tional AEFIs, such as seizures; and inclusion of additional evidence, if available, in the CA to support a potential causal association of an AEFI with vaccination. Based on the qualitative analysis from the evaluation exercise GACVS also provided suggestions to clarify some aspects of the methodology and supporting guidance documents. The Committee looked forward to the publication and online availability of the revised AEFI causality assessment manual; the updating of the AEFI causality assessment software with the revised inputs; and the translation into additional UN languages of both the manual and electronic tools.

Guidance on prevention and management of immunization-triggered stress responses

During its December 2015 meeting, GACVS was presented with literature and mainstream and social media reports from several countries where clusters of anxiety-related reactions following immunization affected immunization programmes had drawn negative attention from the media and public.¹⁵ Following the meeting, GACVS convened an expert working group to explore and understand the etiology of such events and their characteristics, and prepare a guidance document that would help guide public health efforts and programme managers and immunization staff in prevention and management.

The expert working group systematically reviewed the available literature along with information gathered from social media, and used the findings to initiate discussion with subject experts. The group prepared a draft guidance document aimed to equip immunization programme managers and health-care providers at local, regional and national levels with the knowledge to manage both individual and clusters of such events. The emphasis was to obtain clarity on the spectrum of anxiety-related manifestations, including their epidemiology and associated risk factors, and to better understand the context of their occurrence. The objective was to produce a document providing a framework and guidance to understand, prevent, diagnose and manage such events; to explain the context of their occurrence; to clarify the reporting mechanisms and the communication approaches when such events occur; and to identify research gaps and strategies to move forward.

GACVS was presented with a draft manual for programme managers to prevent, identify and respond to stress related events associated with immunization. During discussions, it was clarified that the term, “immunization anxiety related reaction” did not capture

d'évaluer l'accord entre évaluateurs concernant les réponses fournies; l'inclusion d'autres MAPI, telles que les convulsions; et l'inclusion de données probantes supplémentaires, lorsqu'elles sont disponibles, dans l'évaluation de la causalité pour appuyer un lien potentiel de cause à effet entre une MAPI et la vaccination. En s'appuyant sur l'analyse quantitative de l'exercice d'évaluation, le Comité a aussi fourni des suggestions pour clarifier certains aspects de la méthode et des documents d'orientation correspondants. Le Comité se félicite à la perspective de la publication et de la disponibilité en ligne du manuel révisé pour l'évaluation de la causalité des MAPI; de la mise à jour du logiciel correspondant compte tenu des éléments révisés; et de la traduction dans d'autres langues officielles des Nations Unies du manuel et des outils électroniques.

Orientations concernant la prévention et la prise en charge des réactions de stress déclenchées par la vaccination

Au cours de la réunion tenue en décembre 2015, le Comité a pris connaissance des publications scientifiques, des articles issus des médias traditionnels et des médias sociaux de différents pays où les programmes de vaccination ont été confrontés à des grappes de réactions anxieuses postvaccinales, qui ont attiré l'attention des médias et du public.¹⁵ À la suite de la réunion, le Comité a réuni un groupe d'experts chargé d'étudier et de comprendre l'étiologie de ces manifestations et leurs caractéristiques, et d'établir un document d'orientation qui contribuerait à orienter les efforts dans le domaine de la santé publique, et à aider les administrateurs de programme et le personnel chargé de la vaccination à prévenir et prendre en charge ces réactions.

Le groupe d'experts a procédé à un examen systématique de la littérature disponible, ainsi que des informations issues des médias sociaux, et a utilisé les conclusions pour entamer des discussions avec des experts dans ce domaine. Le groupe a établi un projet de document d'orientation visant à doter les administrateurs des programmes de vaccination et les prestataires de soins aux niveaux local, régional et national des connaissances nécessaires pour gérer à la fois les cas individuels et les grappes de telles réactions. L'accent était mis sur l'obtention de précisions sur la gamme des manifestations d'anxiété, y compris leur épidémiologie et les facteurs de risque associés, et une meilleure compréhension du contexte de leur survenue. L'objectif était de produire un document fournissant un cadre et des orientations pour comprendre, prévenir, diagnostiquer et prendre en charge de telles manifestations; d'expliquer dans quel contexte elles surviennent; de clarifier les mécanismes de notification et les méthodes de communication lorsque de telles manifestations se produisent; et de recenser les lacunes dans la recherche et les stratégies pour y remédier.

Un projet de manuel à l'intention des administrateurs de programme visant à prévenir et identifier les manifestations de stress associées à la vaccination, et à y répondre a été présenté au Comité. Au cours des discussions, il a été précisé que le terme «réaction anxieuse postvaccinale» ne couvrirait pas

¹⁵ See No. 3, 2016, pp. 21–23.

¹⁵ Voir N° 3, 2016, pp. 21-23.

the spectrum of such events. A new term, “Immunization Triggered Stress Response” (ITSR) was therefore proposed which incorporates all events that manifest just prior to, during, or after immunization. ITSR can be subcategorized to peri-immunization stress response, post-immunization stress response and other disorders or syndromes that can occur post-immunization, such as the occurrence of anxiety, fear, phobia with immunization, and associated anxiety disorders including “needle phobias” and conversion disorders. Complex syndromes that may have a stress component are also considered in possible relation to immunization and outlined in the document in a biopsychosocial context.

GACVS discussed the proposed terminologies and the classification. It was clear that further research is still needed to better understand the rate of occurrence of such events, their relationship to age and mechanisms of occurrence. There is a need to link ITSR with pain mitigation and pain management following injections. Better guidance to prevent stress-related events is needed, particularly for parents, vaccinators and health-care providers to address the needs of older children, adolescents and adults prior to vaccination. The exploitation of ITSR by anti-vaccine groups was also mentioned. To avoid mismanagement, screening to differentiate between ITSR and actual vaccine reactions, such as anaphylaxis, is critical; incorporating this into training materials for health-care providers will be helpful. GACVS recommended that the manual be circulated for consultation to relevant stakeholders and that training materials be developed to accompany the new document.

Harmonized approaches for the vigilance of interventions during pregnancy

In 2013, GACVS examined the safety of the increasing number of vaccines intended for pregnant women as well as inadvertent vaccinations in pregnancy.¹⁶ The difficulty of differentiating the risks of pregnancy from the risks of interventions on pregnancy outcomes was noted. Given the limited amount of clinical trial data on pregnant women, risks should be closely assessed through enhanced pharmacovigilance in the post-licensure phase and in different geographical settings.

Several promising vaccines to protect mothers and infants in the first few weeks of life before infant vaccination are being developed. Safety monitoring of vaccines administered during pregnancy will require enhanced vigilance mechanisms and standardized case

toute la gamme de ces manifestations. Un nouveau terme, «réaction de stress déclenchée par la vaccination», a par conséquent été proposé pour englober l'ensemble des manifestations qui se produisent juste avant, pendant, ou après la vaccination. Ces réactions peuvent être subdivisées en réactions de stress péri-vaccinales, réactions de stress postvaccinales et autres troubles ou syndromes susceptibles de survenir après une vaccination, tels que des manifestations d'anxiété, de crainte, de phobie de la vaccination, et les troubles anxieux associés, y compris «la phobie des piqûres» et les troubles de conversion. Les syndromes complexes qui peuvent avoir une composante liée au stress sont aussi considérés comme présentant un lien possible avec la vaccination et présentés dans le document dans un contexte biopsychosocial.

Le Comité a débattu de la terminologie et de la classification proposée. Il est apparu clairement qu'il convient de poursuivre encore les recherches pour mieux comprendre la fréquence de telles manifestations, leur lien avec l'âge des patients et les mécanismes de leur survenue. Il est nécessaire d'établir un lien entre les réactions de stress déclenchées par la vaccination et l'atténuation et la prise en charge de la douleur à la suite des injections. Des orientations mieux adaptées sont nécessaires pour prévenir les manifestations liées au stress, en particulier pour que les parents, les vaccinateurs et les prestataires de soins puissent répondre aux besoins des enfants les plus grands, des adolescents et des adultes avant la vaccination. La question de l'exploitation des réactions de stress par les groupes antivaccins a également été abordée. Pour éviter toute erreur dans la prise en charge, l'examen permettant de différencier une réaction de stress déclenchée par le vaccin d'une véritable réaction au vaccin, telle que l'anaphylaxie, est essentiel; il sera utile d'intégrer ce point dans les documents de formation destinés aux prestataires de soins. Le Comité a recommandé que le manuel soit diffusé pour examen auprès des parties prenantes pertinentes et que des documents de formation soient élaborés pour accompagner le nouveau document.

Approches harmonisées pour la vigilance à l'égard des interventions pendant la grossesse

En 2013, le Comité a examiné l'innocuité du nombre croissant de vaccins destinés aux femmes enceintes ainsi que les vaccinations par inadvertance au cours de la grossesse.¹⁶ La difficulté de différencier les risques liés à la grossesse des risques liés aux interventions sur les issues de la grossesse a été notée. Compte tenu du nombre limité de données provenant d'essais cliniques sur les femmes enceintes, il convient d'évaluer étroitement les risques moyennant une pharmacovigilance accrue au cours de la phase qui suit l'homologation et dans différents contextes géographiques.

Plusieurs vaccins prometteurs pour protéger les mères et les nourrissons au cours des premières semaines de vie avant la vaccination du nourrisson sont en cours de mise au point. Le suivi de l'innocuité des vaccins administrés au cours de la grossesse nécessitera des mécanismes de vigilance accrue et des

¹⁶ Global Advisory Committee on Vaccine Safety. Safety of Immunization during Pregnancy. A review of the evidence. World Health Organization, 2014. Available at: http://www.who.int/vaccine_safety/publications/safety_pregnancy_nov2014.pdf, accessed December 2017.

¹⁶ Comité consultatif mondial de la sécurité vaccinale. Innocuité de la vaccination pendant la grossesse - Examen des données factuelles. Organisation mondiale de la Santé, 2014. Disponible à l'adresse: www.who.int/vaccine_safety/publications/Pregnancy_web_FR.pdf, consulté en décembre 2017.

definitions of key events in pregnant women and newborns. In June 2016, GACVS reviewed the work conducted by the Global Alignment of Immunization Safety assessment in pregnancy (GAIA) project, and considered important not only the need for good health data, but also compatibility with the longstanding and established use of terminology coding underpinning disease monitoring (the International Classification of Diseases – ICD) or drug regulation (the Medical Dictionary for Regulatory Activities – MedDRA). The Committee also suggested that assessment of applicability of the case definition in different settings with limited health-care services be conducted. Immunization, however, is only one of many medical interventions during pregnancy and early childhood. Adequate vigilance requires that harmonization of methods be compatible with the work of other stakeholders including several WHO programmes.

During the meeting GACVS was informed of a stakeholders meeting on maternal interventions vigilance that took place in Geneva, 20–21 November 2017. The objectives of the meeting were to review current methods to monitor outcomes of maternal immunization and other interventions, with a particular focus on vigilance; assess available methodologies and identify where harmonization is needed; assess the global applicability of vigilance methodologies for maternal immunization and other interventions; and propose coordination mechanisms to support vigilance harmonization across programmes and partners working on improving pregnancy and early childhood health events. The stakeholders invited included WHO Collaborating Centres in pharmacovigilance, technical agencies with an interest in immunization in pregnancy;¹⁷ academic experts from all WHO regions;¹⁸ and regulatory experts with an interest in pregnancy interventions.¹⁹ Discussions addressed global applicability of vigilance methodologies for maternal health interventions during pregnancy. Several situations were highlighted that will affect the quantity and quality of data available; for example, during clinical research, there is likely to be a higher possibility of a specific diagnosis, compared with public health surveillance, where diagnoses may be based on minimal requirements. Likewise, weak civil registration systems can prevent the identification of vital events. It was therefore proposed that harmonized sets of data be collected so that studies and evaluations of the health of pregnant women can be developed. These sets should be tailored according to study char-

définitions normalisées des cas de manifestations clés chez les femmes enceintes et les nouveau-nés. En juin 2016, le Comité a examiné les travaux menés par le projet GAIA visant à l'harmonisation mondiale de l'évaluation de l'innocuité de la vaccination pendant la grossesse, et a jugé importante non seulement la disponibilité de données sanitaires de qualité, mais aussi la compatibilité avec le codage terminologique utilisé depuis longtemps et bien établi qui sous-tend la surveillance des maladies (Classification internationale des maladies – CIM), ou la réglementation des médicaments (the Medical Dictionary for Regulatory Activities – MedDRA). Le Comité a également suggéré qu'une évaluation de l'applicabilité des définitions de cas dans différents contextes où les services de soins sont limités soit menée. La vaccination n'est toutefois que l'une des nombreuses interventions médicales au cours de la grossesse et de la petite enfance. Une surveillance appropriée requiert que l'harmonisation des méthodes soit compatible avec le travail d'autres parties prenantes, dont plusieurs programmes de l'OMS.

Au cours de la réunion, le Comité a pris connaissance de la tenue d'une réunion des parties prenantes sur la surveillance des interventions maternelles qui a eu lieu à Genève les 20 et 21 novembre 2017. Les objectifs de la réunion étaient d'examiner les méthodes actuelles de suivi des issues de la vaccination maternelle et d'autres interventions, en mettant en particulier l'accent sur la surveillance; d'évaluer les méthodes disponibles et d'identifier les domaines où une harmonisation est nécessaire; d'évaluer l'applicabilité mondiale des méthodes de vigilance pour la vaccination maternelle et les autres interventions; et de proposer des mécanismes de coordination pour favoriser l'harmonisation de la vigilance entre programmes et partenaires œuvrant à faire régresser les événements indésirables pour la santé intervenant au cours de la grossesse et de la petite enfance. Parmi les parties prenantes invitées figuraient les Centres collaborateurs de l'OMS pour la pharmacovigilance, les organismes techniques concernés par la vaccination au cours de la grossesse;¹⁷ les spécialistes scientifiques de toutes les Régions de l'OMS;¹⁸ et les experts en matière de réglementation concernés par les interventions pendant la grossesse.¹⁹ Les discussions ont porté sur l'applicabilité mondiale des méthodes de surveillance aux interventions concernant la santé maternelle au cours de la grossesse. Plusieurs situations qui auront une incidence sur la quantité et la qualité des données disponibles ont été mises en lumière; au cours de la recherche clinique par exemple, la probabilité d'un diagnostic spécifique est sans doute plus élevée, par comparaison à la surveillance en santé publique où les diagnostics peuvent reposer sur des exigences cliniques minimales. De même, des systèmes d'enregistrement des données d'état civil de médiocre qualité peuvent empêcher l'identification des faits d'état civil. On a par consé-

¹⁷ PATH, Brighton Collaboration, GAPPS, the US Centers for Disease Control and Prevention, INCLEN, INDEPTH, IMPRINT, CROWNE, IABS.

¹⁸ University of Witwatersrand, South Africa; Washington State University, USA; University of Washington, USA; Baylor College, USA; Johns Hopkins Bloomberg School of Public Health, USA; Makerere University, Uganda; London School of Hygiene and Tropical Medicine, UK; Monash University, Australia; University of Alberta, Canada; University of Utrecht, the Netherlands; Liverpool School of Tropical Medicine, UK.

¹⁹ US Food and Drug Administration, industry umbrella organizations and the Council for International Organizations of Medical Sciences.

¹⁷ PATH, Brighton Collaboration, GAPPS, Centers for Disease Control and Prevention des États-Unis d'Amérique, INCLEN, INDEPTH, IMPRINT, CROWNE, IABS.

¹⁸ University of Witwatersrand, Afrique du Sud; Washington State University, États-Unis d'Amérique; University of Washington, États-Unis d'Amérique; Baylor College, États-Unis d'Amérique; Johns Hopkins Bloomberg School of Public Health, États-Unis d'Amérique; Makerere University, Ouganda; London School of Hygiene and Tropical Medicine, Royaume-Uni; Monash University, Australie; University of Alberta, Canada; University of Utrecht, Pays-Bas; Liverpool School of Tropical Medicine, Royaume-Uni.

¹⁹ Food and Drug Administration des États-Unis d'Amérique, industry umbrella organizations et le Council for International Organizations of Medical Sciences.

acteristics, ranging from minimal to optimal infrastructure and clinical conditions.

GACVS noted the similar data needs for both clinical surveillance and public health vigilance, and that data coding and data systems should be usable for both purposes. The Committee agreed that minimal data elements will need to be assessed for their availability in different settings and for different types of studies. The November meeting has already resulted in plans for the GAIA definitions to be considered by those working on updating and refining ICD 11 as part of the ICD's rolling programme for updating terms. ICD updates consider stakeholders, including obstetrics and gynaecology services, an essential part of the work in promoting ownership and use of ICD coding.

GACVS noted that as part of developing a roadmap for improving maternal, neonatal and child health programmes and assessments of vaccine safety in pregnancy, a WHO interdepartmental task force will be established to address harmonization of coding and data systems. The task force will include several stakeholders, including WHO regional and country offices and service providers. The aim of such a task force, over the next few years, is to establish a common platform to assess pregnancy related outcomes for any intervention delivered to women during pregnancy. GACVS welcomed this initiative and indicated that joint efforts to enhance access to quality data on pregnancy outcomes will benefit the broad community of stakeholders working to improve the health of mothers and their infants. ■

quent proposé de collecter des ensembles de données harmonisées afin de pouvoir mener à bien des études et des évaluations de la santé des femmes enceintes. Ces ensembles de données doivent être adaptés en fonction des caractéristiques de l'étude, l'éventail des infrastructures et des conditions cliniques allant de minimal à optimal.

Le Comité a noté que les besoins en données de la surveillance clinique et de la surveillance en santé publique étaient similaires, et qu'il conviendrait d'utiliser le codage et les systèmes de données à ces deux fins. Le Comité est convenu qu'il conviendra d'évaluer la disponibilité des éléments de données minimaux dans différents contextes et pour différents types d'études. À la suite de la réunion de novembre, il est déjà prévu que les définitions du projet GAIA soient soumises aux personnes chargées, dans le cadre du programme d'actualisation continue de la Classification, d'actualiser et de perfectionner la CIM-11. Dans le contexte de cette actualisation, le rôle des parties prenantes, y compris les services d'obstétrique et de gynécologie, est considéré comme essentiel pour favoriser l'appropriation et l'utilisation du codage de la CIM.

