World Health Organization

Department of Immunization, Vaccines and Biologicals (IVB)

SAGE

October 2018

Strategic Advisory Group of Experts on Immunization
23 - 25 October 2018

Centre International de Conférences (CICG)
Geneva, Switzerland

SAGE October 2018

This booklet contains key background documents for the meeting of the
Strategic Advisory Group of Experts (SAGE) on Immunization
23 - 25 October 2018

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

SAGE/meetings/2018/October

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

Agenda

23 - 25 October 2018

CICG, Geneva, Switzerland

Draft 25 September 2018

Tuesday, 23 October 2018

Time	Session	Purpose of session, target outcomes and questions for SAGE	Duration
09:15	**Welcome – introduction of participants** A. CRAVIOTO. Chair of SAGE.		15 min.
09:30	**Report from Director, IVB and Regional Updates– Session 1** Global report including key updates and challenges from Regions. M. FRIEDE. WHO. 30 min. Discussion 1 h. **WHO Focal point** M FRIEDE, REGIONAL ADVISERS **SAGE Focal Point** A. CRAVIOTO	**FOR INFORMATION;**	1 h 30 min.
11:00	**Coffee/tea break**	**Break**	**30 min.**
11:30	**Report from Gavi, the Vaccine Alliance– Session 2** Report from Gavi, the Vaccine Alliance. S. BERKLEY. Gavi, the Vaccine Alliance. 15 min. Discussion 15 min. **WHO Focal point** L. KAMARA **SAGE Focal Point** A. CRAVIOTO	**FOR INFORMATION**	30 min.
12.00	**Reports from other Advisory Committees on Immunization– Session 3** Report from Global Advisory Committee on Vaccine Safety (GACVS). R. PLESS. GACVS Chair. 10 min. Discussion 10 min. **WHO Focal point** P. ZUBER **SAGE Focal Point** K. JOHANSEN	**FOR INFORMATION** Report from June 2018 meeting	1 h 30 min.

	Report from Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC). W. ORENSTEIN. 10 min. Discussion 10 min. **WHO Focal point** R. HUTUBESSY **SAGE Focal Point** C. WIYSONGE	Report from September 2018 meeting	
12:40	**Lunch**	**Break**	**1 h 05 min.**
13:45	**Cont. Reports from other Advisory Committees on Immunization– Session 3** Report from Immunization Practice Advisory Committee (IPAC). C. MORGAN. Chair of IPAC. 10 min. Discussion 10 min. **WHO Focal point** A-L. KAHN **SAGE Focal Point** I. JANI	Report from July meeting	
	Report from Product Development for Vaccines Advisory Committee (PDVAC). D. KASLOW. PDVAC Chair. 20 min. Discussion 10 min. **WHO Focal point** B. GIERSING **SAGE Focal Point** A. CRAVIOTO	• Report from June meeting to highlight progress on product development of selected vaccines and monoclonal antibody candidates for PDVAC prioritized pathogens • Brief discussion on the role of controlled human infection models in licensure and policy decisions	
14:35	**Global Vaccine Action Plan (GVAP)– Session 4** Update from the GVAP Secretariat. C. STEFFEN. WHO. 5 min Summary of GVAP implementation progress review and recommendations for additional efforts. N. MACDONALD, Chair of SAGE Decade of Vaccines Working Group. 25 min. Discussion 1 h.	**FOR DECISION** SAGE is asked to produce an independent annual report on progress with the Decade of Vaccines Global Vaccine Action Plan. Specially, SAGE will be asked to: • Review the DoV WG "Assessment report on DoV progress 2018 " based on the "GVAP Secretariat report 2018", the regional reports on the implementation of regional vaccine action plans, and some independent	2 h 15 min.

		stakeholder submissions. This year's review encompasses in addition a focus on the GVAP research and development indicators. • Identify successes, challenges and areas where additional efforts or corrective actions by countries, regions, partners, donor agencies or other parties, are needed.	
16:05	**Coffee/tea break**	**Break**	**30 min.**
16:35	**Cont. Global Vaccine Action Plan (GVAP)– Session 4** Process to develop a post-2020 Global Immunization Strategy 2021-2030. P. LYDON. WHO. 15 min. Discussion: 30 min. **WHO Focal point** C. STEFFEN **SAGE Focal Point** N. MACDONALD	**FOR DISCUSSION** • SAGE will also be presented with a high-level perspective on the development of a post-2020 immunization strategy • Discuss the articulation with the current GVAP reporting and monitoring process.	
17:20	**Report of activities from international immunization partners– Session 5** Introduction M. GURAIIB. WHO. 10 min. PREVENT initiative - Pregnant Women & Vaccines Against Emerging Epidemic Threats: Ethics Guidance for Preparedness, Research, & Response R. KARRON. 15 min. Discussion 15 min. **WHO Focal point** M. PERUT AND P LAMBACH **SAGE Focal Point** A. CRAVIOTO	**FOR INFORMATION** • Global Guidance For Managing Ethical Issues In Infectious Disease Outbreaks **FOR INFORMATION** Roadmap for the ethically responsible, socially just, and respectful inclusion of the interests of pregnant women in the development and deployment of vaccines against emerging pathogens. A draft guidance to support that pregnant women and their offspring • could benefit from advances in vaccine technologies • are not excluded from participating in vaccine studies, • could benefit from vaccines to protect them against emerging and re-emerging pathogenic threats.	40 min.
18:00	**End of Day 1, Cocktail**		

Wednesday, 24 October 2018

Time	Session	Purpose of session, target outcomes and questions for SAGE	Duration
09:15	**Polio– Session 6** Overview of the Global Polio Eradication Initiative. M. ZAFFRAN. WHO. 25 min. Independent evaluation of the eradication program in Afghanistan, Pakistan and Nigeria by the "Independent Monitoring Board". S. L. DONALDSON 20 min. Report from SAGE Polio Working Group. P. FIGUEROA. SAGE Polio Working Group Member. 20 min. Discussion: 55 minutes **WHO Focal Point** O. MACH **SAGE Focal Point** I. JANI	**FOR INFORMATION / DISCUSSION** Current status of the polio eradication program; Independent evaluation of the progress; Appraisal of options regarding certification of polio eradication.	2 h.
10:45	**Coffee/tea break**	**Break**	**30 min.**
11:15	**Cont. Polio– Session 6** Discussion		
11:45	**Measles and Rubella– Session 7** Session introduction. N. TURNER. SAGE member. 5 min. Global update. A. DABBAGH. WHO. 10 min. Discussion 15 min. Feasibility of MR eradication. B. MOSS. Measles and Rubella Working Group member. 15 min. Discussion 20 min.	**FOR INFORMATION** • Global and regional update **FOR DISCUSSION** • Presentation of the plan to address the feasibility and financial resource requirements for measles and rubella eradication. • Guidance from SAGE on the approach to addressing the feasibility question	2 h 15 min.
12:50	**Lunch**	**Break**	**1 h 10 min.**
14.00	**Cont. Measles and Rubella– Session 7** Co-administration of the YF vaccine with measles containing vaccines. J. HARRIS. Centers for Disease Control and Prevention. 15 min.	**FOR DECISION** • Presentation of studies on potential interference between	