Le Comité a noté que dans le cadre de l'élaboration d'une feuille de route pour améliorer les programmes pour la santé de la mère, du nouveau-né et de l'enfant, un groupe spécial interdépartemental sera créé au sein de l'OMS pour aborder la question de l'harmonisation du codage et des systèmes de données. Le groupe spécial intégrera diverses parties prenantes, y compris les bureaux régionaux et les bureaux de pays de l'OMS et les prestataires de services. L'objectif de ce groupe spécial est d'établir, au cours des prochaines années, une plateforme commune pour évaluer les issues liées à la grossesse de toute intervention auprès des femmes au cours de la grossesse. Le Comité s'est félicité de cette initiative et a indiqué que les efforts conjoints visant à améliorer l'accès à des données de qualité sur les issues de la grossesse seront profitables à la vaste communauté des parties engagées dans l'amélioration de la santé de la mère et du nourrisson. ■

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Monthly report on dracunculiasis cases, January–November 2017

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

Rapport mensuel des cas de dracunculoze, janvier-novembre 2017

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

| Country – Pays | Date of receipt of the report ^a Date de réception du rapport ^a | Total no. of rumours ^b of suspected dracunculiasis cases in 2017 – Nombre total de rumeurs ^b de suspects de dracunculose en 2017 | No. of new dracunculiasis cases reported in 2017 ^c – Nombre de nouveaux cas de dracunculose signalés en 2017 ^c | | | | | | | | | | | | Total no. of reported cases for the same months of 2016 – Nombre total de cas signalés pour les mêmes mois en 2016 | Total no. of villages reporting cases for the same months in – Nombre total de villages signalant des cas pour les mêmes mois en | | Month of emergence of last reported indigenous case – Mois d'émergence du dernier cas autochtone signalé ^e |
|---|---|--|--|--------------------|--------------|---------------|-----------|-------------|----------------|---------------|-----------------------|-------------------|---------------------|------|--|--|----|---|
| | | | January – Janvier | February – Février | March – Mars | April – Avril | May – Mai | June – Juin | July – Juillet | August – Août | September – Septembre | October – Octobre | November – Novembre | 2017 | | 2016 | | |
| | | | Endemic countries – Pays d'endémie | | | | | | | | | | | | | | | |
| Chad – Tchad | 10 Jan. 2017 – 10 jan. 2017 | 2984 | 0 | 1 | 2 | 1 | 1 | 3 | 2 | 1 | 2 | 1 | 0 | 14 | 15 | 13 | 11 | Oct. 2017 – Oct. 2017 |
| Ethiopia – Éthiopie | 22 Dec. 2017 – 22 déc. 2017 | 12087 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 3 | 1 | 13 | 3 | 5 | 3 | Nov. 2017 – Nov. 2017 |
| Mali | NR | 314 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND | 0 | 0 | 0 | Nov. 2015 – Nov. 2015 |
| South Sudan – Soudan du Sud | NR | 14 725 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND | ND | ND | 0 | 6 | 0 | 3 | Nov. 2016 – Nov. 2016 |
| Precertification countries – Pays au stade de la précertification | | | | | | | | | | | | | | | | | | |
| Kenya | 15 Dec. 2017 – 15 déc. 2017 | 31 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Oct. 1994 – Oct. 1994 |
| Sudan – Soudan | NR | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND | 0 | 0 | 0 | 0 | Sept. 2013 – Sept. 2013 |
| Total | | 30 148 | 0 | 1 | 2 | 1 | 1 | 3 | 2 | 1 | 11 | 4 | 1 | 27 | 24 | 18 | 17 | |

Source: Ministries of Health – Ministères de la Santé.

^a Each monthly report is due by the 20th of the following month. – Chaque rapport mensuel est attendu pour le 20 du mois suivant.

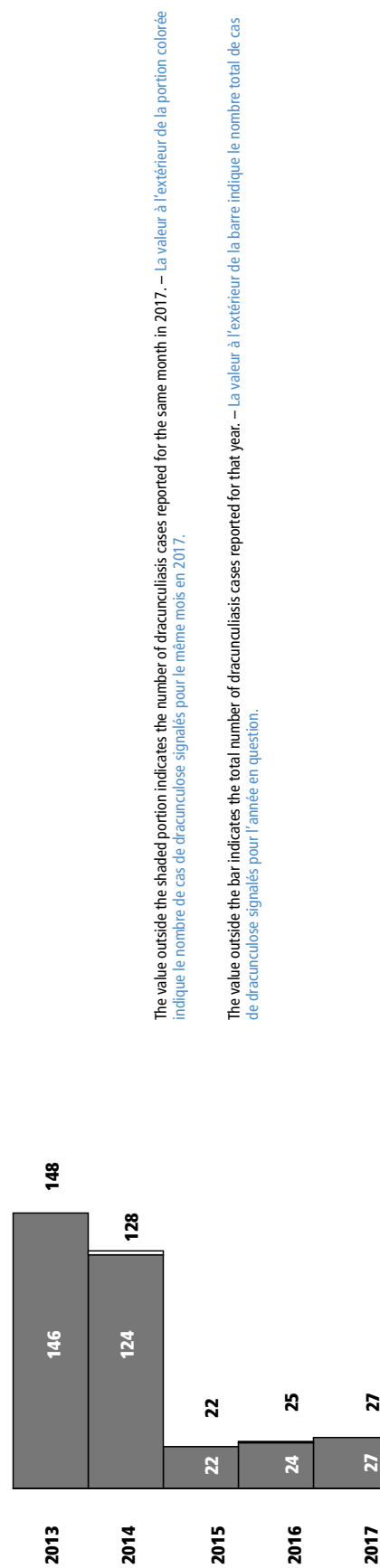
^b Rumour of dracunculiasis. Information about an alleged case of dracunculiasis (Guinea-worm disease) obtained from any source (informants). – Rumeur de dracunculose. Information au sujet d'un cas présumé de dracunculose (maladie du ver de Guinée) obtenue à partir de n'importe quelle source (informateurs).

^c The total number of dracunculiasis cases includes both indigenous and imported cases. – Le nombre total de cas de dracunculose regroupe les cas autochtones et les cas importés.

NR: No report received on surveillance indicator for the reporting month. – Aucun rapport reçu sur les indicateurs de la surveillance au cours du mois de déclaration.

ND: Data not available. – Pas de données disponibles.

Number of dracunculiasis cases reported worldwide, 2013–2017 – Nombre de cas de dracunculose signalés dans le monde, 2013–2017



Exploration of future immunization policies for measles and rubella: The need for continued investment and the potential benefits of eradication

Kimberly M. Thompson, Kid Risk, Inc. - Background materials for SAGE presentation on “The measles and rubella investment case” – 3/21/2018

Executive Summary

Measles and rubella viruses continue to pose health and economic costs despite widespread use of highly-effective, safe, and relatively inexpensive vaccines that provide lifelong protection from the serious adverse health effects caused by both viruses. Decades of national and regional measles and rubella control activities led to significant progress toward achieving regional elimination targets, but a recent review found that despite tremendous gains, the progress toward regional elimination goals and the Global Vaccine Action Plan targets remains off track. Significant delays in the achievement of global polio eradication and post-polio eradication transition planning raise questions about global investments and targets to manage vaccine-preventable diseases, and increase demands for the justification of expenditures on a wide range of competing health priorities. This analysis explores the case for global investment in measles and rubella immunization by estimating the incremental potential health and economic benefits associated with a scenario that seeks to eradicate both diseases as quickly as possible within the constraints of historical programmatic performance (as an upper bound of the potential benefits of future investments) relative to maintaining the 2016 *status quo*.

The first section provides context about measles and rubella viruses and vaccines, and the current landscape for measles and rubella control and elimination targets. Readers familiar with measles and/or rubella may wish to skip or skim this section. The second section provides high level context about the integrated model used for this analysis and an annex provides more details. The third section presents preliminary results, and the fourth section briefly discusses insights. The fifth section discusses next steps for this work and the final section provides references.

1. Introduction

Measles virus infections remain a leading preventable cause of estimated child deaths worldwide,¹ and congenital rubella syndrome (CRS) caused by rubella virus infection in early pregnancy represents one of the leading infectious disease causes of congenital birth defects globally.² These continued global burdens of disease occur despite the availability over many decades of highly-effective, safe, and relatively inexpensive vaccines that provide lifelong protection from serious adverse health effects caused by both viruses.^{3,4} By 1980, all World Health Organization (WHO) Member States introduced measles vaccine (first-licensed in the US in 1963) into their national immunization programs.⁴ In contrast, rubella vaccine (first licensed in the US in 1969) experienced more gradual global introduction, with some national immunization programs still yet to introduce it.⁴ The licensure of combination vaccines containing measles and rubella (e.g., MR, MMR) created an opportunity for sharing the costs of vaccine administration, and all countries that include rubella vaccine in their national immunization schedules use a combination vaccine.⁴ A large body of literature demonstrates the excellent cost-effectiveness and high net health and economic benefits of measles and rubella

immunization.^{5,6} Notably, a recent analysis for 94 relatively low-income countries estimated a net return on investment for 10 vaccines of about 16 times greater than costs, and found the highest returns came from averting measles, at 58 times the cost (uncertainty range: 28-105).⁷

Despite the significant health and economic benefits, recognizing the full potential of using measles and rubella vaccines remains uneven geographically. The US launched the first national measles elimination goal in 1967.⁸ Indicative of the challenges of national elimination, after establishing three different national measles elimination initiatives over several decades, the US successfully stopped indigenous measles⁹ and rubella¹⁰ virus by 2004. Since the introduction of the vaccines, national goals to eliminate measles and/or rubella emerged at various times. The WHO Region of the Americas, under the leadership of the Pan American Health Organization (PAHO), established the first WHO regional elimination goals for measles and rubella: in 1994, to eliminate indigenous measles virus transmission by the year 2000,¹¹ and in 2003, to eliminate indigenous rubella virus transmission by the year 2010.¹² The WHO Region of the Americas declared indigenous rubella eliminated in 2015¹² and indigenous measles eliminated in 2016,¹¹ following successful regional elimination activities. The other 5 WHO regions also established target years for regional measles elimination, all by 2020 or earlier.¹³

Over the last several decades, the World Health Assembly (WHA) established several goals for related to measles and rubella, including:

- In 1974, recommending “that Member States develop or maintain immunization and surveillance programmes against measles” (resolution 27.57)¹⁴
- In 1978, resolving to “by 1990 make measles vaccine available to every child in the world as part of the Expanded Programme on Immunization” (resolution 31.53)¹⁵
- In 1989, resolving to “by 1995 reduce measles cases by 90% and measles deaths by 95% compared to pre-immunization levels” (resolution 42.32)¹⁶
- In 2003, resolving to “by 2005 reduce measles deaths by 50% compared to 1999 levels” (resolution 56.20)¹⁷
- In 2005, resolving “as part of the Global Immunization Vision and Strategy, 2006-2015 (GIVS),¹⁸ by 2010 reduce measles deaths by 90% compared to 2000 levels” (resolution 58.15)¹⁹
- In 2010, discussing milestones for global eradication of measles and endorsing by 2015 “to reduce measles mortality by 95% or more in comparison with 2000 estimates” (provisional agenda A63.18).²⁰
- In 2012, resolving “as part of the Global Vaccine Action Plan (GVAP),²¹ by 2015 to “eliminate measles in four WHO regions and rubella/congenital rubella syndrome in at least two WHO regions and by 2020 eliminate measles and rubella in at least five WHO regions” (resolution 65.17)²²

In November 2010, the WHO Strategic Advisory Group of Experts (SAGE) concluded: “measles can and should be eradicated. A goal for measles eradication should be established with a proposed target date based on measurable progress made towards existing goals and targets.”²³ The International Task Force for Disease Eradication in 2009 identified measles as a good candidate for global eradication²⁴ and reached the same conclusions for measles and rubella in 2016.²⁵

For a variety of reasons, including the very high coverage needed to achieve and maintain measles elimination and insufficient political commitment and resources, global progress toward reducing measles incidence and mortality slowed during the past several years, which makes on-time achievement of the GVAP targets unlikely.¹³ A recent review^{26, 27} of the status of the Global Measles and Rubella Strategic Plan 2012-2020²⁸ reached a similar conclusion that progress remains off track, while noting the tremendous gains made toward both measles and rubella elimination since 2001.^{26, 27} The recent review conclusions included that “measles eradication is the ultimate goal but it is premature to set a date for its accomplishment[, existing] regional elimination goals should be vigorously pursued to enable setting a global target by 2020[, and the] basic strategic approaches articulated in the Global Measles and Rubella Strategic Plan 2012-2020 are valid to achieve the goals but have not been fully implemented (or not appropriately adapted to local situations).”^{26, 27}

Recognizing the variability that exists in national immunization programs, the WHO SAGE continues to update its immunization recommendations for measles- and rubella-containing vaccines. Providing all children with 2 doses of measles vaccine became the standard for all national immunization programs in 2009, with the second dose delivered either through supplemental immunization activities (SIAs) or through routine health services.²⁹ In 2011, the WHO SAGE updated its guidance on the preferred strategy for the introduction of rubella vaccine into national routine immunization (RI) schedules, including an initial vaccination campaign usually targeting children aged 9 months-15 years.³⁰ As of December 2014, 140 countries included rubella vaccine in their national immunization schedules, which reflected an increase up from 99 countries in 2000.² As of the end of 2016, 152 WHO member states included rubella vaccine in RI.³¹ Part of this increase reflected support of over \$500 million from Gavi, the Vaccine Alliance, to facilitate rubella vaccine introduction into the Gavi countries without rubella vaccine in their RI schedules as of 2012.³² In December 2015, the Gavi Board strengthened its commitment to measles and rubella immunization.³³ In 2016, the WHO SAGE recommended the inclusion of a second dose of measles vaccine in all national immunization schedules as part of routine health services.³⁴

Disease eradication represents the ultimate opportunity to achieve global equity with respect to eradicable diseases, and in this context measles and rubella eradication would help to advance the achievement of the United Nations 2030 Sustainable Development Goal 3 “to end preventable deaths of newborns and children under 5 years of age”³⁵ by increasing vaccination coverage to levels needed to end vaccine-preventable disease (VPD) deaths in children. Although population immunity and immunization coverage at the local level determine transmission (or lack thereof), aggregation to national, regional, and global levels provide an important perspective for VPDs that transmit easily across borders. At the global level, slow progress of measles elimination implies high on-going health and financial burdens associated with indefinitely sustaining relatively high immunization coverage in countries that eliminated indigenous transmission.³⁶ Consistent with the series of WHA targets to reduce measles and rubella burdens, despite the variability that exists between countries and regions, measles and rubella appear relatively highly controlled at a global level.³⁶

In countries that successfully eliminate measles and/or rubella, importations from endemic areas pose a threat of local transmission and expensive outbreak response activities.³⁶ Given the

available combination vaccines and the much lower transmissibility of rubella virus (compared to measles), rubella eradication could easily occur in the context of a measles eradication effort, which would prevent additional health and financial costs.³⁷ Moreover, in some countries with good disease control, children neither vaccinated nor exposed to these viruses remain susceptible as they reach older ages and even adulthood, which makes the task of stopping measles and rubella virus transmission epidemiologically more complex, expensive, and programmatically difficult to achieve.

Within the complex global context, exploring the case for continued and further investment in measles and rubella control and elimination goals may provide useful insights for national, regional, and global policy makers. Launched in 2001, the Measles & Rubella Initiative³⁸ remains committed to efforts to ensure “that no child dies from measles or is born with congenital rubella syndrome” and to “help countries to plan, fund and measure efforts to stop measles and rubella for good,”³⁸ although its funding and global support from key eradication donors pales in comparison to funds spent on the Global Polio Eradication Initiative (GPEI) and malaria eradication.³⁹ As the GPEI continues with the process of transitioning its responsibilities and any residual assets to countries, the significant support provided by the GPEI that benefits other VPDs, including measles and rubella, emerges as a concern. Notably, an April 2017 WHO report highlighted that: (i) 16 countries (i.e., Afghanistan, Angola, Bangladesh, Cameroon, Chad, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Myanmar, Nepal, Nigeria, Pakistan, Somalia, South Sudan, and Sudan) account for “90% of all the GPEI supported polio infrastructure;” (ii) budget decreases for 2017-2019 (compared to 2016) already led to a “substantial number of staff receiving termination notices, particularly in the African region;” (iii) “all of AFRO’s 47 WHO country offices receive GPEI seed surveillance funding on a quarterly basis to allow countries to conduct active surveillance activities for, not only Acute Flaccid Paralysis (AFP) but other VPD surveillance activities” (including measles and rubella); and (iv) for 2016, “WHO globally spent US\$587 million on polio eradication, which is 27% of its total expenditure in 2016.”⁴⁰ The report also notes that the “loss of approximately 20% of WHO’s biennium budget would have grave consequences for WHO’s capacity at the country level in member states that have weak health systems or in fragile states, especially at the provincial and district levels.”⁴⁰

Given the current changes in national, regional, and global investments in VPD management and the demands from the GVAP for the development of investment cases to support difficult decisions related to expenditures on competing health priorities,⁴¹ this analysis seeks to explore the bounds of the global incremental health and financial benefits that may arise from increased investment in measles and rubella immunization by comparing a scenario of eradication of both diseases as soon as possible to maintaining the 2016 *status quo*.