	Discussion 15 min. Country classifications and guidance to increasing population immunity . S. REEF. Measles and Rubella Working Group member. 20 min. Discussion 20 min. **WHO Focal Point** A. DABBAGH **SAGE Focal Point** N. TURNER	MCVs and YF vaccine including the findings of the most recent RCT in Argentina. **FOR DECISION** • A roadmap for countries towards closing immunity gaps and achieving elimination. • Recommendations for key priorities for countries according to their level of control.	
15.10	**Human papilloma virus (HPV) vaccines– Session 8** Session introduction and key questions. R. AGGARWAL. SAGE Member. 5 min. Update on HPV vaccine introduction and programmatic perspective. T. GOODMAN. WHO. 15 min. Overview of evidence regarding HPV immunization on different disease outcomes A. POLLARD. SAGE member. 15 min.	**FOR DECISION** Present SAGE with updated evidence on HPV-related burden, HPV vaccines, impact of HPV immunization programmes, and modelling of impact of HPV immunization schedules and strategies. SAGE is requested to consider the following questions: • What are the potential effect and cost effectiveness of various vaccination strategies towards the achievement of cervical cancer elimination? • What is the potential contribution of HPV vaccination towards cervical cancer elimination? • What are the interim goals that can be achieved through immunization as part of the efforts towards cancer elimination. •What are the indicators to monitor the accomplishment of these interim goals? • What is additional research related to vaccines and immunization needed to attain these goals and outline potential innovations that may ease the achievement of these goals?	2 h.
15:45	**Coffee/tea break**	**Break**	**30 min.**
16:15	**Cont. Human papilloma virus (HPV) vaccines– Session 8** Forecast impact of different immunization strategies and screening scenarios towards cervical cancer elimination. M. BRISSON. Laval University. 20 min. Conclusions and proposed recommendations by SAGE Working Group. R. AGGARWAL. SAGE Member. 10 min. Discussion: 50 min **WHO Focal point** A.M. HENAO RESTREPO, T GOODMAN **SAGE Focal Point** R. AGGARWAL		
17:40	**End of Day 2**		

Thursday, 25 October 2018

Time	Session	Purpose of session, target outcomes and questions for SAGE	Duration
08:45	**Ebola and other unlicensed vaccines for emergency use - Session 9** Session introduction and key questions. F. WERE. SAGE Member and Co-Chair of the Working Group. 5 min. Overview of Ebola epidemiology. D. HEYMANN. LSHTM and Chatham House. 15 min. Update on candidate Ebola vaccines: available data on immunogenicity, efficacy and safety, timelines for licensure and Expanded Access/Compassionate Use experience. A.M. HENAO-RESTREPO. WHO. 15 min. Benefits and risk analysis of vaccination of pregnant women with rVSV-ZEBOV as part of Expanded Access/ Compassionate Use during Ebola outbreaks. C. JARVIS and J. EDMUNDS, LSHTM. 15 min. Observed and forecasted impact of different Ebola candidate immunization strategies and targeted populations. A. CAMACHO. EPICENTRE. 15 min. Questions for clarification. 15 min. Proposed recommendations by SAGE Working Group. H. REES. Working Group Member. 15 min. Discussion 40 min. **WHO Focal point** A.M. HENAO RESTREPO **SAGE Focal Point** F. WERE	**FOR DECISION** SAGE is asked to provide recommendations on the use of such unlicensed vaccines and the anticipated impact of various vaccination strategies. SAGE is requested to consider the following questions: • Is the current evidence sufficient for SAGE to adjust current recommendations regarding the use of Ebola vaccines in case of another Ebola outbreak? If yes, which recommendations can be proposed? And, what key data are missing? • What are the conclusions from the benefits and risk analysis of vaccination of pregnant women with rVSV-ZEBOV as part of Expanded Access/ Compassionate Use during Ebola outbreaks? • Are there remaining challenges that may prevent access to Ebola vaccines in future outbreaks, and, if yes, can SAGE make recommendations on how these might be addressed?	2 h 15 min.
11:00	**Coffee/tea break**	**Break**	**30 min.**
11:30	**Lessons learned from Diphtheria outbreaks: opportunities for early warning and preventive action- Session 10** Introduction to session. F. QADRI. SAGE Member, 5 min. Case study – Diphtheria Outbreak in Cox Bazaar. S. BAHL. WHO., SEARO, Regional Office. 10 min.	**FOR INFORMATION AND DISCUSSION** Purpose of this session is to review and discuss programmatic data available at HQ and how it can be strengthened or analysed differently to anticipate or prevent outbreaks of VPDs. The diphtheria outbreak in Cox's Bazaar will be used as a case study. In addition, SAGE will be presented with two approaches being explored. A pragmatic approach (excel-based) using	1 h 45 min.

	Global Opportunities and Gaps in Preventing Diphtheria Outbreaks. M. GACIC-DOBO. WHO. 20 min. Country level risk assessment tool for Diphtheria: an example of possible approaches to guide country level actions (work in progress). S. HADLER. Task Force Global Health. 15 min. Vaccine decision information systems (work in progress) W. PANHUIS. University of Pittsburgh. 10 min. Discussion and proposed next steps. 45 min. **WHO Focal point** S. DESAI AND AM HENAO RESTREPO **SAGE Focal Point** F. QADRI	routinely available data at the country level to predict the prospective risk of diphtheria. The second is an approach using subnational data for risk analysis to strengthen vaccination strategies. SAGE is requested to note these ongoing efforts and to suggest additional actions for this area of work, including but not limited to other data elements to consider and other analytical approaches that should be explored.
13:15	**Closing**	
13:30	**End of meeting**	

World Health Organization

Current 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 and 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.

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)*

7.	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 ☐

Version: 3 May 2016

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. <u>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.</u>**

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				

<u>CONSENT TO DISCLOSURE</u>. 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.

<u>DECLARATION</u>. 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_____

Version: 3 May 2016

World Health Organization

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)

Version: 3 May 2016

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.

World Health Organization

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).

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.

Composition

SAGE Members

- Noni MacDonald: Dalhousie University, IWK Health Centre, Canada. (Chair of the Working Group of June 2017 to replace Narendra Arora)

Updated: Sept 2018

- 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)
- Qinjian 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 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)

Updated: Sept 2018

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 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 INCLEN Trust International, New Delhi
- 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: Manhiça Health Research Centre, Mozambique
- Cristiana Toscano: Federal University of Goiás, Brazil

6. 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

7. 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.

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.

8. SAGE Working Group on HPV (established June 2018)

Terms of Reference

- To critically appraise the evidence and potential effect and cost effectiveness of various vaccination strategies towards the achievement of cervical cancer elimination.
- To review the potential contribution of HPV vaccination towards cervical cancer elimination.
- To develop and propose interim goals that can be achieved through immunization as part of the efforts towards cancer elimination.
- To develop and propose indicators to monitor the accomplishment of these interim goals.
- To discuss and propose additional research related to vaccines and immunization needed to attain these goals and outline potential innovations that may help enhance the achievement of these goals.

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World Health Organization

Strategic Advisory Group of Experts (SAGE) on Immunization
23 - 25 October 2018
Centre International de Conférences, (CICG), Geneva, Switzerland

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Meeting of the Strategic Advisory Group of Experts on immunization, April 2018 – conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization[1] met on 17–18 April 2018. This report summarizes the discussions, conclusions and recommendations.[2]

Report from the WHO Department of Immunization, Vaccines and Biologicals and Regional updates

The report from the Director of the WHO Immunization Vaccines and Biologicals programme focused on the theme "Immunization in a changing world." In line with WHO's mission to keep the world safe, promote health, and serve the vulnerable, as detailed in the WHO 13th Global Plan of Work (GPW 13), it was noted that immunization makes important contributions to all 3 objectives.[3] The Global Vaccine Action Plan (GVAP) goal on new vaccine introduction has been accomplished, but other GVAP goals have not yet been achieved. In particular, gaps and inequity in coverage remain. Population growth, population migration within and between countries, and ever increasing urbanization challenge even the current coverage levels. Population growth in Africa causes coverage to plateau even though ever more children are being vaccinated – African countries need to vaccinate half a million additional children every year just to keep up with growth. The recent diphtheria outbreaks in Bangladesh, Bolivarian Republic of

[1] See www.who.int/immunization/sage/en/index.html, accessed April 2018.

[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/2018/april/en (accessed April 2018).

[3] WHO. Draft thirteenth general programme of work 2019–2023 (available at http://www.who.int/about/what-we-do/gpw-thirteen-consultation/en/, accessed April 2018).