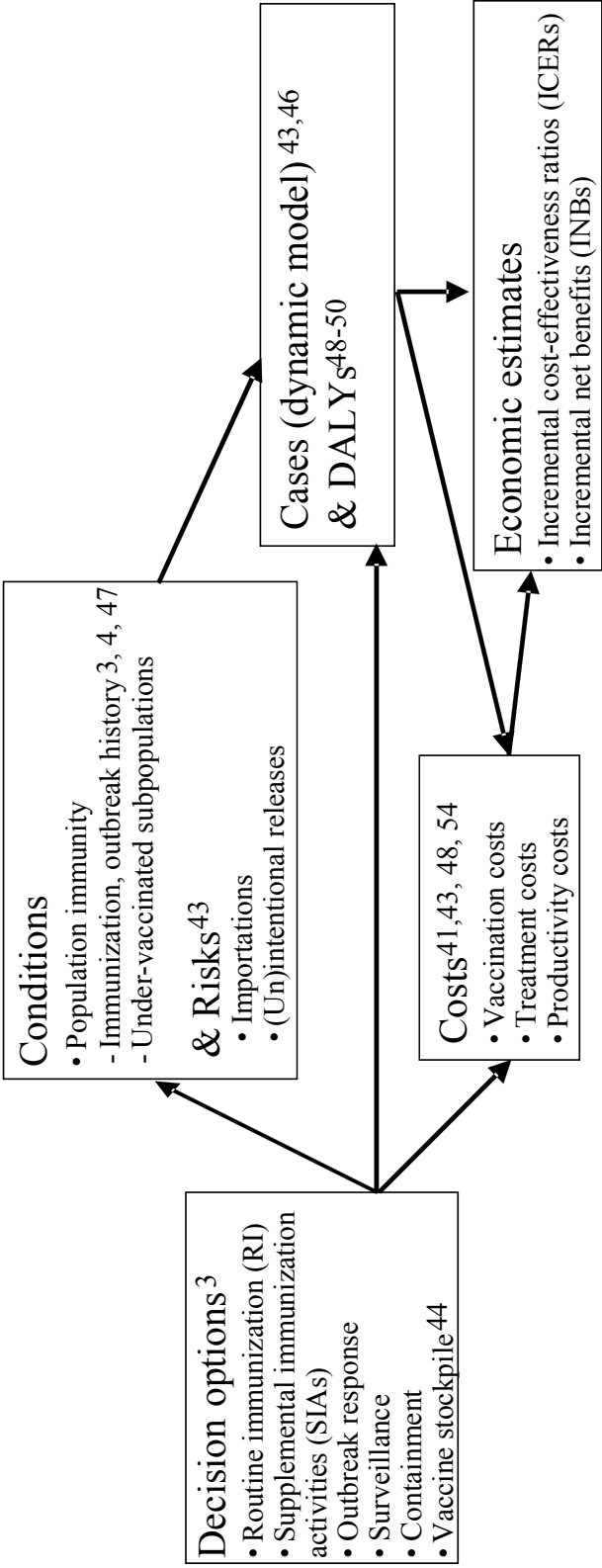
2. Methods

Similar to a model developed and used over a decade to support deliberations by the GPEI partners for polio eradication,⁴² this analysis uses an integrated dynamic risk and economic model developed for measles and rubella.⁴³ The measles and rubella model includes multiple components, described at a high level in Figure 1, which includes references to the publications that provide details about the inputs and assumptions. Briefly, the model considers different

decision options that national, regional, and global policy makers consider, with a focus on RI and SIAs³ and including some consideration of the importance of ensuring sufficient availability of vaccine.⁴⁴ The model characterizes national conditions that impact measles and rubella transmission (i.e., population immunity as a function of experience with historical immunization and reported incidence,⁴ population structures,⁴⁵ and virus transmission conditions⁴⁶). The model simulates transmission for each area separately for 180 WHO Member States and three other areas (i.e., Puerto Rico, Hong Kong, Macao)⁴³ with sufficient demographic and immunization data.⁴ (For context, the population in the model represented >99.5% of the estimated global population of 7.16 billion people in 2013.⁴⁵) The model⁴³ includes consideration of maternal immunity and tracks pregnancies to capture the dynamics of rubella virus infections in pregnancy⁴³ (see review⁴⁶ for the different types of assumptions used in published measles and rubella virus transmission models). The model⁴³ uses assumptions about historical RI and SIAs based on a review of the evidence,⁴ and we characterize country-specific basic reproduction numbers (R_0 s) for measles and rubella, and mixing and seasonal amplitude assumptions based on fitting the dynamic transmission model to the historical time series of incidence available for all countries for measles since 1980 and for rubella and since 2004⁴ and data from serological studies available from many countries.⁴⁷ The estimates of incidence from the transmission model provide the basis for estimating the adverse health outcomes over time for each country, including estimated rates of complications from infections and vaccine-associated adverse events. The estimates of health outcomes support estimates of the associated disability-adjusted life years (DALYs) and the costs associated with treatment.⁴⁸⁻⁵⁰ The DALY and economic estimates use available cost and valuation inputs by World Bank Income Level (WBIL).⁴⁸ For health and economic outcomes, the model includes discounting at a 3% rate.⁵¹

For this global investment case analysis, this work focuses on prospective modeling at the global level, with some consideration of variability that exists in the world accounted for by modeling costs as a function of WBIL. The annex in the web materials provides more technical details about the analysis. For purposes of projection, and recognizing the long time horizon of the potential benefits of investments in measles and rubella immunization, this analysis compares the health benefits and costs of immunization that extends over a time horizon from 2016-2055 (i.e., 40 years), with benefits extending for the entire lifetime of individuals vaccinated during the intervention time horizon. The analysis considers two scenarios developed to provide insights if the future looked like the path of the scenario (i.e., the analysis describes possible futures but does not predict the future). Briefly, the first scenario represents a *status quo* (SQ) immunization strategy as of 2016, which uses the 2016 WHO-UNICEF reported vaccine schedules and coverage,⁵² except that it allows for rubella vaccine introduction to occur through the end of 2017, based on actual historical introductions and assuming rubella coverage match measles coverage in RI for 2018 on. The second scenario represents an aggressive trajectory of model assumptions that lead to eradication of measles and rubella virus transmission as soon as possible (ASAP) (within some bounds associated with historical program performance), which includes rubella vaccine introduction in all countries by 2023 (see annex). Consistent with the time horizon, the model uses updated input data for immunization and population inputs, and updated estimates for immunization-related costs (increased to US\$2016) using adjustment based on the US Consumer Price Index.⁵³ The analysis for the ASAP scenario includes a cost premium for associated with achieving increased coverage to achieve high levels of population immunity.⁵⁴

Figure 1: Components of the integrated measles and rubella model



3. Preliminary Results

This section presents preliminary results from the analysis. Figures 2 and 3 show the results of the time series of modeled measles and rubella incidence for the 2 scenarios, respectively. Figure 4 shows the modeled measles mortality, and Figure 5 shows the modeled burden of CRS (including fetal and infant mortality attributed to rubella infection in susceptible mothers in early pregnancy). Some of the CRS burden appears in infant mortality statistics and probably does not get attributed to rubella infection in pregnancy or CRS.

The introduction of rubella vaccine into all countries by 2024 with associated appropriate catch-up campaigns can lead to rubella eradication by 2026. If the *status quo* continues, then rubella and CRS may increase slightly due to the demographic shifts in countries without rubella vaccine. In reality, countries that do not currently use rubella vaccine will likely continue to gradually introduce it such that the 2016 *status quo* scenario represents a worst-case scenario with respect to rubella vaccination policy. The analysis suggests, however, that in the context of widespread availability of MR combination vaccines that allow shared vaccine administration costs, ongoing efforts to increase measles vaccine coverage to reach measles mortality goals, and regional elimination targets, rubella eradication looks like “low hanging fruit.” Rubella eradication could occur prior to measles eradication once all countries introduce rubella immunization into their national programs.

Maintaining the 2016 *status quo* for measles vaccination leads to significant ongoing disease burden, predominantly in the lowest-income and most-disadvantaged countries, but with continued exportation of measles virus into countries and regions that successfully interrupted indigenous measles virus transmission leading to the threat of periodic outbreaks. Prevention of the outbreaks caused by reintroduction of imported viruses will continue to necessitate the expensive maintenance of high measles immunization coverage and reactive response efforts when outbreaks occur. Maintaining the status quo comes at a real cost for immunization on the order of \$3 billion (in US\$2016) globally per year (i.e., high control), or over \$100 billion for the time horizon of 2017-2055. The eradication ASAP scenario considers the experience of the GPEI and the reality that some countries will likely fail to achieve and maintain sufficient measles immunization coverage to stop transmission until the world reaches the point of declaring any transmission of measles global emergencies (i.e., focusing on intensive activities in the last reservoirs). The model assumes that with a realistic global commitment to measles eradication, global measles transmission could stop by 2030. If the global commitment to measles and rubella eradication led to more significant commitments, then eradication could potentially occur sooner. The eradication of both diseases ASAP leads to relatively high short-term immunization costs, but lower treatment costs and productivity losses in the short term and lower all around health and financial costs for the long term. Following eradication, the treatment costs and productivity losses associated with measles and rubella infections disappear because the viruses die out and immunization continues. Similar to other eradicable diseases, after successful eradication, immunization policy changes could occur that would allow for a reduction of immunization costs (e.g., switching to schedules that deliver a single dose at a relatively higher age, stopping immunization complete at some point in time).

Figure 2: Modeled measles incidence for the 2 scenarios (curves overlap until 2016)

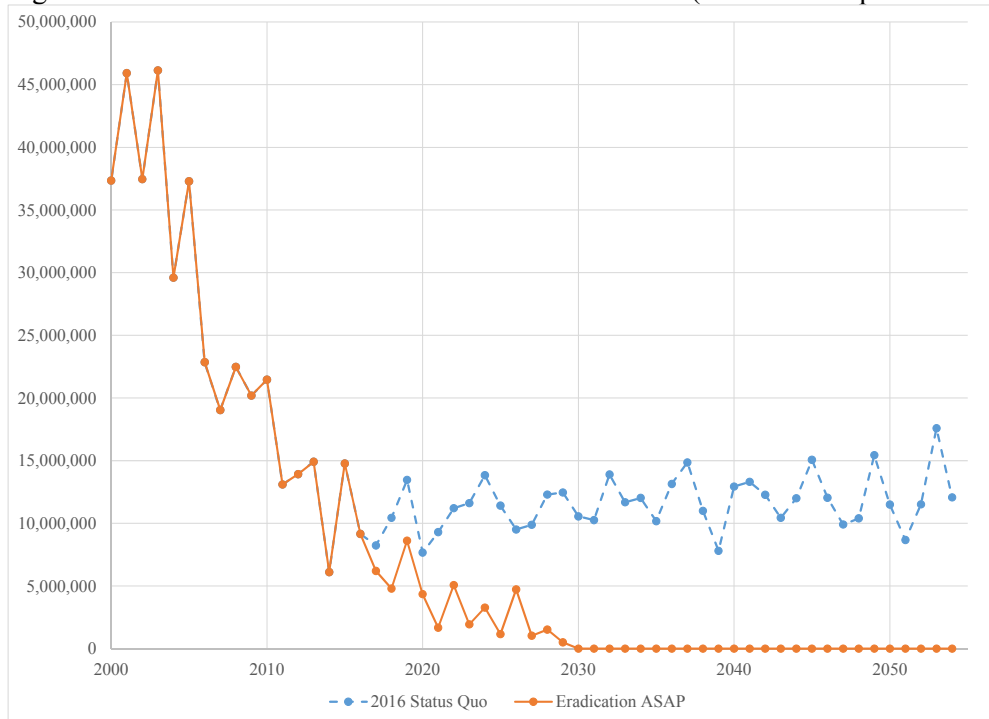


Figure 3: Modeled rubella incidence for the 2 scenarios (curves overlap until 2016)

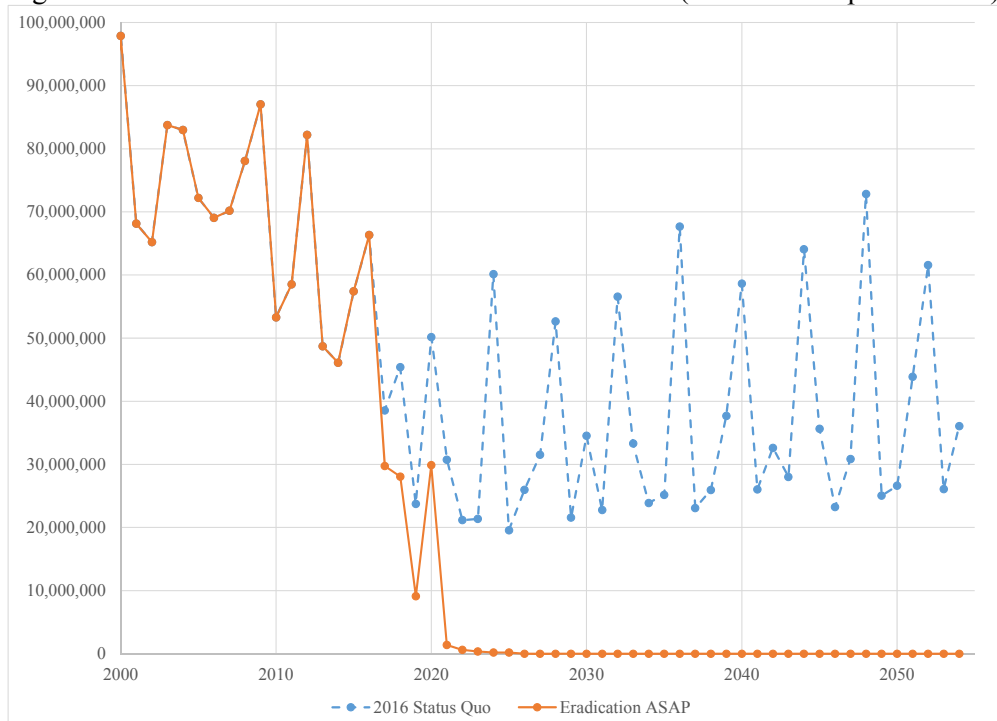


Figure 4: Modeled measles mortality for the 2 scenarios (curves overlap until 2016)

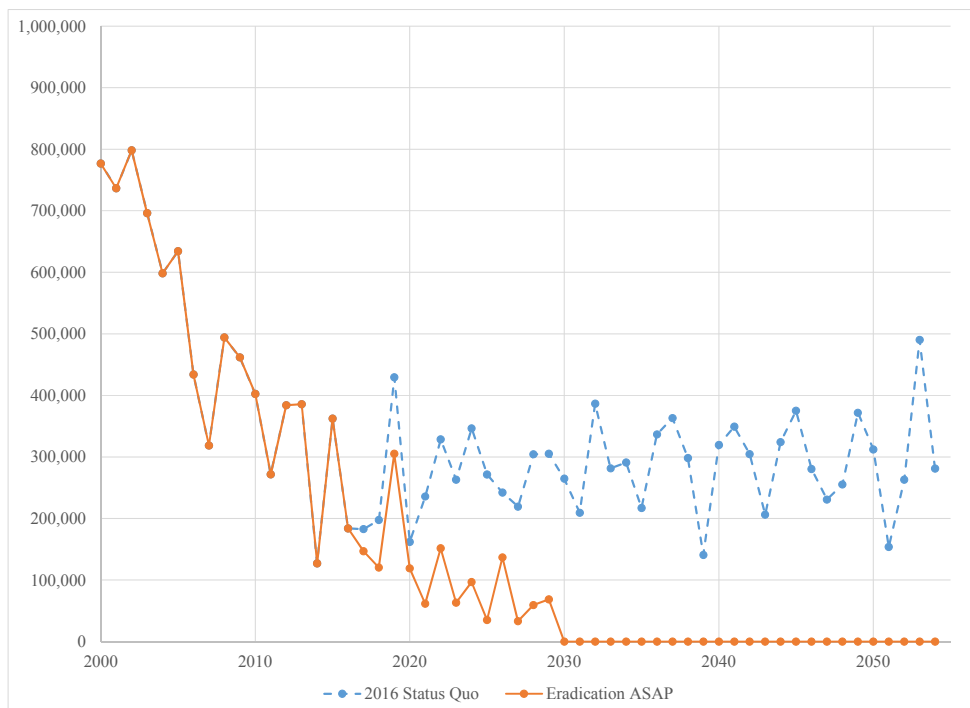
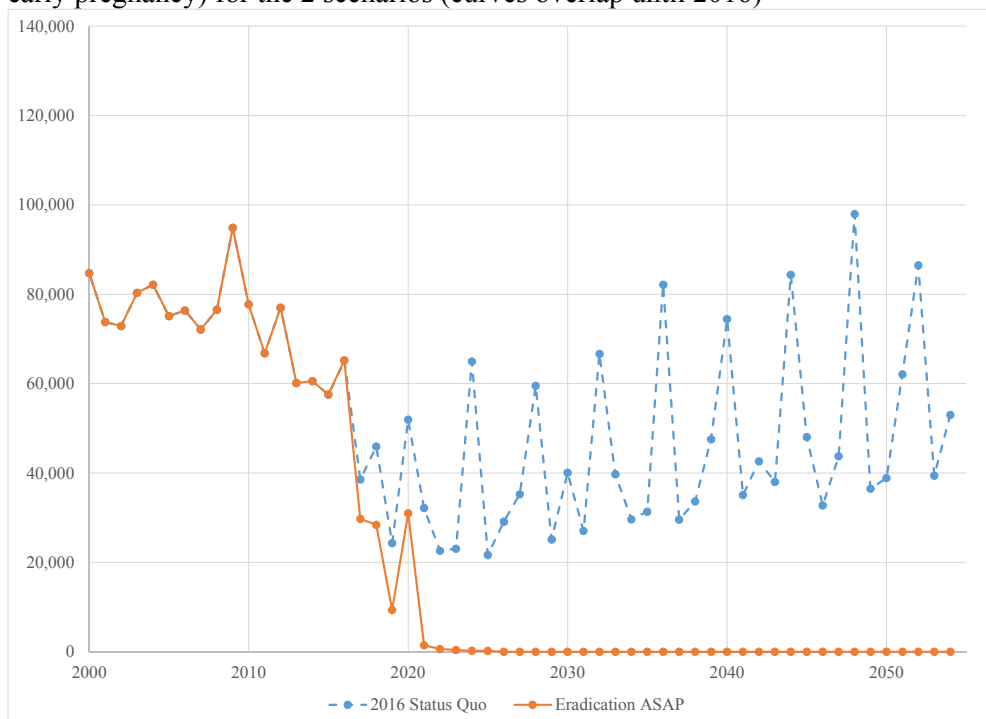


Figure 5: Modeled CRS cases (including infant and fetal mortality from rubella infections in early pregnancy) for the 2 scenarios (curves overlap until 2016)



Considering the discounted costs of immunization, treatment, and productivity over the time horizon of 2017-2055, and accounting for a premium associated with increasing immunization coverage in the short term needed to stop transmission as soon as possible, the costs of vaccination for the eradication ASAP scenario exceed the costs for the *status quo* by approximately \$12 billion (US\$2016), with over half of that amount representing the costs paid to increase coverage up until the time of eradication of both diseases. However, the reduced burden of disease leads to significantly greater incremental savings in expected treatment costs, with the eradication ASAP scenario leading to on the order of \$100 billion saved in treatment costs compared to the *status quo*. Accounting for productivity losses avoided by ending transmission of both measles and rubella the eradication ASAP leads to expected net savings of over \$1.5 trillion. Combined, the expected incremental net benefits of eradicating measles and rubella as soon as possible exceeds \$1.6 trillion. Notably, this analysis does not consider the long-term risks, costs, or benefits associated with any dramatic changes in immunization strategy following eradication. The analysis simply seeks to provide an indication of the space of potential global health and financial costs for measles and rubella control and eradication.

4.0 Discussion

The failure to maintain or intensify MR vaccination will lead to sustained or increased burdens of disease at high costs. Countries and regions that successfully eliminate(d) measles and/or rubella will continue to need to invest in immunization programs that maintain high coverage to prevent transmission of virus exported from endemic areas. In the context of widespread availability of MR combination vaccines that allow shared vaccine administration costs, introducing rubella vaccine as quickly as possible into all countries with appropriate catch-up campaigns could lead to global rubella eradication relatively quickly.

Numerous limitations of the model warrant mention. First, all models depend on the information and assumptions that go into them. While this model attempted to use the best available historical information, all future projections remain inherently uncertain. The model seeks to provide a perspective at the global level related to the incremental net benefits of eradicating both diseases as soon as possible. Second, the model uses simplistic assumptions about exportations that limit its ability to reflect the true range of stochastic possibilities. Third, the model does not account for potential long-term risks associated with the containment of measles and rubella viruses that may exist in laboratories. Fourth, the costs represent a first look that focuses on the increase in immunization costs required to achieve global eradication of both measles and rubella viruses as soon as possible (with some reality included based on some lessons learned from experiences with past and current measles and rubella goals and prior disease eradication efforts). Future efforts will need to consider any increased resource needs for surveillance, coordination, and any required regional and global support activities. Fifth, all of the limitations associated with the various components of the model aggregate into the global analysis.

This background document and the presentation at SAGE aim to provide a high-level perspective and global comparison of the health and economic costs for potential future measles and rubella eradication discussions. Eradication of rubella will not occur until all countries include rubella

vaccine in their immunization schedules, and thus the timing of rubella vaccine introduction directly influences the timing of potential rubella eradication. For both measles and rubella, achieving the programmatic performance required to stop transmission and then maintain high population immunity to prevent any importations from restarting transmission will imply on-going high costs for all countries that have eliminated until the last country stops transmission.

5.0 Next steps

Following review of the estimates used to support the cost premium and additional analyses, the preliminary estimates will be updated and finalized, and this work will be developed into a manuscript for peer review. The preliminary results provide some perspective on the direction and magnitude of the likely expected savings from eradicating measles and rubella as soon as possible, but the numbers presented here are not intended to represent final estimates and should not be cited or quoted. More importantly, the estimates depend on the assumptions used for the scenarios, and the actual costs and benefits that the world will realize will depend on the choices that national, regional, and global leaders make with respect to measles and rubella eradication. As an incremental analysis, the model accounts for the savings associated with reduced outbreaks due to importations for countries that have already eliminated measles and rubella, but it does not account for potential cost savings that could occur with respect to the potential reduction in required vaccination.

This preview of the analysis provides an opportunity for members of SAGE to see the scope and nature of the analysis. The analysis will undergo review by IVIR-AC in September 2018 and a peer review journal. Comments received during the review process will lead to further improvements in the analysis.

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Report for the SAGE Working Group on Measles and Rubella

17–18 April 2018, Geneva

The Roadmap to Immunity

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BACKGROUND

All six World Health Organization (WHO) regions have established a measles elimination goal for 2020 at the latest¹ and three WHO regions have a rubella elimination goal². A standardized method to classify countries has been proposed for global and regional use to document countries' progress toward measles and rubella elimination.³ Categorizations are based on assessment against the five lines of evidence for documentation of the elimination of measles and rubella. The four proposed categories are: (1) endemic; (2) eliminated/interrupted but not verified; (3) eliminated and verified; and (4) re-established endemic transmission post-verification.⁴ Formal verification is provided by Regional Verification Commissions (RVCs). The country categorization should be used to develop tailored immunization and surveillance strategies to assist countries to attain and sustain measles and rubella elimination.⁵

In October 2017, SAGE reviewed and endorsed the four proposed categories for classifying countries as appropriate, providing a standardized approach to country classification, and encouraged their use by RVCs.⁶ SAGE noted that countries in the endemic category included countries at different levels of control and that further sub-categories should be explored to facilitate development and implementation of strategies to improve vaccine coverage and increase population immunity.

SAGE also reviewed data on the level of immunity necessary for achieving and sustaining measles elimination.⁷ SAGE reiterated that achieving “at least 95% immunity across all age groups, geographical regions, and population subgroups.... should remain the primary strategy of measles elimination” and that “countries should attempt to identify specific age groups and subpopulations with immunity gaps, i.e. those with below 95% immunity, and offer vaccination accordingly.” However, they also acknowledged that “there is no perfect measure of immunity” and asked the SAGE Measles and Rubella Working Group to develop guidance on estimating age-specific immunity gaps.

It was suggested that a “Roadmap to Immunity” be developed, similar to the roadmap for elimination standard surveillance published in 2017.⁸ Two integral parts of progressing along the spectrum from control to elimination which entails (1) understanding the general epidemiologic profile of a country in regards to MR elimination and (2) identifying and estimating the scale of immunity gaps within a country. Furthermore, countries need to understand the strengths and weaknesses of possible data sources and methodologies used to understand their epidemiologic profiles and assess immunity gaps. With an understanding of a country’s epidemiology and immunity gaps, countries can best target their interventions to raise population immunity and close gaps.

METHODS

Roadmap to Immunity

To develop the roadmap to immunity, we reviewed existing recommendations and received expert opinions on the most pertinent activities for assessing a country’s immunity profile and determining priority activities for control/elimination. The activities identified were:

- 1- Utilizing country-level epidemiologic profiles to identify and prioritize activities to increase population immunity
- 2- Using data sources and methodologies to estimate immunity gaps
- 3- Applying specific interventions to address specific immunity gaps

All of these activities should be conducted with a commitment to Continuous Quality Improvement (CQI). CQI is a philosophy that states that health care implementers should continue to assess how they are doing and how they could be performing better. It emphasizes a cyclical process, with repeated assessments of clinical and programmatic activities. Based on this philosophy, we recommend that all three activities are conducted through a CQI framework for ongoing identification of immunity gaps, taking measures to address them, reviewing progress and re-assessment of immunity gaps (Figure).

Utilizing country-level epidemiologic profiles to identify and prioritize activities to increase population immunity

To assist countries to determine the most appropriate activities to increase population immunity, we proposed sub-categories for endemic countries based on their overall epidemiologic profiles for measles and rubella. For countries that have not introduced RCV, there is another specific sub-category. Each of these epidemiologic profiles is reflective of underlying population immunity, and consideration of the epidemiologic profile together with the characteristics of outbreaks provides direction as to the immunity gaps that require filling. In approaching these immunity gaps it is essential to consider program capacity. Based on these characteristics, we outlined each sub-category's priorities for control and elimination through routine immunization system strengthening and supplementary immunization activities (SIAs). Finally, we discussed the data sources and analytic methodologies that are likely to be most useful for further assessing the immunity gaps for each category. It should be emphasized that this is not a rigid grid but rather a spectrum both across and within categories. As such, few quantitative cut-offs (e.g. >XX%) were used to recognize that each country's situation is unique.

Methods for estimating immunity gaps for countries at different levels of measles and rubella control/elimination

To help countries to describe immunity gaps using data and methodologies that are likely to be most useful to them given their position on the elimination spectrum, we assessed several methods of estimating immunity gaps based on evidence in the literature. We reviewed peer-reviewed and grey literature for reports that discussed and utilized the following data sources and analytic methods/tools for estimating immunity gaps: 1) case-based surveillance data, 2) outbreak investigations, 3) historical coverage data (administrative and WUENIC), 4) population coverage surveys (including post-campaign, Multiple Indicator Cluster Surveys [MICS], Demographic and Health Surveys [DHS], etc.), 5) serosurveys, 6) WHO Measles Strategic Planning (MSP) tool and other excel-based tools, 7) data triangulation, and 8) mathematical modeling.

To identify evidence for the application of these methods for estimating immunity gaps, we used the following:

1. Internet search of relevant guidelines and other documents on the websites of the WHO headquarters and regional offices
2. Requesting relevant materials from the measles and rubella focal persons at each of the WHO regional offices
3. Review of manuscripts generated from a PubMed search using the search terms (*measles OR rubella*) AND (*"immunity profile" OR "susceptibility" OR "herd immunity" OR "immunity gaps"*)
4. Targeted PubMed searches for additional manuscripts describing methods for estimating immunity gaps that were underrepresented in the first PubMed search results (e.g., *"rubella outbreak"*)

In two summary tables, we provided a brief description and described the strengths and limitations of each of the data sources (Table 2a) and analytic methods and tools (Table 2b). We considered data quality, guidance that can be obtained, and implementation issues such as cost and feasibility. We also considered the best use for each data source and method. In Appendix 1, we provide examples of prior use of each data source and analytic method to estimate immunity gaps, and where available, policy and practice outcomes that resulted from estimation of immunity gaps.

Interventions to assess specific immunity gaps

Using existing guidelines and expert opinion, we created a list of immediate actions and long-term activities to address immunity gaps in specific age groups and populations.

RESULTS

Utilizing country-level epidemiologic profiles to identify and prioritize activities to increase population immunity

In discussions of appropriate interventions to raise coverage in countries where measles and rubella is endemic, it was acknowledged that endemic countries have widely varying epidemiologic profiles, with different short-term control and elimination goals. Country-level epidemiologic profiles for endemic countries are stratified in Table 1. In order to assign a country to the correct stratum, a complete picture of the measles and rubella epidemiology is needed and should be based on all available sources of surveillance and coverage data. The table columns entitled “Population Immunity”, “Program Capacity” and “Outbreak Investigations” are meant to help identify characteristics that are typical of countries with the epidemiological profile described in the first column. Because each sub-category is a simplification, a spectrum between sub-categories and within sub-categories is to be expected, and a country may have characteristics that fall into more than one sub-category. The “Control/Elimination Priorities,” “Routine/System Interventions” and “SIAs” columns are provided to help countries prioritize activities. The “Tools to Assess Immunity Gaps” column will guide countries towards the most helpful tools to assess immunity gaps. It should be recognized that as a country approaches elimination, identification of remaining immunity gaps will likely require review of a wider range of data sources and a more intense level of scrutiny. Furthermore, immunity gaps will occur in increasingly focal population groups (e.g., smaller geographic areas, fewer birth cohorts, and/or smaller underserved populations).

Defining immunity gaps for countries at different levels of measles and rubella control/elimination

Tables 2a and 2b present an overview of the data sources and analytic methods for estimating measles and rubella immunity gaps. The Appendix complements the overview by highlighting several examples from the literature of the use of these tools and their

outcomes. We briefly describe each data source/method and provide one example below. Prior to using any of these methods, countries need to critically evaluate the quality of their collected data. This will greatly impact the accuracy of the data sources and analytic tools discussed below. In addition, while each data source is described separately, they should all be analyzed and considered in relation to each other, in order to provide the most complete epidemiologic profile of a country.

Data Sources

1. Case-based surveillance data: All confirmed cases (and a proportion of suspected cases) indicate people who were susceptible to disease, and highlight the susceptibility that exists even with high reported vaccination coverage. The ability to accurately estimate immunity gaps using case-based data depends on the quality and sensitivity of the surveillance system as well as the extent of virus circulation in the population. If surveillance sensitivity varies across the population, estimated immunity gap detection and description may be biased. Case-based surveillance is most useful to estimate immunity gaps in settings where there is virus circulation. Sensitive surveillance, even without any confirmed cases, will provide some information on immunity gaps if vaccination status is consistently collected for suspected cases. Case-based surveillance is recommended to be ongoing in all countries and its utility increases as the system achieves and maintains elimination-standard surveillance.

Example: Guris et al. analyzed case-based surveillance data from 1989-2001 to calculate measles incidence by age group in Turkey (Appendix 1).⁹ The majority (90%-95%) of measles cases were among children <15 years old in most years. Overall, the highest incidence was in children aged <1 year and 5-9 years. Turkey's Ministry of Health launched a comprehensive program for 2002-2010 targeting measles elimination, and called for a high-coverage ($\geq 95\%$) national mass vaccination campaign among all children aged 9 months to 14 years.

2. Outbreak investigations: Outbreak data can identify immunity gaps when characteristics of cases such as age and place of residence are systematically documented. Outbreak investigation data can be used in all settings, and can be helpful when high reported vaccination coverage suggests low population susceptibility. The accuracy of data provided depends on the sensitivity and quality of the outbreak investigation data, and if sensitivity varies by case characteristics (e.g. age group, geographic location, timing during the outbreak), estimates of the immunity profile may be biased. In countries that have eliminated or nearly-eliminated measles or rubella, outbreak investigations are very important to understand underlying issues that led to accumulation of susceptible persons in the population.

Example: Goodson et al. conducted an investigation of an outbreak in Dar es Salaam, Tanzania during 2006-2007 (Appendix 1).¹⁰ Cases peaked among individuals aged <2 years, 5-7 years, and 18-30 years. In response to the outbreak and based in part on the outbreak investigation, a sub-national campaign was conducted in 2006 in Dar es Salaam targeting children 6 months to 14 years, and a nationwide follow-up immunization campaign was conducted in 2008 targeting children 6 months to 10 years of age.

3. Historical coverage data (administrative and WUENIC): Administrative vaccination coverage data or WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) data can be used to estimate the proportion of each birth cohort that is immune based on vaccination with 1 or 2 doses of vaccine, adjusted for age-specific vaccine effectiveness. Alternatively, a simplified standard of 95% coverage with 2 doses can be used to classify a population as having sufficient immunity. However, these data do not account for immunity due to SIAs or natural infection and administrative coverage is often inaccurate. This is a particular problem for measles because the margins of error are so small. Coverage data can be used to estimate immunity gaps in countries in all categories on the elimination spectrum. It is most accurate, and thus most useful for estimating immunity gaps, in countries where disease incidence is low, and most people gain immunity through routine vaccination rather than through natural infection or SIAs. Every effort should be made to accurately record routine immunization doses administered.

Example: The WHO publishes annual reported coverage data and WUENIC estimates on their website each year. Looking at Ethiopia's MCV1 coverage from 2005-2016, administrative coverage has risen from ~60% to ~93% while WUENIC estimates have only reached ~70%. While the administrative coverage suggests they are approaching the target of 95%, the WUENIC estimates suggest that a large proportion of each birth cohort is still not receiving MCV1 vaccine and that high quality follow-up campaigns are needed along with strengthening of routine immunization.¹¹

4. Population coverage surveys (including post-campaign, MICS, DHS, etc.): Population-based coverage surveys are typically cluster surveys that target individuals in a specified age range. Data from population coverage surveys can be adjusted for vaccine effectiveness to estimate immunity among individuals of a specific age. Coverage surveys typically provide more accurate estimates than administrative data and can be used to validate SIA or routine immunization coverage. They can identify geographic gaps, if designed to provide estimates with sufficient precision at the district level or lower. Coverage surveys can collect detailed demographic data that may not be available from other sources, which can be useful to define sub-populations with immunity gaps. However, the accuracy of coverage survey data is contingent upon surveying a representative sample of the population. Coverage surveys are most useful to estimate vaccine coverage gaps in countries that have difficulty obtaining accurate administrative coverage data and/or lack immunization registries.

Example: Analysis of the 2013-2014 DHS in the Democratic Republic of Congo (DRC) shows vaccination coverage stratified by several demographic characteristics including sex, birth order, province, mother's education level, and socio-economic quintile (Appendix 1).¹² The DHS estimate for MCV1 for children aged 12-23 months was 71.6% (compared with official and WUENIC estimates for MCV1 in DRC in 2014 at 89% and 77%, respectively). The DHS results are probably a more accurate coverage estimate and show that a large proportion of the birth cohort evaluated is susceptible to measles. This suggests that a high quality follow-up campaign is needed along with strengthening of routine immunization.

5. Serosurveys: Serosurveys can provide a direct measurement of population immunity and can include individuals of all ages, as there is no need for records or recall of vaccination, although waning antibody levels may influence interpretation. The sampling frame should be designed to ensure that results are representative of the population in order to avoid biased estimates. Validated laboratory methods calibrated to WHO standards should be used. Because serosurveys are typically less granular than coverage surveys (due to intensive resource requirements), they may not identify immunity gaps in population sub-groups, especially marginalized sub-groups, unless the study is designed to over-sample such groups. Serosurveys are most useful when coverage data are unreliable. Although serosurveys can be conducted in countries of all classifications, careful consideration of the cost and availability of the technical expertise that can address sampling, laboratory, and data interpretations issues are needed before a decision to use a serosurvey.

Example: In a 2002 study from the region of Catalonia in Spain, representative samples of children and adults were used to estimate the seroprevalence of antibodies against measles, mumps, and rubella in children five years and older and adults of all ages (5-year age bands) (Appendix 1).¹³ Based on these data, the author recommended MMR vaccination for susceptible children aged 5-14 years and adolescents/young adults age 15-24, identified using pre-vaccination screening.

Analytic Tools and Methods

1. WHO MSP tool and other excel-based tools: The WHO MSP Tool facilitates analysis of national immunization and surveillance data and calculates a baseline immunity profile for a country's population age 0-20 years using routinely available data (MCV1 and MCV2 coverage data, SIA coverage, surveillance data, and age-specific population estimates). It is a simple Excel interface that is based on underlying statistical models that account for vaccine effectiveness, probability of infection, and case-fatality ratios. Other similar Excel-based tools have been developed that take into account protection from multiple sources: maternal antibodies, routine immunization, SIAs, etc. Accuracy of the results produced by the MSP and other tools depends on the quality of the data used; if coverage, population, or surveillance data are poor quality, the results will be inaccurate. The MSP and other similar tools are most useful for estimating immunity gaps in countries that have high quality coverage and surveillance data. This tool has been well accepted by countries in SEAR, though it requires some revision including the addition of dynamic calculation to reflect transmission patterns in countries that are close to elimination and expansion of the assessment beyond 20 birth cohorts.

Example: Simons et al. developed a baseline immunity profile for children aged 0-14 years in Kenya in 2008 generated by the MSP tool (Appendix 1).¹⁴ This takes into account their historical coverage, SIAs, population and surveillance data that was entered into the tool. It estimates that ~30% of children 3 years and younger were susceptible to measles, as these birth cohorts had not yet been exposed to an SIA. The estimated immunity in older cohorts

was close to 100%, with 60-70% of the children immune due to routine immunization and 30-40% protected by SIAs.

2. Data triangulation: Data triangulation is a process of reviewing existing data from multiple data sources, assessing the quality and external validity of the different sources, and comparing for concordance across data types that measure similar issues. For assessing gaps in immunity, all available sources of surveillance and coverage data should be reviewed. The methodology for triangulating data for purposes including estimation of immunity gaps has not been standardized. Countries in all classifications should use data triangulation to assess immunity gaps. Critically examining and comparing available data provides a more complete picture and understanding of the population immunity situation. As demonstrated in countries in the Americas, very few countries have perfect data for all indicators, but can still achieve and sustain elimination. Data gaps can be compensated for through good analysis of the data that are available as well as triangulation of different sources. In countries that have eliminated measles, their surveillance data may not contain confirmed cases, but surveillance indicators should still be evaluated while considering coverage estimates to identify potential gaps.

Example: Bhatnagar et al. triangulated all available administrative and coverage data in India, taking into account the reliability of each estimate and using methodology based on WUENIC methodology (Appendix 1).¹⁵ This included consideration of things that may have affected coverage like stock outs and a comparison of data across different vaccines to look for inconsistencies. Estimates of coverage for routine child immunization were generated for 17 states and then combined into a national estimate to provide both national and state-level estimates.