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, avril 2018 – conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination[1] s'est réuni les 17 et 18 avril 2018. Le présent rapport résume les discussions, conclusions et recommandations auxquelles il est parvenu.[2]

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

Le directeur du programme Vaccination, vaccins et produits biologiques de l'OMS a présenté un rapport axé sur le thème «Vaccination dans un monde en évolution». Il a observé que la vaccination contribue de manière importante aux 3 objectifs de la mission de l'OMS, tels qu'énoncés dans le 13e programme général de travail (PGT13) de l'OMS: préserver la sécurité mondiale, promouvoir la santé et servir les populations vulnérables.[3] Parmi les objectifs du Plan d'action mondial pour les vaccins (GVAP), celui qui traite de l'introduction des nouveaux vaccins a été atteint, mais d'autres restent inachevés. Il subsiste en particulier des lacunes et des inégalités en matière de couverture vaccinale. La croissance démographique, les migrations de population à l'intérieur des pays et d'un pays à l'autre, ainsi que l'urbanisation toujours croissante, présentent d'importantes difficultés, ne serait-ce que pour maintenir les niveaux de couverture actuels. En Afrique, la croissance démographique se traduit par un plafonnement de la couverture, bien que le nombre d'enfants vaccinés ne cesse d'augmenter: pour suivre le rythme de la croissance, il

[1] Voir www.who.int/immunization/sage/en/index.html, consulté en avril 2018.

[2] Les communications et les documents de travail utilisés pour la réunion du SAGE, ainsi que la liste des membres du SAGE et une synthèse de leurs déclarations d'intérêts sont disponibles à l'adresse: www.who.int/immunization/sage/meetings/2018/april/en (consulté en avril 2018).

[3] OMS. Projet de treizième programme général de travail 2019-2023 (disponible à l'adresse: http://www.who.int/about/what-we-do/gpw-thirteen-consultation/fr/, consulté en avril 2018).

Venezuela (Venezuela), Haiti, Indonesia and Yemen are consequences of conflicts, migration and economic downturns that challenge and impede immunization and health systems. Global use of diphtheria anti-toxin increased from 200 vials in 18 years (2000–2017) to 18 000 vials during 2017–2018. Pockets of unvaccinated and under-vaccinated populations associated with these outbreaks indicate the need for a greater degree of granularity in coverage data in order to direct timely preventive action.

faudrait que les pays africains vaccinent un demi-million d'enfants supplémentaires chaque année. Les récentes flambées de diphtérie au Bangladesh, en Haïti, en Indonésie, en République bolivarienne du Venezuela (Venezuela) et au Yémen sont le résultat de conflits, de migrations et de récessions économiques qui entravent le bon fonctionnement des systèmes de vaccination et de santé. La quantité d'antitoxine diphtérique utilisée dans le monde est passée de 200 flacons sur une période de 18 ans (2000-2017) à 18 000 flacons en 2017-2018. Ces flambées ont été associées à la présence de poches de populations non vaccinées ou insuffisamment vaccinées, ce qui indique qu'une plus grande granularité des données de couverture est nécessaire pour permettre une mise en œuvre ciblée et rapide des mesures de prévention.

For immunization, the changing world also entails changes in available funding, including graduation by countries from GAVI support, and the polio transition. Fragile and polio priority countries account for a disproportionate share of the unvaccinated and under-vaccinated children. However, inadequate vaccination coverage is not only an issue for low-income countries. For example, in the European Region, middle-income countries without GAVI support have the highest proportions of unvaccinated children. Regarding new vaccines, more ambitious targets are now being defined for human papilloma virus vaccine as part of the WHO GPW 13 and sustainable development goal 3.7 and with the creation of a broad alliance aiming towards the long-term goal of elimination of cervical cancer. Building and strengthening vaccine delivery platforms across the life-course requires work but also offers further opportunities for preventing more diseases and creating more opportunities for catch-up vaccinations that were missed earlier and increase coverage, as well as providing opportunities for integration with other health services. Efforts are underway to align immunization work with emerging global health and development agendas. WHO will convene partners to develop the post-2020 immunization agenda in a manner that will put country level impact at the centre and align with WHO's strategic objectives.

Un monde en évolution implique également un changement des financements disponibles aux fins de la vaccination, notamment dans le cadre de l'affranchissement de certains pays du soutien de l'Alliance GAVI et de la transition pour la poliomyélite. Les pays fragiles et les pays prioritaires pour la poliomyélite représentent une part disproportionnée des enfants non vaccinés ou sous-vaccinés dans le monde. Cependant, une couverture vaccinale inadéquate est un problème qui ne se pose pas uniquement dans les pays à faible revenu. Par exemple, dans la Région européenne, les pays à revenu intermédiaire ne bénéficiant pas de l'aide de GAVI enregistrent la plus forte proportion d'enfants non vaccinés. Concernant les nouveaux vaccins, des cibles plus ambitieuses sont en cours de définition pour le vaccin contre le papillomavirus humain dans le cadre du 13e PGT de l'OMS et de l'objectif 3.7 de développement durable, avec la création d'une vaste alliance dont l'objectif à long terme est d'éliminer le cancer du col de l'utérus. La mise en place et le renforcement de plateformes assurant une distribution des vaccins tout au long de la vie représentent beaucoup de travail, mais offrent également de nouvelles opportunités, permettant de prévenir un nombre accru de maladies, de faciliter la vaccination de rattrapage en cas de doses omises, d'accroître la couverture vaccinale et de favoriser l'intégration de la vaccination avec d'autres services de santé. Des efforts sont en cours pour aligner les activités de vaccination sur les nouveaux programmes mondiaux de santé et de développement. L'OMS réunira divers partenaires afin d'élaborer le programme de vaccination de l'après-2020, qui devra donner une place centrale à l'impact de la vaccination dans les pays et s'aligner sur les objectifs stratégiques de l'OMS.

The WHO African Region (AFR) reported on progress towards the goals of the regional strategic plan. Two countries in the Region are currently transitioning from GAVI support which will require coordination of all stakeholders to ensure sustainability of immunization. Efforts to ensure additional funding with special attention to middle-income countries (MICs) that are not GAVI-eligible should be intensified. As the pace with which immunization improves in the Region does not match the pace of the demographic changes, including growth of the younger populations and increasing urbanization, more nuanced approaches to immunization are necessary. In April 2018, the implementation of the Eliminate Yellow Fever Epidemics (EYE) strategy was launched. The next regional meeting of the technical advisory group (TAG) will take place in June 2018.

La Région africaine de l'OMS a rendu compte des progrès accomplis vers la réalisation des objectifs du plan stratégique régional. Deux pays de la Région sont en voie de s'affranchir de l'aide de l'Alliance GAVI; cette transition exigera une coordination entre toutes les parties prenantes pour veiller à la pérennité de la vaccination. Des efforts accrus devront être déployés pour mobiliser des fonds supplémentaires, en accordant une attention particulière aux pays à revenu intermédiaire qui ne répondent pas aux critères fixés pour recevoir une aide de l'Alliance GAVI. Étant donné que la vaccination dans la Région ne progresse pas au même rythme que les changements démographiques, comme l'augmentation de la proportion de jeunes dans la population et l'urbanisation croissante, des approches plus nuancées de la vaccination s'imposent. En avril 2018, la stratégie d'élimination de la fièvre jaune (EYE) a été lancée. La prochaine réunion régionale du groupe consultatif technique aura lieu en juin 2018.

The WHO Region of the Americas (AMR) reported progress and challenges for their immunization programmes. Sustaining high levels of coverage in all districts is of major concern. The Region reported outbreaks of diphtheria, measles and yellow fever. Cases of measles in 11 countries were mainly imported cases. However, an important measles outbreak has been underway in Venezuela since 2017 and has led to cases in Brazil, Ecuador, and Colombia. Supplementary immunization activities (SIAs) are being carried out in Venezuela. A major yellow fever outbreak occurred in Brazil in areas hitherto unaffected by the virus, triggering a massive vaccination campaign. A special Regional TAG meeting took place in March 2018 to discuss the responses to the yellow fever and measles outbreaks. Special attention was given to the use of fractional yellow fever vaccine. Several vaccine communication campaigns are linked to the upcoming World Immunization Week and the 16th Vaccination Week of America.

La Région OMS des Amériques a rendu compte des progrès accomplis et des défis rencontrés par les programmes de vaccination. Le maintien d'une couverture vaccinale élevée dans tous les districts présente d'importantes difficultés. Des flambées de diphtérie, de rougeole et de fièvre jaune ont été notifiées dans la Région. Les cas de rougeole signalés dans 11 pays étaient principalement des cas importés. Toutefois, une importante flambée de rougeole sévit au Venezuela depuis 2017, entraînant des cas au Brésil, en Colombie et en Équateur. Des activités de vaccination supplémentaire (AVS) sont en cours au Venezuela. Une flambée de fièvre jaune de grande ampleur s'est produite au Brésil dans des zones jusqu'alors non touchées par le virus, conduisant à une campagne de vaccination de masse. Une réunion spéciale du groupe consultatif technique régional s'est tenue en mars 2018 pour examiner les activités de riposte aux flambées de fièvre jaune et de rougeole. Une attention particulière a été portée à l'administration de doses fractionnées du vaccin antiamaril. Plusieurs campagnes de communication sur les vaccins sont prévues en liaison avec la prochaine Semaine mondiale de la vaccination et la 16e Semaine de la vaccination dans les Amériques.

The WHO Eastern Mediterranean Region (EMR) is a highly heterogeneous Region. Regarding immunization, it includes many very well performing countries and others among the lowest performing in the world. Coverage >90% with 3 doses of diphtheria-tetanus-pertussis vaccine (DTP3) has been reported annually by 14 countries for many years. Countries that have not achieved the target for DTP3 coverage are mainly those suffering from ongoing humanitarian emergencies. The Region is moving forward with verification of measles and rubella elimination in the 7 countries that had measles incidence <1/million population in 2017. Somalia continues to have measles vaccination coverage <50% and repeatedly experiences major measles outbreaks.

La Région OMS de la Méditerranée orientale est une région très hétérogène. En matière de vaccination, de nombreux pays de la Région affichent de très bons résultats, tandis que d'autres comptent parmi les moins performants du monde. Depuis plusieurs années, 14 pays enregistrent chaque année une couverture >90% par 3 doses de vaccin antidiphtérique-antitétanique-anticoquelucheux (DTC3). Les pays n'ayant pas atteint la cible de couverture par le DTC3 sont principalement ceux qui sont confrontés à des situations d'urgence humanitaire. La Région poursuit ses activités de vérification de l'élimination de la rougeole et de la rubéole dans les 7 pays où l'incidence de la rougeole était <1 cas/million d'habitants en 2017. En Somalie, la couverture de la vaccination antirougeoleuse demeure <50% et des flambées majeures de rougeole se déclarent régulièrement.

The WHO European Region (EUR) will present a full progress report at the October 2018 SAGE meeting, when the European Vaccine Action Plan mid-term review will have been completed. The large majority of the under-vaccinated individuals in the Region are living in MICs that are not eligible for GAVI support. In February 2018, 11 health ministers of non-GAVI eligible MICs met and committed to the development of a road map on immunization. France and Italy have recently implemented mandatory vaccination, and a dialogue is needed on the impact of such strategies. A European Commission Joint Action on Vaccination (which is complementary to the regional action plan) will be launched this year. The Region requested SAGE to maintain the momentum and interest in promoting dialogue on vaccine demand, hesitancy, and acceptance.

La Région européenne de l'OMS présentera un rapport de situation complet lors de la réunion du SAGE d'octobre 2018, une fois que l'examen à mi-parcours du Plan d'action européen pour les vaccins sera achevé. La grande majorité des personnes insuffisamment vaccinées de la Région vivent dans des pays à revenu intermédiaire (PRI) ne pouvant prétendre au soutien de l'Alliance GAVI. En février 2018, 11 ministres de la santé de PRI non éligibles à l'aide de GAVI se sont réunis et se sont engagés à élaborer une feuille de route sur la vaccination. La France et l'Italie ont récemment mis en œuvre de nouvelles obligations vaccinales et un dialogue doit être engagé sur l'impact de ces stratégies. La Commission européenne lancera cette année une action commune sur la vaccination (qui s'inscrira en complément du plan d'action régional). La Région a demandé au SAGE de préserver l'élan et l'intérêt qui se manifestent actuellement en faveur de l'instauration d'un dialogue sur la demande, l'acceptation et la réticence à l'égard des vaccins.

The WHO South-East Asia Region (SEAR) reported that the Region has maintained its polio-free status for more than 7 years and has had no circulating vaccine-derived poliovirus (cVDPV) outbreaks since December 2015. Bangladesh, India and Sri Lanka are using fractional IPV in routine immunization services, and Nepal is planning to do so. To mitigate the programmatic and

La Région OMS de l'Asie du Sud-Est a indiqué qu'elle était parvenue à maintenir son statut de région exempte de poliomyélite depuis plus de 7 ans et qu'elle n'avait connu aucune flambée due à des poliovirus circulants dérivés d'une souche vaccinale (PVDVc) depuis décembre 2015. Le Bangladesh, l'Inde et le Sri Lanka administrent des doses fractionnées de VPI dans le cadre de la vaccination systématique, et le Népal prévoit de

financial risks associated with polio transition, the Region is finalizing polio transition plans and exploring alternative sources of funding. Measles elimination and rubella/congenital rubella syndrome control is a flagship programme of the Region. Bhutan and Maldives have been verified as having eliminated measles in 2016. Efforts to close immunity gaps for measles and rubella continue by strengthening routine immunization services and conducting supplementary immunization activities (SIAs) using measles-rubella vaccine. Nearly 113 million children in the Region have received measles-rubella vaccine since January 2017, with plans to vaccinate an additional 364 million in the next year. The Region has applied innovative approaches to strengthen routine immunization services and to improve equity in vaccination coverage. Most notable has been the effort in India to improve immunization coverage in the lowest performing 190 districts of the country, with vaccination of 5.3 million children and 1.7 million pregnant women between September 2017 and January 2018. Close to 12.5 million individuals in Myanmar were vaccinated against Japanese encephalitis during the 4th quarter of 2017. Following the sudden influx of migrants from Myanmar into Cox's Bazar (Bangladesh) in late 2017, a swift immunization response was mounted in the area, with 7 vaccination campaigns conducted between September 2017 and March 2018. Several vaccines were used during each of the campaigns and 3.5 million doses of vaccines were administered, averting potential measles and cholera outbreaks and controlling the diphtheria outbreak. Routine immunization services and surveillance for vaccine-preventable diseases have been established for both migrant and local populations in Cox's Bazar.

The WHO Western Pacific Region (WPR) reported further progress towards measles and rubella elimination. After recording historically low measles incidence in 2012, a region-wide resurgence of measles was experienced between 2013 and 2016. The new Regional Strategy and Plan of Action for Measles and Rubella Elimination was endorsed by the Regional Committee in October 2017. Several countries are developing or updating their national plans of action for measles and rubella elimination in alignment with this strategy and plan. The regional measles incidence reached its lowest recorded level in 2017. Lao PDR successfully stopped a massive polio outbreak due to cVDPV type 1 by means of intensive mass vaccination campaigns from 2015 to 2017. The Region has successfully maintained its polio-free status since this was declared in 2000. The Philippines achieved maternal and neonatal tetanus elimination (MNTE) in 2017. Only one country in the Region has yet to achieve MNTE elimination by 2020. The Region is using disease elimination initiatives to strengthen immunization and health systems and to enhance immunization service delivery. In 2016, the Region as a whole achieved DTP3 coverage of 97% and 22 countries and areas reached the GVAP goal of >90% coverage. A formal process for development of the vision and strategy for the next decade will start with the next Regional TAG meeting in June 2018.

faire de même. Afin de limiter les risques programmatiques et financiers associés à la transition pour la poliomyélite, la Région met actuellement la dernière main aux plans de transition et explore d'autres sources de financement. L'élimination de la rougeole et la lutte contre la rubéole et le syndrome de rubéole congénitale constituent un programme phare pour la Région. L'élimination de la rougeole a été vérifiée au Bhoutan et aux Maldives en 2016. Des efforts continuent d'être déployés pour combler les déficits de l'immunité antirougeoleuse et antirubéoleuse en renforçant les services de vaccination systématique et en menant des activités de vaccination suplémentaire (AVS) avec le vaccin antirougeoleux-antirubéoleux. Près de 113 millions d'enfants de la Région ont été vaccinés contre la rougeole et la rubéole depuis janvier 2017, et il est prévu d'en vacciner 364 millions de plus l'année prochaine. La Région a adopté des approches innovantes pour renforcer les services de vaccination systématique et rendre la couverture vaccinale plus équitable. L'initiative le plus notable est celle qui a été menée en Inde en vue d'améliorer la couverture vaccinale dans les 190 districts les moins performants du pays, menant à la vaccination de 5,3 millions d'enfants et de 1,7 million de femmes enceintes entre septembre 2017 et janvier 2018. Au Myanmar, près de 12,5 millions de personnes ont été vaccinées contre l'encéphalite japonaise au cours du 4e trimestre 2017. À Cox's Bazar (Bangladesh), l'afflux soudain de migrants venus du Myanmar à la fin 2017 a donné lieu à une intervention vaccinale rapide, avec 7 campagnes de vaccination menées entre septembre 2017 et mars 2018. Plusieurs vaccins ont été utilisés dans chacune de ces campagnes et 3,5 millions de doses de vaccins ont été administrés, ce qui a permis de prévenir d'éventuelles flambées de rougeole et de choléra et de juguler la flambée de diphtérie. Des services de vaccination systématique et de surveillance des maladies évitables par la vaccination ont été mis en place pour les populations migrantes et locales de Cox's Bazar.