3. Mathematical modeling: Mathematical modeling can estimate age and geographic gaps in immunity using population-based disease transmission and susceptibility models. Mathematical models can be used in settings where there are not currently any cases, using historical data to estimate future patterns of disease, and can be used to estimate what immunity profiles might be under different policy/programmatic decisions such as vaccination campaigns conducted at varying time intervals and targeting various age groups, routine immunization doses administered at varying ages, supplementing with a second dose, etc. However, the quality of the estimated outputs from a model are only as good as the data that go into it and the assumptions that the model is based upon. It may be difficult for countries to conduct mathematical modeling in-country, since modeling requires statistical expertise and specialized mathematical modeling skills. Mathematical modeling is most useful when assessing the impact of theoretical interventions on immunity gaps, particularly when there are known limitations to the data (e.g. coverage estimates are inaccurate) or in order to account for multiple factors and build assumptions into the estimates.

Example: Takahashi et al. used generalized additive models and Demographic and Health Survey data to quantify spatial patterns of measles vaccination in ten contiguous countries in the African Great Lakes region during 2009-2014 (Appendix 1 posted on the SAGE website).¹⁶

The model shows that over 14 million children <5 years of age live in 'cold spots' where vaccine coverage is below the WHO target of 80%, and a total of 8–12 million children are unvaccinated. This clustering of low vaccination areas allows for pockets of susceptibility that could sustain circulation despite high overall coverage.

Interventions to assess specific immunity gaps identified

To achieve the regional and national goals, countries should identify specific immunity gaps and conduct corrective actions. After a country identifies its immunity gaps, it should review potential vaccination and surveillance options, taking into account the program capacity. Interventions to assess specific immunity gaps are shown in Table 3. For each population group we present immediate approaches to address the gap for a 2–5 year period as well as long term strategies to avoid the accumulation of susceptible persons in the population.

CONCLUSIONS

To achieve the GVAP and regional measles and rubella elimination goals, all countries should continue to repeatedly monitor and review case-based surveillance and immunity gaps using a CQI approach. A roadmap for elimination standard surveillance has been published¹⁷ and all countries should commit to achieving this quality of surveillance. Of equal importance is that all countries prevent the accumulation of further immunity gaps. The most effective way of achieving this is to ensure 95% or higher coverage with two doses of measles and rubella containing vaccine (MRCV) in each birth cohort.

In order to increase immunity levels to those needed for elimination, countries must first identify where immunity gaps exist in their populations. We presented here several methods that can be used to help identify immunity gaps, each of which is most useful in certain settings and has certain strengths and limitations. Countries should determine which method or set of methods to use in order to estimate immunity gaps based on the availability and quality of data, and based on their current status with regards to control/elimination of measles and rubella. All countries, regardless of their categorization, should continue to strengthen their health systems, improve their surveillance, and improve vaccination coverage systems to ensure high data quality.

Figure 1. Continuous Quality Improvement (CQI) framework for countries to assess immunity gaps.

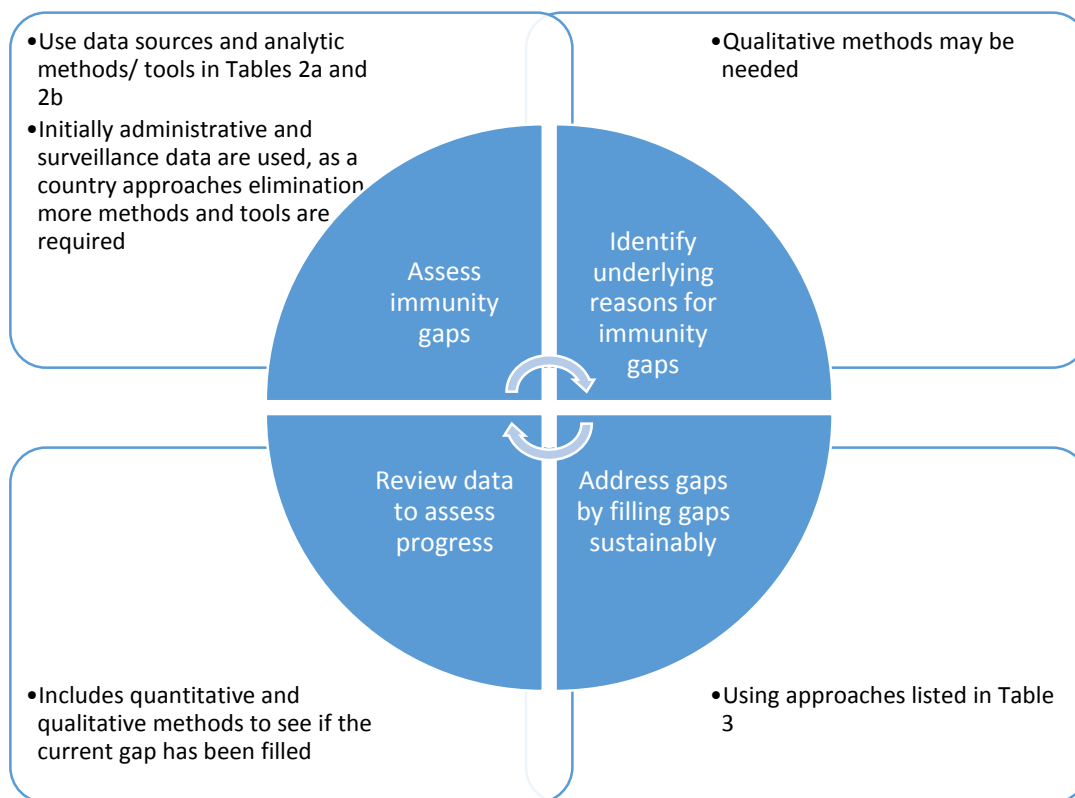


Table 1. Country-level epidemiologic profiles.

| General Epidemiology of Country Based on Triangulation of Surveillance and Coverage Data (all sources of each) | General Characteristics of Countries in this Category (assume spectrum across and within each category) | | | Control/Elimination Priorities | Control Strategies (see Table 3) | | Tools to Assess Immunity Gaps (see tables 2a and 2b) |
|---|--|--|---|---|---|---|--|
| | Population Immunity | Programme Capacity | Outbreak Investigations | | Routine/System Interventions | SIAs | |
| Low incidence of measles/rubella. Irregular, infrequent outbreaks, temporally- (generally <12 months duration) or geographically-limited, predominantly adolescents/adults or children too young to be immunized. | High population immunity, particularly among children; however, may have age or geographic immunity gaps resulting in occasional outbreaks. | Consistent high coverage (e.g. ≥90%) with both doses of MRCV1*. Good demonstrated capacity to conduct high-quality campaigns. Highly sensitive surveillance systems. | Outbreaks are infrequent and irregular. Each outbreak investigation is well conducted including looking for the source and documenting the end of transmission. Investigations provide valuable information on immunity gaps in the population. | Elimination: Increase routine coverage with both doses to at least 95%; actively look for age-specific, sub-population and geographic immunity gaps and address them so that outbreaks are quickly contained. | Increase MRCV1* and MRCV2# coverage to ≥95% in all districts/areas and maintain this level of coverage. Set up country policy and establish vaccination of HCWs if not in place. Extend school entry checks to other entry points into education where feasible, e.g., high school, university, or college. Promote vaccination (and develop innovative strategies) for migrants/travelers. Gain political support. | May not be needed if coverage with both MRCV1* and MRCV2# are greater than 90% unless an immunity gap is identified. In that situation, SIAs will likely be targeted to the identified gaps rather than nationwide follow-up campaigns. | Triangulation of case-based surveillance data, vaccine coverage data (administrative, WUENIC, available coverage surveys), and outbreak assessments. Consider serosurveys or modeling to assess gaps that may be unidentified if there is very little circulating virus. |
| Regular outbreaks that are contained. Majority of cases in children <15 years. | Inadequate population immunity in children <5 years old; may have gaps in older age groups. Most older children have had opportunities for 2 doses | Suboptimal MRCV1* and MRCV2# coverage (e.g. 85 - 90%), either nationally or sub-nationally). MRCV2# may not be introduced. SIAs are of | Outbreak investigations provide additional information on immunity gaps. | Increase quality of routine services with aim to eventually decrease reliance on follow-up SIAs. | Strengthen routine immunization services (logistics, cold chain, demand, coverage, etc.). Consider PIRIs, more outreach sessions. Focus on strategies to increase coverage with both MRCV1* and MRCV2# to >95% so that regular SIAs will not be necessary. | Conduct follow-up SIAs, focusing those not reached through routine immunization services. Generally the SIAs will be for children <5 years; consider wider age range SIAs where the epidemiologic data | Triangulation of case-based surveillance data, vaccine coverage data (administrative, WUENIC, available coverage surveys), and outbreak assessments. Consider serosurveys if quality of available data is poor and |

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|--|---|-------------------|---|--|---|---|---|--|--|--|
| On-going, endemic transmission and regular large-scale, long duration outbreaks even shortly after SIAs. Majority of cases in children <5 years (as adults were either vaccinated or had prior infection). | Inadequate immunity in multiple age groups, most significant gaps in children <5 years old. | adequate quality. | Due to the large-scale outbreak, investigations are inadequate. | Control: Address quality of SIAs to quickly raise overall population immunity while strengthening routine immunization services. | Ensure opportunistic screening and vaccination during health care visits (the MOV Strategy). Implement school entry checks if feasible and would not risk reducing school enrollment. Gain political support. | Strengthen routine immunization services (logistics, cold chain, demand, coverage, etc.). Consider PIRIs, more outreach sessions. Introduce MRCV2# if not introduced. | Ensure opportunistic screening and vaccination during health care visits (the MOV Strategy). Implement school entry checks if feasible and would not risk reducing school enrollment. Gain political support. | Address quality of SIAs. Determine why children are being missed and address the problems. Conduct follow-up SIAs for children <5 years at regular intervals. Focus strategies on reaching those not reached through routine immunization. Where the epidemiologic data indicate immunity gaps in children >5 years old, national or subnational wide age range SIAs may be considered if effective strategies to reach the under- or unvaccinated are in place. | Indicate immunity gaps in children >5 years. | better information is needed on immunity gaps in order to target SIAs. |
|--|---|-------------------|---|--|---|---|---|--|--|--|

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|---|--|---|---|-------------------------------------|--|--|--|
| For RUBELLA: The rubella epidemiology is that of the pre-vaccine era with most cases occurring among children. Rubella outbreaks usually among children; CRS cases, particularly during rubella outbreaks. | Immunity due to natural infection; rubella vaccine not introduced into the national program. | Rubella outbreaks are frequent and may go undetected. Outbreaks may or may not be investigated. | Rubella outbreaks may or may not be investigated. | Set up basic structure for control. | Strengthen MR case-based surveillance; consider establishment of CRS surveillance and introduction of RCV. Strengthen routine immunization services. | Conduct RCV introductory catch-up SIA and then introduce RCV into the routine program as MR vaccine. | Triangulation of case-based surveillance data, vaccine coverage data (administrative, WUENIC, available coverage surveys), and outbreak assessments. |
|---|--|---|---|-------------------------------------|--|--|--|

Abbreviations: CRS = congenital rubella syndrome; HCW = health care worker; MOV Strategy = missed opportunity for vaccination strategy; MR = measles and rubella; MRCV = measles- and rubella-containing vaccine[†] (or MCV); MRCV1* = first dose of measles- and rubella-containing vaccine (or MCV1); MRCV2# = second dose of measles- and rubella-containing vaccine (or MCV2); PIRI = periodic intensification of routine immunization; RCV = rubella-containing vaccine; SIA = supplementary immunization activity; WUENIC = WHO-United Nations Children's Fund (UNICEF) coverage estimate.

Table 2a. Data sources for estimating immunity gaps.

| Description | Case-Based Surveillance Data | Outbreak Investigations | Historical Coverage Data (Administrative and WUENIC) | Population Coverage Surveys (Including Post-Campaign, MICS, DHS, etc.) | Serosurveys |
|-------------|--|---|---|--|--|
| | <p>Case-based surveillance is the WHO-recommended surveillance standard for measles and rubella. Case-based surveillance is used to detect and investigate suspected measles and rubella cases. A standardized case definition is used to classify suspected cases as lab-confirmed, epi-linked, clinically compatible, or discarded. Case data typically include for each case demographics, date of onset, medical care, vaccination status and history, epidemiological linkage to a known case, and serum specimen testing. In addition, exposure status (imported, endemic) can be determined. WHO recommends routine reporting of measles and rubella cases by each country where measles is endemic, with reports by district (third administrative level), age group, and immunization status. In low-incidence or elimination settings, case-based surveillance can be used to quickly identify measles/rubella outbreaks early in the outbreak, and every suspected measles/rubella case should be reported and investigated immediately in order to quickly halt an outbreak.</p> <ul style="list-style-type: none"> Confirmed cases indicate actual susceptibility, and | <p>Outbreak investigation data can be used to estimate measures such as distribution of case characteristics, outbreak size and duration, size and number of chains of transmission, and proportion of imported and import-related cases. The investigation should also investigate the causes for the outbreak and identify issues related to immunization service delivery and community access to immunizations that are contributing to the immunity gaps. Outbreak data can be useful in identifying susceptibility gaps because characteristics (age, place of residence) can be identified for cases that occur during an outbreak period.</p> | <p>Use administrative or WUENIC coverage data, adjusted for vaccine effectiveness, to estimate the proportion of each birth cohort that is immune based on vaccination with 1 or 2 doses of measles- and rubella-containing vaccines in the cohorts born since vaccine introduction. As this is coverage, rather than immunity data, it needs to be adjusted for vaccine effectiveness. Alternatively, a simplified standard of 95% coverage with 2 doses is often used to classify a specified population as having sufficient immunity.</p> | <p>Population-based surveys are typically cluster surveys such as WHO Vaccination Coverage Cluster Surveys, DHS, and MICS. Surveys typically target a specified age range, i.e. 12-23 or 24-35 months. When coverage surveys are conducted following SIAs, they typically include all ages targeted during the SIA. History of vaccination prior to the SIA can be included in post-SIA surveys, but data reliability is low for older children and adults that do not have written records of their vaccination history. If using coverage surveys to estimate immunity and gaps in immunity, coverage needs to be adjusted to account for vaccine effectiveness.</p> | <p>Serologic measurements can provide a direct measurement of population immunity. A population-based (representative) sample of the population of interest is recommended, hence cluster survey procedures (as described in the section on population coverage surveys) are typically followed. Specimens may be collected specifically for the serosurvey, or specimens previously collected may be used. If specimens from a previous survey/study are used, these results need to be interpreted carefully, with recognition of sampling procedures, as they may not be a representative sample of the population.</p> |
| Strengths | <ul style="list-style-type: none"> Confirmed cases indicate actual susceptibility, and | <ul style="list-style-type: none"> Shows where actual cases are occurring during an outbreak | <ul style="list-style-type: none"> Data readily available Data is typically available for | <ul style="list-style-type: none"> Obtain more accurate coverage estimates than administrative | <ul style="list-style-type: none"> Serologic testing provides direct measurement of immunity |

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|--------------------|--|--|--|---|--|
| | <p>show where there are susceptible groups in the population</p> <ul style="list-style-type: none"> • Can be used to determine exposure status: imported and import-related cases • Highlights susceptibility that may not otherwise be evident due to high reported vaccination coverage • If a case-based surveillance system is already in place and maintained in a country, ongoing nationwide surveillance data should be readily available • Countries have ownership of the data | <p>period</p> <ul style="list-style-type: none"> • Can be used to estimate measures such as generations of transmission, imported and import-related cases, and reproduction numbers, which can enhance understanding of disease transmission in addition to population susceptibility patterns • Can be used to estimate susceptibility in settings where there is high reported vaccination coverage which would indicate low susceptibility, but an outbreak still occurs • Collection of outbreak data builds upon the existing case-based surveillance system, so if a high-quality surveillance system is already in place in a country, these data should be available with minimal additional effort • Generates solid evidence for policy changes to improve vaccination service delivery and/or vaccine demand | <p>many years, at multiple levels, often since vaccine introduction</p> <ul style="list-style-type: none"> • Countries have ownership of the data | <p>data since survey data do not depend on poor quality data on doses administered and population estimates</p> <ul style="list-style-type: none"> • Can validate (or provide more accurate estimate) of SIA or routine immunization coverage • Less expensive and easier to implement than a serosurvey • Can collect data on communication channels and reasons for non-vaccination • Can collect detailed demographic data, not available from other sources | <ul style="list-style-type: none"> • No need for vaccination records or population data • All ages can participate, as there is no need for records/recall of vaccination that may have happened many years prior |
| Limitations | <ul style="list-style-type: none"> • Some data analyses (age, sex, residence of cases) is only feasible when there are confirmed cases; however vaccination history should be attained from all suspected cases and can be another measure of immunity gaps • Sensitivity of surveillance may vary by age group, geographic location, population sub-groups, etc., thus biasing estimates of the immunity profile • Relies on passive surveillance | <ul style="list-style-type: none"> • Can only be used when there is an outbreak • Depends on sensitivity and strength of the surveillance system; cases are likely to be missed if the surveillance system has low sensitivity or if the surveillance system is overwhelmed as in the case of a large outbreak • Sensitivity of surveillance during an outbreak may vary by age group, geographic location, population sub-groups, timing of the outbreak, etc., thus | <ul style="list-style-type: none"> • Does not account for protection from SIAs, catch-up vaccination, natural infection • Administrative coverage is often inaccurate due to inaccurate denominator data. Poorly documented numerator data can also affect estimates • WUENIC estimates are only available at a national level, hence sub-national gaps in immunity are not evident • WUENIC data are the best estimates of coverage, though their accuracy is unknown | <ul style="list-style-type: none"> • Require technical/statistical expertise and detailed data on population settlements in order to select a representative sample • May not get representative sample of population if surveyors cannot access all selected settlements (especially applicable in countries with security concerns) • Household surveys are difficult to implement in some settings and some populations (e.g., dense cities, places where both | <ul style="list-style-type: none"> • The sensitivity and specificity of the test used to detect measles or rubella IgG need to be taken into consideration • Waning antibodies may affect results in persons sampled many years after vaccination • Measles and rubella IgG testing does not distinguish between antibodies induced by vaccination versus those induced by natural infection • High cost: serosurveys have the same costs and technical needs as a coverage survey, plus the |