La Région OMS du Pacifique occidental a fait état de nouveaux progrès sur la voie de l'élimination de la rougeole et de la rubéole. Alors que la Région avait enregistré un niveau historiquement faible d'incidence rougeoleuse en 2012, une importante résurgence de la rougeole a été observée entre 2013 et 2016. En Octobre 2017, le Comité régional a approuvé une nouvelle stratégie et un nouveau plan d'action régional pour l'élimination de la rougeole et de la rubéole. Plusieurs pays ont entrepris d'élaborer ou de mettre à jour leurs plans d'action nationaux pour l'élimination de la rougeole et de la rubéole, conformément à cette stratégie et à ce plan régional. L'incidence régionale de la rougeole a atteint son niveau le plus bas en 2017. La République démocratique populaire lao est parvenue à endiguer une flambée massive de poliomyélite due à des PVDVc de type 1 grâce à d'intensives campagnes de vaccination de masse menées entre 2015 et 2017. Depuis que la Région a été déclarée exempte de poliomyélite en 2000, elle a réussi à maintenir ce statut. Les Philippines ont éliminé le tétanos maternel et néonatal (TMN) en 2017. Seul un pays de la Région doit encore parvenir à l'élimination du TMN d'ici à 2020. La Région s'appuie sur les initiatives d'élimination des maladies pour renforcer les systèmes de vaccination et de santé et améliorer la prestation des services de vaccination. En 2016, la couverture régionale globale par le DTC3 était de 97% et 22 pays et zones de la Région avaient atteint l'objectif du GVAP visant une couverture >90%. Le processus d'élaboration de la vision et de la stratégie pour la prochaine décennie débutera officiellement à l'occasion de la prochaine réunion du groupe consultatif technique régional en juin 2018.

Report from GAVI, the Vaccine Alliance

SAGE plays an important role in providing GAVI with policy and technical guidance and SAGE members are involved in the decision-making processes of GAVI – including in the Programme and Policy Committee, the 2018 Vaccine Investment Strategy and the Vaccine Innovation Prioritization Strategy.

With more countries transitioning from GAVI support, in November 2017 the GAVI Board approved continued GAVI engagement with transitioned countries and targeted support under its Partners' Engagement Framework. The Board also approved extension of the grace period for applying for new vaccine introductions from 1 year to 5 years during the accelerated transition phase. A Board decision is pending in relation to the transitioning of Nigeria from GAVI support.

Several questions with significant implications for GAVI funding were posed to SAGE: How can coverage and equity be improved in non-fragile countries and what additional approaches are needed for fragile countries? What further specific guidance to countries on measles control strategies could be provided? How might yellow fever vaccination through routine immunization be strengthened to achieve vaccination coverage that would prevent epidemics? How much Ebola vaccine is required for stockpiling and for preventive use?

Development of the GAVI Vaccine Investment Strategy is ongoing; the prioritization methodology was defined recently and vaccine investment portfolio shortlist options were developed. The options include hepatitis B vaccine birth dose, preventive cholera vaccination, multivalent meningococcal vaccine, diphtheria-tetanus-pertussis booster doses, respiratory syncytial virus vaccine development, and rabies post-exposure prophylaxis.

GAVI is also assessing vaccine investments for epidemic preparedness and response and strategic support to pandemic influenza preparedness. As part of the reflection on the new 5-year strategy, GAVI is considering 4 trajectories: the further reduction of under-5 mortality, contributions to global health security, possible engagement to reach unreached populations in MICs, and better use of immunization platforms to advance other health interventions. GAVI is also moving forward in: defining its vaccine innovation prioritization strategy (VIPS); possible new investment in strengthening yellow fever surveillance and laboratory capacity; calls for tried and tested innovations that have the potential to improve vaccine delivery as part of the Innovation for Uptake, Scale and Equity in immunization initiative (INFUSE); and the timeline of its mid-term review and its funding replenishment for 2021–2025.

Rapport de l'Alliance GAVI

Les orientations politiques et techniques du SAGE constituent une contribution importante pour l'Alliance GAVI. Les membres du SAGE participent en outre au processus de prise de décision de l'Alliance – notamment dans le cadre du Comité des programmes et des politiques, de la Stratégie d'investissement en faveur de la vaccination pour 2018 et de la Stratégie d'établissement des priorités en matière d'innovation vaccinale.

En novembre 2017, alors que les pays en voie de s'affranchir de l'aide de l'Alliance GAVI étaient de plus en plus nombreux, le Conseil d'administration s'est dit favorable à ce que l'Alliance continue de travailler en étroite collaboration avec les pays ayant opéré cette transition et qu'elle leur apporte un soutien ciblé au titre de son Cadre d'engagement avec les partenaires. Le Conseil d'administration a également accepté que la période de grâce pour les demandes relatives à l'introduction de nouveaux vaccins soit prolongée, passant de 1 an à 5 ans, pendant la phase de transition accélérée. Le Conseil n'a pas encore rendu sa décision concernant la transition du Nigéria et son affranchissement de l'aide de l'Alliance.

Plusieurs questions présentant d'importantes ramifications pour le financement de l'Alliance ont été posées au SAGE: Comment améliorer la couverture et l'équité dans les pays non fragiles et quelles actions supplémentaires sont nécessaires dans les pays fragiles? Quelles autres orientations spécifiques pourraient être fournies aux pays concernant les stratégies de lutte contre la rougeole? Comment renforcer la vaccination contre la fièvre jaune dans le cadre de la vaccination systématique afin d'obtenir une couverture vaccinale suffisante pour prévenir les épidémies? Quelle quantité de vaccin anti-Ebola est nécessaire pour constituer des stocks de réserve et répondre aux besoins de prévention?

La Stratégie d'investissement de l'Alliance GAVI en faveur de la vaccination est en cours d'élaboration; la méthode d'établissement des priorités a été définie récemment, ainsi que la liste de présélection des options vaccinales pour le portefeuille d'investissement. Parmi ces options figurent la dose à la naissance du vaccin anti-hépatite B, la vaccination préventive contre le choléra, le vaccin antiméningococcique multivalent, les doses de rappel de vaccin antidiphtérique-antitétanique-anticoquelucheux, la mise au point d'un vaccin contre le virus respiratoire syncytial et la prophylaxie antirabique postexposition.

L'Alliance GAVI évalue également les investissements à consentir pour les vaccins destinés aux activités de préparation et de riposte aux épidémies, ainsi qu'au soutien stratégique à des fins de préparation à la grippe pandémique. Dans le cadre de sa nouvelle stratégie quinquennale, l'Alliance mène une réflexion autour de 4 grands axes: continuer de réduire la mortalité chez les enfants de moins de 5 ans, contribuer à la sécurité sanitaire mondiale, étudier les possibilités de coopération pour atteindre les populations non vaccinées dans les pays à revenu intermédiaire, et mieux exploiter les plateformes de vaccination pour faire progresser d'autres interventions de santé. L'Alliance avance également dans les domaines suivants: définition de la stratégie d'établissement des priorités en matière d'innovation vaccinale; nouveaux investissements possibles pour renforcer la surveillance de la fièvre jaune et les moyens de laboratoire; appels à propositions pour des innovations éprouvées susceptibles d'améliorer la distribution des vaccins dans le cadre de l'initiative INFUSE (Innovation for Uptake, Scale and Equity in Immunization); et calendrier de l'examen à mi-parcours et de la reconstitution des ressources pour 2021-2025.

Malaria Vaccine Implementation Programme

SAGE was provided with an overview of the Malaria Vaccine Implementation Programme (MVIP) and an update on the status of preparatory activities in the 3 countries (Ghana, Kenya and Malawi) where the MVIP pilot studies will be conducted. These studies are planned in response to the recommendations made by SAGE and the Malaria Policy Advisory Committee (MPAC) in October 2015, on the need to have further clinical information on the safety and implementation of the RTS,S/AS01 malaria vaccine before SAGE could make a recommendation about its general use by countries. The programme, which is financed jointly by GAVI, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and UNITAID, has 3 components: (i) subnational introduction of the malaria vaccine, in areas with moderate to high malaria transmission, led by country immunization programmes; (ii) rigorous evaluation, supported by country-based research institutions, to measure the programmatic feasibility of delivering RTS,S/AS01, the vaccine's impact on mortality (overall and sex-specific), and the vaccine's safety in the context of routine immunization, with emphasis on meningitis and cerebral malaria; and (iii) manufacturer-led observational Phase 4 studies with hospital and active surveillance as part of the Risk Management Plan agreed between the manufacturer and the European Medicines Agency, to be conducted in a small sub-set of the pilot areas.

SAGE noted the relatively low coverage levels of the second dose of measles vaccine provided to children aged 15–18 months in MVIP countries which could indicate challenges in fully vaccinating children with 4 doses of RTS,S/AS01. SAGE was reassured that uptake of the RTS,S/A01 vaccine, as well as use of other vaccines and other childhood health interventions, will be monitored through countries' routine data monitoring systems. Three consecutive cross-sectional household surveys will provide representative community estimates of RTS,S/AS01 coverage, along with coverage estimates for other vaccines, for recommended malaria prevention and control measures, and for other childhood health interventions of interest. In addition, a qualitative research study will explore and document any changes in health-seeking behaviour that may occur following RTS,S/AS01 introduction. Findings will be shared with immunization and malaria programmes to inform development of additional measures or corrective actions as needed. SAGE re-emphasized the importance of communication and community engagement to ensure acceptance and understanding of the new vaccine in the context of other malaria control interventions. Experience from other efforts related to strengthening the second year of life (2YL) platform could prove useful.

While the implementation follows standard practice, the pilot evaluations will rely on experienced researchers and enhanced surveillance systems to capture key outcome measures. SAGE was reassured that the evalu-

Programme de mise en œuvre de la vaccination antipaludique

Un aperçu du programme de mise en œuvre de la vaccination antipaludique (MVIP) a été présenté au SAGE, ainsi que des informations sur l'avancement des activités de préparation dans les 3 pays où seront menées des études pilotes de ce programme (Ghana, Kenya et Malawi). La réalisation de ces études fait suite aux recommandations formulées en octobre 2015 par le SAGE et le Comité de pilotage de la politique de lutte antipaludique (MPAC), faisant état de la nécessité de recueillir des informations cliniques supplémentaires sur la sécurité et l'introduction du vaccin antipaludique RTS,S/AS01 avant que le SAGE puisse émettre une recommandation sur son utilisation générale dans les pays. Ce programme, financé conjointement par l'Alliance GAVI, le Fonds mondial de lutte contre le sida, la tuberculose et le paludisme et UNITAID, comporte 3 volets: i) introduction infranationale du vaccin antipaludique dans les zones où la transmission palustre est modérée à élevée, sous la direction des programmes nationaux de vaccination; ii) évaluation rigoureuse, avec l'appui d'institutions de recherche nationales, pour mesurer la faisabilité programmatique de la distribution du RTS,S/AS01, l'impact du vaccin sur la mortalité (globale et par sexe) et l'innocuité du vaccin dans le contexte de la vaccination systématique, en accordant une attention particulière à la méningite et au neuropaludisme; et iii) études d'observation de phase 4 sous la direction du fabricant, avec une surveillance active et en milieu hospitalier dans le cadre du plan de gestion des risques convenu entre le fabricant et l'Agence européenne des médicaments, à réaliser dans un sous-ensemble restreint de zones pilotes.

Le SAGE a constaté que les taux de couverture par la deuxième dose de vaccin antirougeoleux, administrée aux enfants âgés de 15 à 18 mois, étaient relativement faibles dans les pays de mise en œuvre du programme MVIP, signe qu'il pourrait être difficile d'assurer la vaccination complète des enfants par 4 doses de RTS,S/AS01. Le SAGE a été rassuré sur le fait que l'adoption du vaccin RTS,S/AS01, ainsi que le recours à d'autres vaccins et d'autres interventions de santé de l'enfant, feront l'objet d'un suivi à l'aide des systèmes de surveillance des données de routine des pays; 3 enquêtes transversales consécutives auprès des ménages fourniront des estimations représentatives de la couverture communautaire du RTS,S/AS01 et d'autres vaccins, permettant de définir les mesures recommandées de prévention et de lutte contre le paludisme, ainsi que d'autres interventions relatives à la santé de l'enfant. En outre, une étude qualitative sera réalisée pour analyser et documenter l'évolution éventuelle des comportements de recours aux soins après l'introduction du RTS,S/AS01. Les résultats seront communiqués aux programmes de vaccination et de lutte antipaludique afin de guider l'élaboration de mesures supplémentaires ou d'actions correctives si nécessaire. Le SAGE a réitéré l'importance que revêtent la communication et la mobilisation communautaire, intégrées à d'autres interventions de lutte antipaludique, pour faire en sorte que la communauté accepte le nouveau vaccin et en comprenne l'utilité. L'expérience acquise dans le cadre d'autres initiatives impliquant un renforcement de la plateforme de vaccination lors de la deuxième année de vie pourrait s'avérer utile.

L'introduction du vaccin se déroulera selon la pratique courante, mais les évaluations pilotes s'appuieront sur la participation de chercheurs expérimentés et sur des systèmes de surveillance améliorés pour mesurer les résultats au regard des principaux

ation has been sufficiently powered to assess whether the safety signals (i.e. meningitis and cerebral malaria) and the imbalance in mortality between males and females identified during the Phase 3 trial are causally related to RTS,S/AS01 vaccination.

SAGE agreed on the importance of having a framework to clarify how data collected through the MVIP might be used to answer identified questions and inform future policy recommendations for vaccine use beyond the pilot introduction. Deliberation on the framework with SAGE and MPAC will provide an opportunity to align views and expectations on requirements for a policy recommendation at the end of the pilots, or prior to that should emerging findings meet certain criteria. SAGE specifically recommended that the modelling inputs incorporate different scenarios and levels of uncertainty to enable interpretation of the MVIP results in the context of real-world settings.

SAGE recommended further development of the framework, with due consideration of the evidence-to-decision framework that is applied in WHO's vaccine recommendation process. Nominated SAGE representatives will serve on a joint working group together with MPAC and MVIP Advisory Group members. Further updates and steps are to be discussed in follow-up calls with SAGE.

Polio eradication

SAGE acknowledged the ongoing efforts of the Global Polio Eradication Initiative (GPEI) and the progress achieved towards wild polio virus (WPV) eradication.

In 2017, 22 WPV1 cases were reported (14 in Afghanistan, 8 in Pakistan), compared to 37 in 2016. In 2018, as of 17 April, 7 WPV1 cases were reported from Afghanistan and 1 from Pakistan.

In 2017, 98 cVDPV type 2 cases were reported (22 in the Democratic Republic of the Congo (DRC), 74 in the Syrian Arab Republic, and 2 in Somalia). In 2018, as of 17 April, 3 cVDPV type 2 cases have been detected in DRC, 3 from Somalia, and 1 from Kenya.

SAGE shared concern over continuing WPV circulation in Afghanistan and Pakistan through the active corridors of transmission, as evidenced by the continued detection of WPV1 in environmental samples during 2016 and 2017.