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|---|---|--|--|--|--|
| | <p>data, the quality of which (including sensitivity) may decline as the incidence of disease declines</p> <ul style="list-style-type: none"> It would be better to identify immunity gaps before there are cases, and prevent cases through vaccination, rather than wait until there are cases to be able to identify immunity gaps Ability to accurately estimate immunity gaps using case-based data depends on the quality of the surveillance system While it is recommended that all countries have a case-based surveillance system, they require substantial resources to maintain; hence some countries do not have high-quality case-based surveillance systems | <p>biasing estimates of the immunity profile</p> <ul style="list-style-type: none"> The age distribution of cases during an outbreak shows what the pre-outbreak susceptibility gaps were. However, individuals infected during the outbreak will convert to immune, and if the outbreak is large enough, susceptibility patterns may change post-outbreak It would be better to identify immunity gaps before an outbreak begins, and prevent cases through vaccination, rather than wait until an outbreak occurs to be able to identify immunity gaps There is a risk that surveillance data collected during an outbreak period has reduced specificity compared with routine case-based surveillance, particularly if relying on non-lab-confirmed cases Quality of results depends on the quality of the investigation | <ul style="list-style-type: none"> Vaccine effectiveness may be lower than accepted estimates in areas with programmatic challenges Quality of results depends on the quality of the data collection and reporting system | <p>parents work away from home, places with older subjects that are typically away from home at school or work)</p> <ul style="list-style-type: none"> Surveys are expensive and costs increase rapidly if sub-national estimates are desired To understand the evolution of coverage levels and have up-to-date data, surveys are recommended to be conducted regularly in most countries (frequency may vary) The accuracy of the assessment of children's vaccination status may depend on how many participants have written vaccination records available for review The availability of written records and the accuracy of recall decrease as time passes between vaccination and the survey (e.g. to increase the accuracy of vaccination history on 10 year old children is more difficult than 1 year old children because parents are less likely to still have vaccination record and/or remember which vaccines their child received) | <p>costs of specimen collection, transport, storage and laboratory testing</p> <ul style="list-style-type: none"> Potential for bias if sample not representative of the population. Due to resource requirements, serosurveys are typically less granular than coverage surveys (which are already a sample of the population). These may not efficiently identify immunity gaps in sub-groups, especially marginalized sub-groups If using samples collected for a purpose other than an intended vaccination serosurvey, the ethical implications of testing the samples need to be considered |
| <p>Best Use of Data Source to Estimate Immunity Gaps</p> | <p>Case-based surveillance is recommended to be ongoing in all countries. It can be useful to estimate immunity gaps for all countries; utility increases as the system achieves and maintains elimination standard surveillance standards.</p> | <p>In endemic countries, outbreak investigations are used to identify target populations for response. As outbreak investigation quality increases, root causes for the outbreak are also identified that can identify gaps to be addressed to stop susceptible populations from accumulating. In countries that have eliminated or nearly-eliminated, outbreak investigations are very important to understand the underlying</p> | <p>Historical coverage should be monitored during all phases of control/elimination. It is most accurate, and thus most useful for estimating immunity gaps, in countries where disease incidence is low, and most people are protected through routine vaccination rather than natural infection or SIAs.</p> | <p>Most useful in countries that have difficulties obtaining accurate administrative coverage data. Most helpful for providing: (1) estimates of SIA coverage, for all age groups targeted in an SIA; and (2) estimates of routine immunization coverage in single birth cohorts. They can identify geographic gaps, but only if designed to provide estimates at the district level or lower, which is very expensive.</p> | <p>Serosurveys are most helpful when coverage data are unreliable and there is little or no circulating disease. Another common use is to test for rubella susceptibility in women of child-bearing age as these age cohorts have not been vaccinated in many countries where rubella-containing vaccine has not yet been introduced or was only recently introduced.</p> |

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| | | issues that led to susceptible persons in the population. | | | | |
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Table 2b. Analytic methods and tools for estimating immunity gaps.

| Description | WHO Measles Strategic Planning (MSP) Tool and Other Excel-Based Tools | Data Triangulation | Mathematical Modeling |
|------------------|--|---|--|
| | <p>The WHO Measles Strategic Planning Tool was developed in the mid-2000s to facilitate analysis of national immunization and surveillance data and estimate the effectiveness and cost effectiveness of different vaccination strategies. It uses formulas built-in to an Excel spreadsheet to create a baseline immunity profile for a country's population age 0-20 years using historical coverage data from routine (MCV1 and MCV2) and SIA vaccination, surveillance data, and age-specific population estimates. Others have developed similar Excel-based tools that take into account protection from multiple sources: maternal antibodies, routine immunization, SIAs, etc.</p> | <p>There are many types and methods of data triangulation. It often includes a process of reviewing existing data from multiple data sources to understand an issue and assist with public health decision making. Data sources can be combined in a quantitative measure like risk assessment tools, however statistical modeling is not typically used with triangulation. Other times the interpretation of triangulated data is more qualitative. There should always be a focus on assessing the quality and external validity of the data sources used and considering this in the interpretation of the data. For assessing gaps in immunization, all available sources of surveillance and coverage data should be reviewed. Data sources should be compared for concordance across data types that measure similar issues, e.g.,</p> <ul style="list-style-type: none"> • Do historical coverage data and coverage survey data show similar trends? If one shows an immunity gap but the other does not, what are the limitations of each source that might lead to the discrepancy? Which is likely to be the "best estimate"? Do you think the "best estimate" is accurate? Or is the true value likely to be higher or lower given the limitations of the data source? • Are the numbers of cases in the case-based and aggregate surveillance system the same? If not, what led to the discrepancies? How does this influence what the true number of confirmed measles cases actually is? <p>Data should also be compared for concordance across different types of data, e.g.,</p> <ul style="list-style-type: none"> • Do outbreak data show that cases are arising in geographic areas with low or high coverage? Does the age distribution of cases align with the perceived levels of population immunity across age groups, based on historical coverage and coverage surveys? • Based on evaluating these and other aspects of the data, where do there appear to be immunity gaps in your population? • Comment: WUENIC estimates of vaccination coverage are developed by triangulating all available data sources on vaccination coverage in a country | <p>Mathematical modeling uses population-based disease transmission and susceptibility models to estimate gaps in immunity and susceptibility. Models use one or several different sources of data including vaccination coverage, historical surveillance data and incidence patterns, transmission patterns, contact patterns, etc. Age-specific differences in data can be accounted for to produce estimates of susceptibility/immunity that are specific to small age strata. One commonly used type of model is the SIR (Susceptible, Infected, and Recovered) Model which models individuals moving between the three states. The equations used in the model estimate transmission of virus between individuals who are infected to those who are susceptible.</p> |
| Strengths | <ul style="list-style-type: none"> • Uses underlying statistical models that take into account | <ul style="list-style-type: none"> • Takes into account several data sources when evaluating a | <ul style="list-style-type: none"> • Can combine several sources of data including vaccination |

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| | <p>vaccine efficacy, probability of infection, and case-fatality ratios but the interface is an Excel spreadsheet that does not require advanced technical skills to use</p> <ul style="list-style-type: none"> • Uses routinely available data • Pre-loaded with data for all countries through 2008 (only data since 2009 needs to be entered into tool) • Can be easily performed at the country level | <p>public health issue</p> <ul style="list-style-type: none"> • Through comparison of data sources, the evaluator is encouraged to consider the strengths and limitations of each source • Uses readily available data; accepts and recognizes the limitations of each type of data | <p>coverage, historical surveillance data, and others to model estimates of gaps in immunity and susceptibility</p> <ul style="list-style-type: none"> • Can use models for settings where there are not currently any cases, using historical data to estimate future patterns of disease • Can include estimates of transmission and contact rates between specific age groups in the model to produce a better estimate of age-specific differences in infection and susceptibility • Mathematical modeling results can be used to estimate what immunity profiles might be under different policy/programmatic decisions such as vaccination campaigns conducted at varying time intervals and targeting various age groups, routine immunization doses administered at varying ages, supplementing with a second dose, etc. |
| Limitations | <ul style="list-style-type: none"> • Accuracy of results depends on the quality of the data used; if coverage, population or surveillance data is poor quality, the results may be inaccurate • Difficult to account for phased and sub-national campaigns as well as outbreak response immunization • Assumes that vaccination through routine immunization and SIAs are independent of each other with regards to probability of a child being vaccinated • The underlying models are somewhat simplified compared to some other modeling strategies, and therefore may be less realistic • Developed for use at the national level. Separate profiles would need to be developed for subnational analysis | <ul style="list-style-type: none"> • Dependent on the quality and generalizability of the data used (see limitations for data sources previously described) • No standard methodology has been developed to triangulate data from multiple data sources (surveillance, coverage, etc.) • Evaluation of different data sources can often only be done qualitatively, hence quantitative estimates are frequently based on 'expert opinion' and dependent on the skill and experience of the experts | <ul style="list-style-type: none"> • Requires statistical expertise and specialized mathematical modeling skills; these skills may not be available in-country, thus an external expert is likely to be required to conduct any modeling • The quality of the outputs from a model are only as good as the data • Models are based on assumptions that go into the model, which may or may not accurately reflect reality • Requires a priori assumptions that may or may not be based on evidence from the specific setting or context; may be based on historical data from settings with different characteristics |
| Best Use of Data Source to Estimate Immunity Gaps | <p>This tool is most useful when countries have fairly good coverage (including national and sub-national SIAs) and surveillance data to input into the tool.</p> | <p>Endemic countries should always triangulate their available data. Critically examining and comparing available data provides a more complete picture and understanding of the situation. In countries that have eliminated measles, their surveillance data may not have confirmed cases, but surveillance indicators should still be evaluated while considering coverage estimates to identify potential gaps.</p> | <p>Mathematical modeling is most useful when assessing the impact of theoretical interventions on immunity gaps. It can be particularly useful when there are known limitations to the data (e.g. coverage estimates are inaccurate) or in order to account for multiple factors and thus build some assumptions into the estimates.</p> |

Table 3. Activities to address recognized/confirmed specific immunity gaps in general population or parts of the population.

| Immunity Gap | Immediate Approach to Address Gap | Long-term Strategy to Avoid Accumulation of Susceptibles |
|------------------------------------|--|---|
| Under 1 | <ul style="list-style-type: none"> - Conduct intensive vaccination (or SIA) of children as young as 6 months ("zero" dose) as indicated in WHO published policy (e.g., outbreak). - Consider source of exposure and consider targeting that group (e.g., adults). | <ul style="list-style-type: none"> - Implement strategies to improve the <u>timeliness</u> of MRCV1* vaccination in countries where vaccine is administered at 9-11 months of age. |
| Age 1 to 5 | <ul style="list-style-type: none"> - Conduct high quality SIAs (nationally or sub-nationally, depending on the extent of the identified gap; consider school-/daycare-based campaigns/strategies). | <ul style="list-style-type: none"> - Identify and address the underlying reasons for the immunity gap. - Strengthen routine MRCV1* and MRCV2# programs and improve coverage. - Ensure that MRCV1* will be given to children after 12 months of age, even if schedule calls for administration at 9 months. - Implement entry checks for daycares, kindergartens and similar institutions. - Implement strategies to avoid missed opportunities for vaccination, e.g., vaccination record checks every time a child visits a health center - Enhance social mobilization, advocacy and communication to increase demand and uptake of immunization services. |
| Children ≥5 and adolescents | <ul style="list-style-type: none"> - Conduct a high quality, wide-age range SIA (nationally or sub-nationally, depending on the extent of the identified gap; consider school-based campaigns/strategies). | <ul style="list-style-type: none"> - Identify and address the underlying reasons for the immunity gap. - Improve MRCV2# coverage and timeliness. - Implement school entry checks for elementary, high schools and universities. - Implement strategies to avoid missed opportunities for vaccination, e.g., vaccination record checks every time a child visits a health center and linkages to adolescent care. |
| Adults | <ul style="list-style-type: none"> - Consider conducting SIA targeting the affected groups. - Make MRCV available free of charge to affected age groups, with priority given to persons that are unvaccinated or vaccinated with only one dose, but available to all regardless of vaccination status. | <ul style="list-style-type: none"> - Introduce immunization of adults as part of occupational health services for health care workers, employees in educational and day-care institutions, and all occupations that are in daily contact with many individuals. - Offer vaccination at medical appointments, post-partum |

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| Migrants | <ul style="list-style-type: none"> - Conduct a high quality SIA targeting migrants as a priority, but with extension to local susceptible populations, under the same condition and rules (strategies used to vaccinate migrants should not be discriminatory). - Offer vaccination through immigration services and migrants organizations/associations/communities. - Offer vaccinations services through the health system, regardless of the patients' residency status and legal/administrative regulations. | <ul style="list-style-type: none"> - care for women, etc. - Offer vaccination before international travel. - Identify and address the underlying reasons for the immunity gap among migrants. - Implement at work permit/visa-based vaccination program. - Establish long-term programs with immigration services and migrant organizations/associations/community. - Create capacities in health systems (through partners, NGOs, or government) that will provide immunization as a part of basic, free of charge service to migrants. - Tailor social mobilization, advocacy and communication activities to increase demand and uptake of immunization services among migrants. |
| Refugees | <ul style="list-style-type: none"> - Provide vaccination at entry/in refugee camps. - Conduct SIA in refugee camps. - Offer vaccination services through the health system, regardless of the patients' residency status and legal/administrative regulations. | <ul style="list-style-type: none"> - Establish systematic immunization activities in refugee camps. - Establish long-term programs with immigration services and migrant organizations/associations/community. - Create capacities in health systems (through partners, NGOs, or government) that will provide immunization as a part of basic, free of charge service to refugees. |
| Populations not vaccinated due to lack of vaccination services (e.g., rural populations) | <ul style="list-style-type: none"> - Conduct periodic intensification of routine immunizations (PIRIs) (or mop-up activities for populations missed during a campaign). | <ul style="list-style-type: none"> - Increase frequency of outreach services and social mobilization/demand-generating activities associated with the outreach. - Enhance social mobilization, advocacy and communication to increase demand and uptake of immunization services to ensure that people come for vaccination. |
| Populations not vaccinated due to "invisibility" to vaccination services (e.g., urban populations) | <ul style="list-style-type: none"> - Conduct SIAs in low coverage areas; consider many types of vaccination sites/mobile teams, e.g., markets, transportation centers, work places. - Increase social mobilization, advocacy and communication (targeting diverse age groups). | <ul style="list-style-type: none"> - Register new inhabitants with health services and include in target population for routine immunization. - Increase social mobilization, advocacy and communication about vaccination services. |
| Populations not vaccinated due to vaccine hesitancy | <ul style="list-style-type: none"> - Identify and address the underlying reasons for vaccine hesitancy - Tailor social mobilization, advocacy and communication | <ul style="list-style-type: none"> - Identify and address the underlying reasons for vaccine hesitancy - Tailor social mobilization, advocacy and communication |

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| | activities to increase uptake of immunization services, considering the unique local context - SIAs/ORI in surrounding communities to ensure high herd immunity in surrounding populations. | activities to increase uptake of immunization services, considering the unique local context |
| Populations not vaccinated due to stock-outs | <ul style="list-style-type: none"> - SIAs in areas where gaps occurred. - Strengthen follow-up services to ensure that the children that missed vaccination come back when the vaccine is in stock. - Ensure sustained confidence in health services/immunization. | - Address root cause that resulted in stock-out and prevent further episodes. |
| Any population identified due to an outbreak | <ul style="list-style-type: none"> - Adjust ORI to population affected (including all ages affected), e.g., geographic area, work place, university, ethnicity, religion, etc. | <ul style="list-style-type: none"> - Identify and address root cause of immunity gap. - Consider periodic SIAs targeted at this population if they are being missed by other vaccination activities. - Review all available information and sources to identify similar populations and address immunity gaps systematically. |

*MRCV1 (or MCV1)

#MRCV2 (or MCV2)

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Full Public Health Value Propositions for Vaccines: Executive summary

The remit of the Initiative of Vaccine Research (IVR) includes facilitating development of vaccines against priority pathogens, and supporting countries with introduction, once those vaccines become available. The over-arching principle of these efforts is to incentivize investment and sustained commitment to the development of vaccines for which there is the greatest public health need, to ensure that the development of vaccines that are suitable for use in low- and middle-income country (LMIC) contexts, and to ensure the concomitant generation of robust evidence that will enable efficient and effective policy decisions.

Historical vaccines have been developed for the expanded programme of immunization (EPI), where there has been a global mortality burden that supports a well characterized market and a clear target product profile. Vaccines were typically recommended on the basis of safety and efficacy against etiologically-confirmed clinical outcomes, in randomized and controlled conditions. Many of the infectious disease vaccine candidates currently in development are unlikely to be universally implemented; rather they are expected to be seasonal, regional or sub-national vaccines, targeted towards certain age groups depending on the burden of disease and context-specific epidemiology. In resource-poor settings, an increasingly convincing rationale will be needed to justify the inclusion of these new vaccines, in addition to other established vaccines within national immunization programs, over and above many other health priorities that are competing for scarce resources. As such, the ability to determine the global market demand, and the willingness to procure at the end of a costly product development pathway is uncertain, and vaccine manufacturers often prioritize high income markets that offer a more immediate and certain return on investment. The result is often a delay between vaccine licensure, and accessibility and availability to these vaccines by LMICs where there is the greatest public health need.

Recently, there have been appeals from several key stakeholders and subject matter experts to broaden the evaluation of vaccine value beyond the demonstration of individual, direct health benefits and related costs that are required to support licensure, to evaluation of the broader economic, societal and indirect impact of vaccination at the population level. A conceptual framework of pathways between immunisation and its proposed broader economic benefits has been developed (Jit et al, 2015), and this informed the Fondation Merieux conference in 2016, resulting in a publication on 'Estimating the full public health value of vaccination' (Gessner et al, 2017). This new public health paradigm considers the population impact of vaccination and encompasses measures of community benefits against a range of outcomes, such as improvements in health inequity, financial risk protection, reduction in long-term/on-going disability and a decrease in the development of antibiotic resistance. Wilder-Smith and colleagues further developed this framework and proposed methods, measures and outcomes to evaluate the broader public health impact of vaccines, to be considered for evidence-informed policy making both pre- and post-licensure (Wilder-Smith et al, 2017).

IVR, under the auspices of its Product Development for Vaccines Advisory Committee (PDVAC) and its Immunization and Vaccine related Implementation Research Advisory Committee (IVIR-AC), is building on these efforts, to develop an approach for developing Full Public Health Value Propositions (FPHVP) for vaccines where there is a clear public health need for, but a lack of interest and/or investment in, developing vaccines for LMIC markets. As such, we are in the process of deriving an annotated template (table of contents included in background materials) for a generic FPHVP that incorporates all elements of a comprehensive framework that will inform both early stage (prior to clinical proof-of-concept) and late stage (as the product transitions to phase III clinical studies) as well as policy decision making. In addition to serving as a roadmap to advance the vaccine through development, these living documents will provide an inventory of available evidence, and identify and prioritize gaps that need to be addressed to incentivize development and facilitate

evidence-informed policy making. Early socialization of this framework has been favorably received by a broad set of stakeholders; however, more work is needed to articulate the priority data needs along the product development and vaccine introduction continuum, as well as to understand how the content should be customized to specific groups of stakeholders.