SAGE noted that the supply of inactivated poliovirus vaccine (IPV) is sufficient to introduce IPV in routine immunization globally in 2018, but not to conduct catch-up campaigns for cohorts that did not receive IPV because of supply constraints. SAGE reviewed the available data on fractional IPV (fIPV) and emphasized that 2 doses of fIPV are superior to 1 full IPV dose. SAGE agreed that IPV should not be used routinely in outbreak response; however in specific situations such as where there is co-circulation of WPV1 and cVDPV2, fIPV should be used. SAGE recommended that instead

critères. Le SAGE a reçu l'assurance que la puissance de l'évaluation sera suffisante pour déterminer si les signaux de sécurité (méningite et neuropaludisme) et l'écart de mortalité entre les sujets masculins et féminins observés au cours de l'essai de phase 3 présentent un lien de causalité avec la vaccination RTS,S/AS01.

Le SAGE a convenu qu'il était important de disposer d'un cadre précisant comment les données recueillies dans le programme MVIP pourraient être utilisées pour répondre aux questions identifiées et guider les futures recommandations politiques sur l'utilisation du vaccin au-delà de la phase pilote d'introduction. Les délibérations du SAGE et du MPAC concernant ce cadre seront l'occasion d'harmoniser les positions et les attentes quant aux exigences à satisfaire pour qu'une recommandation politique soit formulée une fois les projets pilotes terminés, ou plus tôt si les résultats obtenus répondent à certains critères. Le SAGE a expressément recommandé que les données d'entrée utilisées dans la modélisation couvrent différents scénarios et niveaux d'incertitude pour permettre l'interprétation des résultats du programme MVIP dans des situations réelles.

Le SAGE a préconisé de poursuivre le développement de ce cadre en tenant dûment compte du cadre «Evidence to Decision» (passage des preuves à la décision) qui est appliqué par l'OMS pour élaborer les recommandations relatives aux vaccins. Des représentants désignés du SAGE siègeront dans un groupe de travail conjoint avec des membres du MPAC et du Groupe consultatif sur le programme MVIP. Un suivi téléphonique sera assuré avec le SAGE pour faire le point de la situation et discuter des prochaines étapes.

Éradication de la poliomyélite

Le SAGE a salué les efforts déployés par l'Initiative mondiale pour l'éradication de la poliomyélite (IMEP) et les progrès réalisés vers l'éradication des poliovirus sauvage (PVS).

En 2017, 22 cas de poliomyélite dus aux PVS1 ont été notifiés (14 en Afghanistan et 8 au Pakistan), contre 37 cas en 2016. Pour 2018, les données disponibles au 17 avril font état de 7 cas de PVS1 en Afghanistan et 1 au Pakistan.

En 2017, 98 cas dus aux PVDVc de type 2 ont été signalés (74 en République arabe syrienne, 22 en République démocratique du Congo (RDC) et 2 en Somalie). Pour 2018, les cas de PVDVc de type 2 notifiés au 17 avril étaient au nombre de 1 au Kenya, 3 en RDC et 3 en Somalie.

Le SAGE s'est dit préoccupé par la circulation persistante des PVS en Afghanistan et au Pakistan le long de corridors actifs de transmission, comme en témoigne le fait que le PVS1 a continué d'être détecté dans des échantillons environnementaux en 2016 et 2017.

Le SAGE a noté que l'approvisionnement en vaccin antipoliomyélitique inactivé (VPI) est suffisant pour introduire le VPI dans les programmes de vaccination systématique à l'échelle mondiale en 2018, mais pas pour mener des campagnes de rattrapage parmi les cohortes n'ayant pas reçu le VPI suite aux difficultés d'approvisionnement rencontrées. Le SAGE a examiné les données disponibles concernant l'utilisation de doses fractionnées du VPI (VPIf) et a souligné que l'administration de 2 doses fractionnées donne de meilleurs résultats qu'une dose complète unique de VPI. Le SAGE a convenu que le VPI ne doit pas être systématiquement utilisé à titre de riposte aux flam-

of the term "fractional", another term such as "intradermal" might be considered to avoid any impression that fIPV is sub-standard. Studies to examine duration of immunity and protection following 2 doses of fIPV are in progress.

SAGE reviewed the post-certification strategy (PCS) for polio. This is a high-level working document which aims to guide Member States and stakeholders on the polio-essential functions required to sustain a polio-free world after WPV eradication and dissolution of the GPEI. The PCS does not provide specific or detailed country level guidance. Its aim is to serve as a roadmap to ensure that the oversight, infrastructure, and funding are in place to (i) contain polioviruses, (ii) protect populations from polio, and (iii) retain capacity to detect and respond to any poliovirus event. SAGE endorsed the content and approach of the PCS which will be submitted for consideration at the World Health Assembly (WHA) in May 2018.

In order to align the Global Action Plan (GAP) III and SAGE recommendations on IPV immunization schedules, SAGE reviewed recommendations on IPV schedules in countries with poliovirus-essential facilities (PEFs). Currently 29 countries plan to host 92 PEFs. While the majority of countries proposing to host PEFs are located in Europe and North America and have introduced exclusive or sequential IPV schedules, some of the PEF hosting countries are currently using only a single dose of IPV, together with bivalent oral poliovirus vaccine (bOPV), in their immunization schedules.

SAGE endorsed the proposal to align the recommendations of the future IPV schedule for countries hosting PEFs or storing or manipulating WPVs and/or Sabin/OPV. SAGE recommended that those countries with PEFs and using a single dose of IPV should adjust their IPV schedule, coverage targets and geographical scope as soon as possible and no later than at the time of all OPV cessation, as follows:

1. Implement a routine immunization schedule with a minimum of 2 IPV doses (full or fractional, stand-alone or in combination vaccines), with the first dose administered at 4 months and second dose at an interval of at least 4 months after the first dose.
2. Maintain high population immunity with ≥90% of IPV2 coverage in infants in the area surrounding the PEF defined as within a 100 km commutable distance from the PEF. Maintain the GVAP target coverage (90% national coverage and 80% in every district or equivalent administrative unit with all vaccines in national programmes, unless otherwise

bées; toutefois, dans des situations particulières, notamment en présence d'une cocirculation de PVS1 et de PVDVc2, l'administration de VPIf est recommandée. Le SAGE a recommandé d'envisager de remplacer le terme «fractionné» par un autre terme, comme «intradermique», pour éviter de donner l'impression que le VPIf est de qualité inférieure. Des études sont en cours pour évaluer la durée de l'immunité et de la protection conférées par 2 doses de VPIf.

Le SAGE a examiné la stratégie postcertification pour la poliomyélite. Ce document de travail de haut niveau vise à fournir aux États Membres et partenaires des orientations sur les fonctions essentielles nécessaires au maintien d'un monde exempt de poliomyélite après l'éradication des PVS et la dissolution de l'IMEP. La stratégie postcertification ne fournit pas de conseils détaillés ou spécifiquement applicables au niveau national. Son ambition est de servir de feuille de route pour veiller à la mise en place des fonctions de surveillance, des infrastructures et des financements requis pour i) confiner les poliovirus, ii) protéger les populations contre la poliomyélite et iii) conserver la capacité de détecter tout événement lié aux poliovirus et d'y répondre. Le SAGE a approuvé le contenu et l'approche de la stratégie postcertification, qui sera soumise pour examen à l'Assemblée mondiale de la santé en mai 2018.

Afin de veiller à la concordance des calendriers d'administration du VPI recommandés par le Plan d'action mondial (GAP III) et par le SAGE, le SAGE a examiné les recommandations relatives aux calendriers de vaccination par le VPI dans les pays où se trouvent des établissements autorisés à détenir des stocks essentiels de poliovirus («établissements essentiels»). Actuellement, 29 pays prévoient d'héberger 92 établissements essentiels. La majorité des pays qui proposent d'accueillir des établissements essentiels sont situés en Europe et en Amérique du Nord et ont instauré des calendriers de vaccination exclusive ou séquentielle par le VPI, mais certains des pays hébergeant des établissements essentiels n'incluent actuellement qu'une seule dose de VPI, administrée en même temps que le vaccin antipoliomyélitique oral bivalent (VPOb), dans leur calendrier vaccinal.