The rationale for FPHVP approach is to consider, as robustly as possible from the early stages of product development, the global value of vaccines. Defining, measuring, and ultimately confirming the FPHVP of vaccines should increase political will and allow for more accurate prioritization of available resources to avoid unnecessary delays in the uptake of new vaccines in LMICs where there is the greatest public health needs.

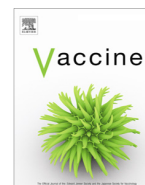
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Conference report

Estimating the full public health value of vaccination

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ABSTRACT

There is an enhanced focus on considering the full public health value (FPHV) of vaccination when setting priorities, making regulatory decisions and establishing implementation policy for public health activities. Historically, a therapeutic paradigm has been applied to the evaluation of prophylactic vaccines and focuses on an individual benefit-risk assessment in prospective and individually-randomized phase III trials to assess safety and efficacy against etiologically-confirmed clinical outcomes. By contrast, a public health paradigm considers the population impact and encompasses measures of community benefits against a range of outcomes. For example, measurement of the FPHV of vaccination may incorporate health inequity, social and political disruption, disruption of household integrity, school absenteeism and work loss, health care utilization, long-term/on-going disability, the development of antibiotic resistance, and a range of non-etiological and etiologically defined clinical outcomes.

Following an initial conference at the Fondation Mérieux in mid-2015, a second conference (December 2016) was held to further describe the efficacy of using the FPHV of vaccination on a variety of prophylactic vaccines. The wider scope of vaccine benefits, improvement in risk assessment, and the need for partnership and coalition building across interventions has also been discussed during the 2014 and 2016 Global Vaccine and Immunization Research Forums and the 2016 Geneva Health Forum, as well as in numerous publications including a special issue of *Health Affairs* in February 2016.

The December 2016 expert panel concluded that while progress has been made, additional efforts will be necessary to have a more fully formulated assessment of the FPHV of vaccines included into the evidence-base for the value proposition and analysis of unmet medical need to prioritize vaccine development, vaccine licensure, implementation policies and financing decisions. The desired outcomes of these efforts to establish an alternative framework for vaccine evaluation are a more robust vaccine pipeline, improved appreciation of vaccine value and hence of its relative affordability, and greater public access and acceptance of vaccines.

1. Introduction

Historically, vaccines have been assessed for inclusion into public immunization programs based on safety and efficacy against

severe etiologically-confirmed disease or against serious sequelae [1]. In randomized controlled trials, many factors, including geography, inclusion and exclusion criteria, age, diagnostic methods, and epidemiological issues, may affect vaccine efficacy. One example of geographic disparity is a group of randomized controlled trials of rotavirus vaccine, where high efficacy against severe rotavirus-confirmed gastroenteritis was seen in the developed world [2,3] with lower efficacy against the same outcome among infants in developing countries [4–6]. Appropriately quantifying the value of vaccines was critical to the WHO decision on the use

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of rotavirus vaccine, and continues to be critical in promoting and sustaining vaccine programs, particularly in resource poor-settings where a strong argument must be made to justify prioritizing immunization programs among many other health priorities competing for scarce resources.

In June 2015, a group of experts discussed criteria to be considered to assess the full public health value (FPHV) of vaccination in addition to efficacy measured in individually randomized clinical trials [7]. It was clear for this group of experts that considering additional outcome measures (e.g., vaccine preventable disease incidence), and designs (e.g., vaccine probe studies and community randomized trials) were valuable, as was the consideration of indirect or community protection and economic and other non-health benefits of vaccines. They also considered that in addition to benefit-risk assessments based on the information collected through the traditional clinical development process, a substantial body of additional information is necessary to more fully inform policy and other required decision-making at the global, national and sub-national levels. Therefore, to assess the wider scope of vaccine benefits, there needs to be an enhanced expectation that studies – including licensing studies – incorporate measurement of these benefits; that greater connections are developed between partners who work on distinct but complementary aspects of vaccine valuation including health, economics, education, productivity, and economic gains; and that data and methods across these domains are shared widely across the vaccine community.

With such an enhanced paradigm and with a focus on low and middle-income countries (LMIC), alternative regulatory pathways could be considered that focus on conditional licensure of vaccines based on outcome results relevant to regulatory and public health decision-makers. This process could increase the development and introduction of vaccines in these countries. These issues will be particularly relevant to inform decision-making for vaccines on the near-term horizon such as those against malaria and dengue.

The components of this new paradigm having been defined [7], the Fondation Mérieux organized a second conference from 5–7 December 2016 (“Les Pensières” Conference Centre, Annecy-France), to evaluate the feasibility of an encompassing assessment of the FPHV of vaccines. The main objectives of the meeting were to advance discussions on the definition, evidence and communication of the FPHV of vaccines by:

- challenging and refining the definition of what constitutes the FPHV of vaccination;
- reviewing examples of FPHV with existing vaccines used in outbreak settings and others used in endemic disease settings;
- proposing designs, measures, and outcomes for assessing the FPHV of vaccination in phase III trials and phase IV assessments and integrated/hybrid phase III/IV strategies;
- applying these concepts to specific vaccines particularly those targeting malaria, dengue, Group B Streptococcus (GBS), Respiratory syncytial virus (RSV), *Neisseria meningitidis* B (NMB), and cholera, and;
- strategizing on how to communicate the FPHV of vaccination to regulatory and program policy makers.

In this paper, we argue for as robust a measure as possible of the FPHV of vaccines to allow authorities to make accurate decisions on whether it will be efficient to invest in a particular vaccine for use in a particular setting and for a particular population, in the context of other public health interventions and programs remaining constant. As an example, the adoption of dengue vaccine should be considered in the context of an integrated management strategy while cholera vaccination should be considered in the context of clean water, sanitation, and hygiene.

2. Defining and assessing the FPHV of vaccines

Vaccine efficacy (VE) (Table 1), usually measured for etiologically-confirmed clinical outcomes, is often given the most weight among vaccine outcome measures considered in regulatory and policy recommendations. However, VE is not a static, robust, universal ‘true’ value as is commonly understood. Rather, it belongs within a list of measures that are useful for informing policy decisions. Indeed, VE can only be interpreted in the context of the population studied and the chosen trial design and can change based on factors such as microbial flora (enteric vaccines), force of infection, serotype distribution of the pathogen, pre-existing immunity, and the local epidemiological situation. Furthermore, VE by itself only indicates if the vaccine works against the target outcome, not whether it represents a good investment for a country.

Currently, most of the economic evaluation of vaccines focuses on a narrow set of vaccination-mediated health benefits [8], measured in quality adjusted life years (QALYs) (Table 1). One of the strengths of this focused view is that it yields a natural decision criterion, the incremental cost effectiveness ratio (ICER), that a policymaker can compare across competing programs. ICER requires comparison with a benchmark value or “threshold”. Demand side estimates of this threshold are generally based on how much individuals are willing to pay or give up to improve their health. However, demand side estimates cannot tell us about opportunity cost imposed by an intervention [9,10]. By contrast, supply side effects – i.e., what improvement in health is possible given existing resources – can be obtained from estimates of the health effects of changes in health expenditure [11,12] and estimates are available for LMICs [13]. Supply side estimates are useful for decision-makers, donors and for prioritizing between a set of cost-effective interventions.

A broader perspective includes non-health benefits of vaccines such as productivity, risk reduction, equity/fairness, and fiscal impacts. A Social Welfare Function (SWF) and Social Rates of Return (SRR) framework could replace the QALYs and ICERs framework. The SWF is the most flexible framework for representing social preferences regarding health. However, since QALYs have important informational content, they remain an important part of SWF/SRR analysis.

To assess the broader economic impact of vaccination (BEIV), the WHO established a conceptual framework of the pathways between vaccines and their proposed benefits [14]. Applying the BEIV framework in practice showed that any broadening of the methodology for economic evaluation must also involve evaluations of non-vaccine interventions, and hence may not always benefit vaccines given a fixed health-care budget [15]. Furthermore, the scope of evaluation should be based on the budget holder and its priorities [15]. Nevertheless, relative to other public health interventions, vaccines have had a large impact on global public health with a relatively low cost. This outcome has been achieved both through the direct protection of vaccinated individuals and indirect protection of unvaccinated persons through reduction in transmission. Furthermore, for some infections – such as those due to measles, rotavirus, pertussis, meningococci, pneumococci, and *Haemophilus influenzae* type b (Hib) – few other effective prevention measures exist. For other infections, prevention measures have proven globally insufficient (e.g., dengue), or insufficient in specific contexts (e.g., malaria and cholera). This is evidenced, for example, by high Hib meningitis rates in Europe and the US in the pre-vaccine era, and the recent resurgence of measles and pertussis cases in the developed world in the context of insufficient vaccination coverage and possibly inadequately efficacious vaccine (see Table 1).

Table 1
Summary of measures used to assess vaccine benefits.

| | Strengths (what it measures) | Weakness (what it does not measure) |
|--|--|--|
| Vaccine effectiveness (VE) | <ul style="list-style-type: none"> • The percentage of an outcome reduced by vaccine • Can be measured for direct, indirect, total, or overall protection • For non-etiotologically confirmed outcomes provides a means to infer outcome specificity • Can be used to calculate VPDI when multiplied by background disease incidence • Can be of potential value to initiate policy discussions | <ul style="list-style-type: none"> • Does not measure the incidence rate reduction of outcomes achievable by vaccine • Does not incorporate quantification of underlying disease burden in the absence of vaccine • For non-etiotologically confirmed outcomes, values will vary substantially depending on the proportion of the outcome due to etiologies not prevented by vaccine • Does not measure population impact and its measurement may reinforce false and strong perceptions of the need for high effectiveness before implementation |
| Vaccine-preventable disease incidence (VPDI) | <ul style="list-style-type: none"> • Also known as the vaccine attributable rate reduction or the incidence rate reduction • Measures the reduction in disease incidence due to vaccine use • Can be measured for direct, indirect, total, or overall protection • For non-etiotologically confirmed outcomes provides a measure of outcome sensitivity • For non-etiotologically confirmed outcomes, values don't depend on the incidence of outcomes due to etiologies not prevented by vaccine • Incorporates and depends on the underlying disease burden in the absence of vaccine • Can be estimated from any robust data source and can be calculated for any vaccine relevant outcome • Can assist health systems planning for outbreak preparedness and policy decisions by estimating impact of immunization program in reducing disease burden over the long-term | <ul style="list-style-type: none"> • Requires incidence data, which is not available from case-control studies • Should be based on complete ascertainment of incidence • Fully quantifying the preventable disease incidence of all relevant outcomes requires community-based and not just hospital-based surveillance data, from various sources, to account for outpatient illness and ill persons who do not present for care |
| Quality adjusted life years | <ul style="list-style-type: none"> • A year of life adjusted for its quality or value, with perfect health assigned a value of 1.0 • Incorporates the quality of life, in addition to its duration, when measuring vaccine impact • Allows broader advocacy for the value of vaccination over the entire life course of an individual going beyond just the health sector (quality of life arguments) | <ul style="list-style-type: none"> • Relies on value judgments • Varies by society, and quality adjustment values not ascertained for most societies • Cannot be measured directly for children below a certain age, who can't assess the value of different health states • Perfect health, as the reference standard, difficult to define • Values may change over time in a society or as individuals age • May overweigh value of interventions for younger, healthier people and thus reduce equity, since by definition it incorporates length of life, and healthier people may have a greater change in the value of health states from baseline • Quality of life is assigned to only an individual experiencing illness, which ignores broader impacts on households, communities, and society as a whole • Quality adjustment factors infrequently updated, so do not account for improvements over time in mitigating and overcoming health problems, improvements in health care delivery and economic development more broadly |
| Incremental cost effectiveness ratio | <ul style="list-style-type: none"> • The difference in cost between two interventions divided by their difference in effect; difference in effect often measured using quality adjusted life years • Can be used as an absolute or relative decision rule for determining whether or not to implement a vaccination program • Provides a relative measure for comparison of different interventions • Can assist in priority setting under urgent scenarios of outbreaks vs routine programs | <ul style="list-style-type: none"> • Requires accurate assessment of costs and burden reduction • May underweight value of preventing potentially epidemic diseases (such as Ebola) until crises have occurred • May undervalue political and equity issues, as these are difficult to cost • May result in widening inequities and disadvantaging some sub-population if cost-effectiveness is higher in wealthier groups (e.g., those with higher costs of medical services) |
| Social Welfare Function | <ul style="list-style-type: none"> • Places the value of vaccination in the broader sphere of better policies to improve social welfare, e.g. education, poverty reduction, gender equality, empowerment of women, etc. | <ul style="list-style-type: none"> • Difficult to measure and disaggregate the various functions, which may vary by time and place |
| Social Rates of Return | <ul style="list-style-type: none"> • Places vaccination in the broader context of greater social impact on populations, including better health, more robust school attendance, equality between males and females, better economic outcomes, etc. • Social justice and equity arguments may have greater political weight than arguments limited to health benefits | <ul style="list-style-type: none"> • Difficult to measure and disaggregate the various components, which may vary by time and place • Can create unintended competition and turf battles between various sectors (e.g. health, education, welfare, etc.) |
| Multi-criteria decision-making processes | <ul style="list-style-type: none"> • Allows for a more robust, inclusive and holistic decision-making process and framework, which takes into account the linkages between various dimensions of immunization programs and beyond | <ul style="list-style-type: none"> • Difficulty to define the nature and strength of the linkages, which criteria are important and, then, assigning appropriate weighting to various criteria • Outcomes that can be measured may not be the most important outcomes for decision-making |
| Extended cost-effective analysis | <ul style="list-style-type: none"> • Allows more rational policy decisions and stronger advocacy especially in situations in many developing countries of limited resources and competing priorities • Allows evidence-based articulation of effectiveness and benefits beyond health outcomes | <ul style="list-style-type: none"> • Difficulty in obtaining appropriate data and subjectivity in defining effectiveness in a broader sense • Inherent limitations in the many analytical and modelling tools used and the many underlying assumptions of such analyses |

There are a variety of methods to make sure vaccines are appropriately valued. Replacing the present common practice of relying on cost-effectiveness with multi-criteria decision-making processes where the full value of vaccines is captured is an example that has been used by the SMART vaccines initiative of the Institute of Medicine [16]. Extended cost-effective analysis (ECEA) is another tool that enables quantifying the equity and financial risk protection benefits of vaccination, supplementing the quantification of health benefits provided by traditional cost-effectiveness analysis [17]. Applying ECEA to evaluate vaccine policy in LMIC provided evidence that ECEA captures important health and non-health implications of scaling up vaccine programs [18]. It incorporates financial risk protection and distributional consequences into the systematic economic evaluation of vaccine policy. It enables selection of vaccine packages based on quantitative inclusion of information of equity and of how much financial risk protection is being bought, in addition to how much health is being achieved for a given expenditure on specific vaccines, which may be useful for progressive prioritization toward universal health coverage and the Sustainable Development Goals [17].

More accurate measurement of vaccination-mediated health benefits should include measures beyond efficacy and safety. Such measures include vaccine preventable disease incidence (VPDI) (also known as the vaccine attributable risk or the incidence rate reduction) and number needed to vaccinate (NNV) as well as assessment of these measures against non-etiological confirmed clinical outcomes. Use of non-etiological confirmed outcomes is useful in all situations [21] but particularly in situations where etiologic confirmation is difficult, such as with non-bacteremic Hib and pneumococcal pneumonia [5,6,19–23]. Other parameters that should be considered beyond efficacy and safety include, case fatality ratio, transmissibility, severity, sequelae, duration of immunity, age distribution, outbreak potential and predictability of disease occurrence, and disruption of health systems.

The latter point was illustrated in the three West African countries severely affected by the Ebola epidemic in 2013–2015. In that case, loss of health care workers to disease and reassignment of health staff towards Ebola response likely led to a decrease in other health services and increase in mortality. A similar situation likely exists for dengue and cholera during large outbreaks or epidemics. For all outbreak driven diseases, given the unpredictability of disease occurrence, it is usually impossible to have adequate resources (staff, facilities, medicines, supplies) available to respond in an efficient way to maximize health through reactive interventions. Vaccines also can be used to mitigate the effects of protracted armed conflicts, where much of the associated morbidity and mortality results from disruption of public health services. This point has long been acknowledged by the WHO-SAGE, and an economic framework for decision making was developed and endorsed by SAGE in 2012 [14]. This was followed by a series of meetings to agree on a package of documents and solutions to guide vaccination in humanitarian emergencies.

Vaccination is also an essential element for promoting (i) health equity, (ii) economic equity (through reducing medical and non-medical costs associated with cases of vaccine-preventable diseases), (iii) social equity (e.g. access to the health care system) and (iv) vertical equity intervention (e.g. vaccines for diseases of poverty). In addition, childhood vaccination is an entry point to the health system for the poor [24], and as such can have effects on other health outcomes. For example, studies on measles case fatality ratios showed drastic differences according to socio-economic group [25,26] and a global literature review revealed how the risks of meningitis sequelae varied substantially according to income [27]. Out-of-pocket costs are the largest source of health expenditures in many LMICs and vaccine preventable diseases can lead to catastrophic health expenditures for poor households

[28,29]. By averting cases of disease, vaccination averts the need for these health expenditures and when delivered equitably can help break cycles of poverty and ill health, which can then lead to improvements in health and economic security.

3. Case studies of the need for full public health value of vaccination analysis

3.1. Vaccines being adopted

3.1.1. Rotavirus

Diarrheal disease caused by rotavirus is a public health problem in young children. The two available vaccines have shown significant impact in reducing all-cause acute gastroenteritis and rotavirus-related hospitalization [30] but also indirect benefits to older children and young adults in the USA [2,3]. These vaccines conferred lower efficacy in the developing world [4–6]. While there were key differences in study design and methodology [31], the lower efficacy in developing countries was likely due to factors such as interference from other co-infecting pathogens, malnutrition, and gut enteropathy.

From a regulatory perspective, this lower efficacy might suggest rotavirus vaccine is a poorer investment in developing countries. However, from a FPHV perspective, where additional criteria should be taken into account when deciding on vaccine implementation of rotavirus vaccine, a different picture emerges. For example, in spite of lower efficacy, the absolute public health impact of these vaccines is anticipated to be higher than in high income settings because of the greater burden of rotavirus disease [20,22,32,33]. This impact is likely to be even greater outside of a clinical trial setting, where access to health care services may be limited [20,22,34]. Enteric infection during early childhood could also lead to early stunting, obesity, metabolic and cardiovascular diseases and cognitive impairment [35]. Assessment of the FPHV of rotavirus vaccination should take into consideration the cost of this triple burden of diarrhoea at the individual and population level and the longer-term benefits on child health of disease prevention. Further, rotavirus vaccines illustrate the importance of health equity, as children in rural areas with poor access to treatment have high incidence of preventable severe gastroenteritis [20].

3.1.2. Maternal immunization with influenza vaccine

Globally, significant morbidity and mortality from vaccine-preventable diseases occurs in pregnant women and in young infants. Immunization of pregnant women against selected infectious diseases is therefore a potential strategy to reduce several diseases in mothers and their new-born infants and may also prevent infection-related foetal outcomes [36–41]. For influenza, uncertainties and logistical challenges have led to limited financing for and demand by low-income countries to implement maternal influenza vaccine [42]. A lack of assessment of the FPHV of maternal influenza immunization also adversely affects decision-making. Areas for additional research include the degree to which influenza precipitates other illness, the impact of influenza illness on prenatal care, and broader issues such as the impact of the lack of a seasonal influenza vaccine strategy in many countries on their ability to access vaccine during a pandemic.

3.1.3. Dengue

Countries have had limited success using traditional strategies to control the geographical spread and increasing burden of dengue. Several vaccine candidates are in the pipeline. The recent first licensure of CYD-TDV (Dengvaxia®, Sanofi-Pasteur, Lyon France) was followed by a WHO recommendation to vaccinate in endemic populations with seroprevalence not lower than 50%, as part of an

integrated management strategy for the control of dengue (IMS-Dengue) [45,47]. Traditional approaches to estimating the value of CYD-TDV have shown efficacy against severe dengue (93%), hospitalized dengue (80%) and laboratory-confirmed clinical dengue (65%), with variable efficacy against the four dengue serotypes (47–83%) and by previous exposure (52–81%) [46]. CYD-TDV is now approved in 17 countries and public sector programs have been initiated.

Calculation of VPDI for the dengue vaccine phase III trial helps illustrate the vaccine's FPHV by illustrating the large preventable burden of disease (Fig. 1). When combined with calculation of NNV, these data demonstrated that dengue vaccine had a public health impact that compared favourably with other vaccines already in use in the trial regions [48]. Moreover, dengue vaccine showed a high VPDI against less severe clinical disease, which is the disease outcome that may have the largest impact on health service utilization [48].

3.2. Vaccines under evaluation

3.2.1. Malaria

RTS,S/AS01, the only malaria vaccine to receive positive regulatory approval so far, provides protection for a few months but this wanes rapidly during subsequent years [43]. Despite these deficiencies, there may still be an important role for imperfect malaria vaccines in malaria control if these are used strategically. Seasonal vaccination might be an appropriate use for a vaccine which has a high level of initial efficacy but which provides only short lived protection. Moreover, a vaccine of limited efficacy could be useful as one component of a mass control campaign aimed at elimination. A malaria vaccine could also have indirect effects including reduction in invasive bacterial infections, especially non-typhoidal salmonella infection; improvement in nutrition; improvement in school attendance and performance; and improvement in productivity. Using mathematical modelling, routine use of the RTS,S/AS01 vaccine in African settings turned out to be highly cost-effective with significant public health impact [44]. From a FPHV point of view, local and national economic benefits as well as gains in productivity are among factors that should be taken into consideration when evaluating malaria vaccines.

3.3. Vaccines in pipeline

3.3.1. Group B *Streptococcus*

Invasive Group B *Streptococcus* (GBS) is a leading cause of neonatal sepsis, morbidity and mortality in both high and low income settings [49,50] even when intrapartum antibiotic prophylaxis during labour of colonized women has been successful in reducing early-onset invasive disease in newborns. Recent advances in the prevention of invasive GBS disease have renewed interest in polyvalent polysaccharide protein conjugate vaccines [51]. The licensure of a GBS vaccine for pregnant women aimed at protection against invasive GBS disease of their newborns will, however, require studies with large sample sizes for an invasive disease endpoint. An alternate licensure pathway, as was the case for meningococcal vaccine, could be premised on establishing a sero-correlate of protection against invasive disease and using this information to license the vaccine based on immunogenicity and safety. This could be followed by post-licensure effectiveness studies against invasive GBS disease, GBS carriage, and non-etiotologically confirmed clinical outcomes such as pneumonia or sepsis of unknown etiology, and low birth weight or preterm birth.

3.3.2. Respiratory syncytial virus

The recognized importance of prevention of acute lower respiratory illness (ALRI) caused by respiratory syncytial virus (RSV)

has led to a robust research and development pipeline with more than 60 vaccines or prophylactic monoclonal antibodies in development and more than 15 being evaluated in clinical trials [52]. Moreover, bacterial-RSV interactions are only beginning to be understood, and suggest that prevention of RSV ALRI could potentially have direct effects on invasive bacterial pulmonary disease [53,54] or indirect effects through alterations in the respiratory microbiome [55,56]. A link between early RSV disease and long-term lung health such as recurrent wheezing [57,58] or childhood asthma [59] has also been reported. A proper assessment of the full impact of RSV vaccines should therefore include indirect outcomes (e.g. all-cause pneumonia, pathogen-pathogen interactions, and pathogen replacement).

4. Discussion

Vaccines are an important contributor to the increase in life expectancy from less than 50 years in 1900 to more than 80 years now. During the last 15 years, there has been substantial advancement in vaccine innovation, a massive increase in the number of countries introducing several new vaccines into National Immunization Programs, and increased coverage with others, e.g., measles. Progress in introduction of three key vaccines supported by Gavi, the Vaccine Alliance (i.e., Hib in the form of pentavalent vaccines, rotavirus vaccine, and pneumococcal conjugate vaccine), has led to protection against some of the major vaccine-preventable causes of child mortality. In spite of their social value, the economic value of vaccines has been underestimated using current traditional economic evaluation methods and the standard evaluation criteria for vaccine licensure. As a consequence, future vaccines are likely to face substantial constraints on policy decision making with the *status quo* approach. This is particularly likely to occur for vaccines that have VE less than currently adopted vaccines, a situation that may occur despite lower efficacy vaccines having broader public health impact as measured by VPDI and NNV.

As illustrated by case studies, application of FPHV of vaccination would change decision-making (e.g., vaccine development timelines, vaccine introduction decisions). Modern cost-benefit vaccine studies have moved beyond safety and efficacy to additional impact measures and strategies which assess reduction of disease burden and reduced inequities among populations, but more efforts are still needed to include wider direct and indirect parameters. Other concepts such as outbreak control, family integrity, local and national economic issues, and different types of inequities should be considered to measure the FPHV of vaccines accurately. However, we face an impasse, with a wall between the traditional approach and an approach that considers a vaccine's FPHV (Fig. 2). To move from the former to the latter, the following questions must be answered: (1) what evaluations should be considered; (2) when should they be done, pre- or post-licensure; and (3) who will see this as their responsibility?

Economic evaluation of vaccination is a key tool to inform effective spending on vaccines. However, traditional methods are too narrow and not always easy to communicate to ministries of finance. To support ministers of health and immunization program directors, Anderson and colleagues identified ten attributes that could help them to prepare better and to provide more convincing arguments before they start negotiation with their ministries of finance [60].

The broader economic evaluation of vaccines include: use of clinically defined outcomes in addition to etiologically-defined outcomes; wider societal benefits (e.g., improved educational achievement, economic growth and political stability); reduced health disparities; medical innovation; reduced pressure on hospital beds; and synergies in economic benefits with non-vaccine

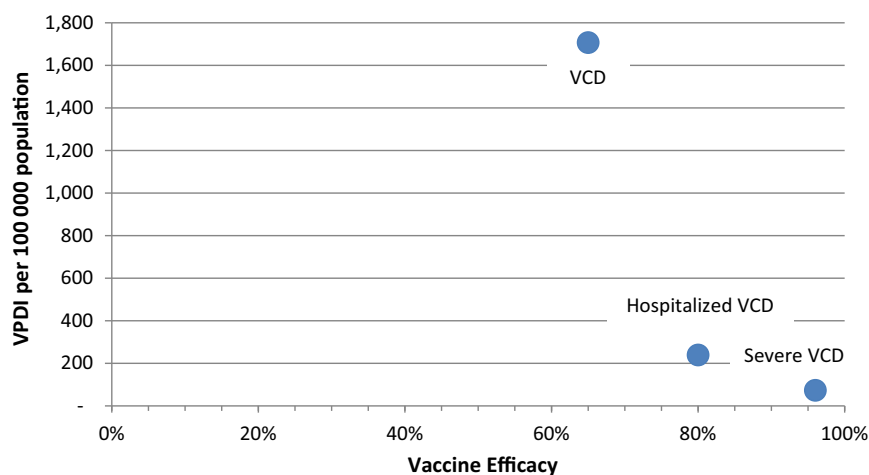


Fig. 1. Comparison of dengue vaccine efficacy and vaccine preventable disease incidence (VPDI*) in Latin America. Moderately efficacious interventions can have high public health value when the background rate of an outcome is high. For example, while the prevention of clinically severe virologically confirmed dengue (severe VCD) and the reduction in the demand for health services such as hospitalization (hospitalized VCD) are public health priorities, the value of dengue vaccination is also reflected in a much higher reduction in less severe clinical disease outcomes, outcomes that result in direct health expenses and loss of productivity at school and work [48]. *High VPDI indicates a greater reduction in disease burden through use of vaccine.

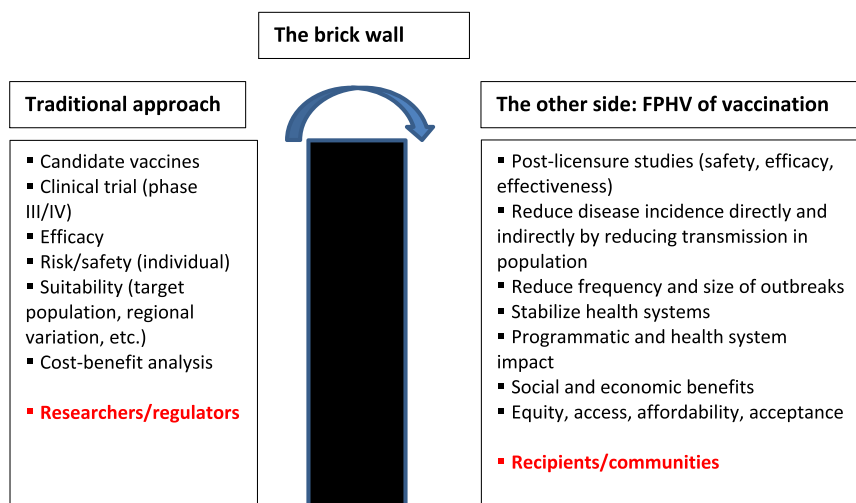


Fig. 2. The brick wall: Moving from vaccines to vaccination.

interventions. Also, the fiscal implications of vaccination programs are not always made explicit. Many of these topics could be incorporated into licensing trials to provide quantitative estimates of these measures.

The scope of a broader economic evaluation should also consider the budget from which vaccines are funded, and the decision-maker's stated objectives for such budgets. As an example, gross domestic product (GDP)-based thresholds show lack of country specificity, which can lead to lack of prioritization, as evidenced by one country electing not to fund vaccination programs demonstrated to be 'very cost effective'. In this and other similar cases, it is likely that other factors beyond cost effectiveness, including the overall budgetary impact, dictate decision-making in LMICs [10]. Information on cost-effectiveness should be used alongside other considerations – e.g. budget availability [10], budget impact and feasibility considerations – rather than in isolation

based on a single threshold value. Additionally, economic and decision-making analysis should go beyond dependence on QALYs as a single outcome measure and incorporate the concepts of SWF/SRR. Once a more context specific decision-making process is developed, this should be supported by legislation; have stakeholder buy-in, for example the involvement of civil society organizations and patient groups; and be transparent, consistent and fair [61]. Such a country-specific process may emphasize to a greater extent the FPHV of vaccines, but final expansion of immunization programs may still be restricted by budget limitations, especially in LMICs.

Strategies for scaling the brick wall (Fig. 2) will require (1) the development of a comprehensive framework for FPHV of vaccines as part of end-to-end vaccine development programs; (2) a research question gap analysis and prioritization, (3) an inventory of FPHV evidence, by vaccine, (4) set-up of an annual score card for

Table 2

Points to be considered by policy makers to achieve the full public health benefits of vaccination.

| |
|---|
| Broader, non-health impacts and externalities and use of methods to capture the full benefits of vaccination (e.g. VPDI, NNV, SRR, BEIV, ECEA, cost/QALY) |
| More balanced view of cost-effectiveness data and balancing value versus access and profit versus public good |
| Accurate assessment of the disease burden reductions and other benefits of moderately effective vaccines; vaccines may have moderate effectiveness yet high public health value if they target diseases that are common, severe, or outbreak driven |
| Knowledge of previously unknown causal associations which can be broken by vaccination (e.g. viruses that predispose to bacterial disease, an association between measles and malnutrition, influenza and chronic disease exacerbation, etc.) |
| Value of post-licensure studies to gather evidence for example on real world effectiveness, indirect protection and herd immunity, number of protective doses needed and duration of immunity |
| Flexibility and local/sub-national contextual factors |
| The need for political commitment, good communication, and evidence-based decisions (e.g. technical aspects of vaccines, vaccine hesitancy and confidence) |

VPDI: Vaccine Preventable Disease Incidence; NNV: Number Needed to Vaccinate, SRR: Social Rates of Return; BEIV: Broader Economic Impact of Vaccination; ECEA: Extended Cost-Effective Analysis; QALY: Quality Adjusted Life Years.

progress on completeness of evidence, (5) advocacy to apply the FPHV approach to novel product development, and (6) dialogues with manufacturers and policy makers. Additional information also will be required including (Table 2): when do policy makers assess vaccine benefits, which benefits count, and assuming the boundaries of the relevant benefits have been defined, what is the best metric for quantifying those benefits?

In conclusion, vaccines have wide-ranging benefits but these benefits are often poorly quantified and not typically captured in regulatory and implementation policy discussions. This was highlighted during the meeting with discussions on the FPHV of vaccines already adopted, i.e., rotavirus and maternal influenza immunization, vaccines being considered for licensure and implementation, i.e., malaria and dengue, and others in clinical development, i.e., GBS and RSV candidates. A change in mind set and further innovations are necessary when considering the FPHV of prophylactic vaccines in the evidence-based decision-making process of vaccine licensure and public health use. Vaccines should be seen not only or even primarily as a cost that increases public health budget needs, but as an investment with sustainable, long term, and large-scale impact. Accurately measuring the FPHV of vaccines will increase the likelihood of adopting this approach by increasing political will and allowing for more accurate prioritization of available resources.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

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Conflict of Interest

CBN is employee of Sanofi Pasteur. BDG performed this work as an employee of AMP and is currently employed by Pfizer. Other authors declare that they have no conflicts of interest to report.

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WHO full public health value proposition (FPHVP) for vaccines

(DRAFT template)

| Table of Contents | | |
|-------------------|--|----|
| 1 | Executive summary and public health value statement | 3 |
| 1.1 | Public health value statement | 3 |
| 2 | WHO public health value propositions for vaccines in early stage development | 4 |
| 2.1 | Target audiences and use of WHO PHVPs | 5 |
| 2.2 | Criteria for selecting vaccines for PHVPs | 5 |
| 2.3 | Methodology for PHVP development | 5 |
| 3 | The global public health need for the vaccine | 6 |
| 3.1 | Disease description | 6 |
| 3.2 | Current methods of surveillance, diagnosis, prevention and treatment | 7 |
| 3.3 | Key gaps in knowledge or research evidence | 8 |
| 4 | **X** vaccine - a strategic priority for WHO | 9 |
| 4.1 | WHO Preferred Product Characteristics (PPCs) | 9 |
| 5 | Stakeholder analysis and involvement | 10 |
| 5.1 | Key gaps in knowledge or research evidence | 10 |
| 6 | Development of the vaccine | 11 |
| 6.1 | Biology of the vaccine | 11 |
| 6.2 | Technical platforms under consideration | 11 |
| 6.3 | Preclinical development: key issues | 11 |
| 6.4 | Clinical development and regulatory pathway: key issues | 11 |
| 6.5 | Vaccine efficacy: key issues | 12 |
| 6.6 | Vaccine safety; key issues | 13 |
| 6.7 | Implementation: key issues | 13 |
| 6.8 | Key gaps in knowledge or research evidence | 14 |
| 7 | Assessment of the vaccine development pipeline | 14 |
| 7.1 | Pipeline summary | 14 |
| 7.2 | Pathway and timescale to licensure | 15 |
| 7.3 | Benchmarking against other vaccines | 15 |
| 7.4 | Probability of success | 16 |
| 7.5 | Key gaps in knowledge or research evidence | 16 |
| 8 | Estimation of disease burden and transmission | 17 |

| | | |
|------|---|----|
| 8.1 | Public health inputs and output for modelling | 17 |
| 8.2 | Transmission modelling | 17 |
| 8.3 | Key gaps in knowledge or research evidence | 17 |
| 9 | Defining the market for the vaccine | 18 |
| 9.1 | Potential market segments | 18 |
| 9.2 | Market validation | 18 |
| 9.3 | Strategic vaccine demand forecast | 20 |
| 9.4 | Key gaps in knowledge or research evidence | 21 |
| 10 | Impact of the vaccine on burden of disease and transmission | 22 |
| 10.1 | Measurement of vaccine benefits | 22 |
| 10.2 | Key gaps in knowledge or research evidence | 22 |
| 11 | Economic analysis of the value of the vaccine | 23 |
| 11.1 | Economic analysis: methodology | 23 |
| 11.2 | Economic analysis: summary of findings | 23 |
| 11.3 | Impact of investment | 25 |
| 11.4 | Estimation of cost effectiveness | 27 |
| 11.5 | Key gaps in knowledge or research evidence | 27 |
| 12 | Financing the development of the vaccine | 28 |
| 12.1 | Likely gaps in funding for development for use in LMICs | 28 |
| 12.2 | Key gaps in knowledge or research evidence | 29 |
| 13 | Conclusions and recommendations | 30 |
| 13.1 | Next steps | 30 |
| 14 | References | 31 |
| 14.1 | Further reading | 31 |
| | Appendix 1. Abbreviations | 32 |
| | Appendix 2. Glossary | 33 |
| | Appendix 3. Overview of the product development process | 37 |
| | Appendix 4. Draft target product profile (TPP) | 38 |
| | Appendix 5. Authors, advisors and stakeholders interviewed | 39 |