Le SAGE a souscrit à la proposition d'harmoniser les recommandations concernant les futurs calendriers de vaccination par le VPI dans les pays qui hébergeront des établissements essentiels ou dans lesquels des PVS et/ou des souches Sabin/VPO seront stockés ou manipulés. Le SAGE recommande aux pays qui abritent des établissements essentiels mais qui n'utilisent qu'une seule dose de VPI de modifier dès que possible, et au plus tard lors de l'arrêt du VPO, leur calendrier d'administration du VPI, les cibles fixées pour la couverture vaccinale et la portée géographique de la vaccination, en procédant comme suit:

1. Adopter un calendrier de vaccination systématique qui comporte au moins 2 doses de VPI (doses complètes ou fractionnées, VPI seul ou vaccin combiné), la première dose étant administrée à l'âge de 4 mois et la seconde dose au moins 4 mois après la première.
2. Maintenir une forte immunité de la population en assurant une couverture ≥90% par le VPI2 chez les nourrissons dans les zones entourant les établissements essentiels, c'est-à-dire dans un rayon praticable de 100 km autour de ces derniers. Au-delà de la zone immédiate de 100 km autour des établissements essentiels, maintenir une couverture conforme aux cibles du GVAP (90% à l'échelle natio-

recommended) beyond the immediate zone of 100 km from the PEF.

3. Have an outbreak plan specifying response to containment breach and conduct outbreak simulation exercises.

SAGE expressed concern about the risks that the large number of PEFs represents. In this context, SAGE requested the programme to explore the extent to which a legal instrument such as the International Health Regulations (IHR) could be used to ensure compliance with poliovirus containment requirements defined in the GAP III and the Containment Certification Scheme.

SAGE endorsed the Containment Management Group proposal to assign a risk score to each PEF, categorizing relative risk to polio eradication.

SAGE noted and agreed with the recommendations made by the SAGE Polio Working Group (WG) regarding revisions of the Polio Outbreak Response Protocol Standard Operating Procedures.

SAGE noted recent discussions held among the chairs of various advisory bodies to the Polio Eradication programme (Global Certification Commission [GCC], IHR-Emergency Committee, SAGE, SAGE Polio WG, Containment Advisory Group, Independent Monitoring Board, and GCC's Containment WG) on the timing of certification of polio eradication in relation to the epidemiology of cVDPVs. SAGE agreed that an Options Appraisal document, outlining the pros and cons of different requirements for certification, should be developed and presented at a future SAGE meeting.

Policy recommendations on the use of the first licensed dengue vaccine

Dengue is a rapidly spreading mosquito-borne virus infection. The first dengue vaccine, CYD-TDV (Dengvaxia®) has been licensed in 20 countries. The key findings from 2 large Phase 3 trials involving over 30 000 participants aged 2–16 years indicated:

- Vaccine efficacy against virologically confirmed dengue, over a 25-month period from the first dose of a 3-dose immunization regimen in the 9–16 year age group was 65.6%, and in this group, vaccination reduced severe dengue by 93% and dengue hospitalizations by 82%.
- An increased risk of hospitalized dengue was seen in the 2–5 year age group in year 3 of follow-up.
- At the time of the April 2016 SAGE meeting, this increased risk was not observed in those aged 9 years and older.

The manufacturer had sought and obtained licensure as of 2015 with an indication of 9 years and older based on the above data and the absence of an

nale et 80% dans chaque district ou unité administrative équivalente pour tous les vaccins prévus dans les programmes nationaux, sauf recommandation contraire).

3. Établir un plan de riposte aux flambées précisant la marche à suivre en cas de défaillance du confinement et effectuer des exercices de simulation de flambées.

Le SAGE a exprimé son inquiétude face aux risques posés par le grand nombre d'établissements essentiels. À cet égard, le SAGE a demandé au programme d'étudier dans quelle mesure un instrument juridique comme le Règlement sanitaire international (RSI) pourrait être utilisé pour garantir le respect des prescriptions relatives au confinement des poliovirus qui ont été définies dans le GAP III et dans le dispositif de certification du confinement.

Le SAGE a approuvé la proposition du Groupe de gestion du confinement visant à attribuer une cote de risque à chaque établissement essentiel, en catégorisant les risques relatifs pour l'éradication de la poliomyélite.

Le SAGE a pris acte des recommandations formulées par le Groupe de travail du SAGE sur la poliomyélite concernant la révision des modes opératoires normalisés du protocole de riposte aux flambées de poliomyélite et les a approuvées.

Le SAGE a pris note des récentes discussions entre les présidents de divers organes consultatifs du programme d'éradication de la poliomyélite (Commission mondiale de certification [GCC], Comité d'urgence du RSI, SAGE, Groupe de travail du SAGE sur la poliomyélite, Groupe consultatif sur le confinement, Comité de suivi indépendant et Groupe de travail sur le confinement du GCC) concernant le moment opportun pour certifier l'éradication de la poliomyélite en fonction de l'épidémiologie des PVDVc. Le SAGE a convenu qu'un document d'évaluation des options, décrivant les avantages et les inconvénients des différentes exigences en matière de certification, devrait être élaboré et présenté lors d'une prochaine réunion du SAGE.

Recommandations politiques sur l'utilisation du premier vaccin homologué contre la dengue

La dengue est une infection virale transmise par les moustiques dont la propagation est très rapide. Le premier vaccin contre la dengue, le CYD-TDV (Dengvaxia®), est homologué dans 20 pays. Les principaux résultats de 2 grands essais de phase 3 menés auprès de plus de 30 000 sujets âgés de 2 à 16 ans ont indiqué que:

- L'efficacité du vaccin contre la dengue virologiquement confirmée était de 65,6% sur une période de 25 mois à partir de la première dose d'un schéma d'administration à 3 doses chez les sujets âgés de 9 à 16 ans; dans cette tranche d'âge, la vaccination entraînait une réduction de 93% des cas de dengue sévère et de 82% des hospitalisations dues à la dengue.
- Il a été constaté que les enfants de 2 à 5 ans présentaient un risque accru d'hospitalisation pour dengue lors de la 3e année de suivi.
- Au moment de la réunion du SAGE d'avril 2016, ce risque accru n'était pas observé chez les sujets âgés de 9 ans et plus.

En 2015, sur la base des données présentées ci-dessus et étant donné qu'aucun risque accru d'hospitalisation n'avait été mis en évidence chez les enfants d'un âge plus avancé, le fabricant

observed increased risk of hospitalized dengue in older children.

WHO issued its position on the use of CYD-TDV in July 2016 based on recommendations provided by SAGE in April 2016, informed by clinical trial data and mathematical modelling which suggested that the public health benefits of vaccination could be maximized if dengue seropositivity was high in the age group targeted for vaccination. The position paper stated that (i) countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings where epidemiological data indicate a high burden of disease, (ii) dengue seroprevalence should be approximately 70% or greater in order to maximize public health impact and (iii) the vaccine was not recommended when seroprevalence was below 50% in the age group targeted for vaccination. While no safety signal was evident at that time, SAGE noted the limited safety data in seronegative populations and recommended that safety studies should be conducted to monitor the occurrence over time of severe dengue illness in vaccinated persons, particularly among vaccinated seronegative persons.

On 29 November 2017, Sanofi Pasteur announced the results of additional studies to better describe the benefit-risk in seronegative individuals. This was made possible through the use of a newly developed NS1-based antibody assay, which distinguishes between antibody responses to the dengue virus and the vaccine. The test was applied to blood samples taken 13 months after vaccination to retrospectively infer dengue serostatus at the time of first vaccination.

The new analyses from the long-term safety follow-up of clinical trial participants indicated that:

- Overall population-level benefit of vaccination remains favourable, but the vaccine performs differently in seropositive and seronegative individuals.
- Vaccine efficacy against virologically confirmed symptomatic dengue in the 25 months after the first dose of vaccine was higher among participants aged ≥9 years inferred as seropositive at baseline: 76% (95% CI: 63.9–84.0%), but much lower among participants inferred as seronegative at baseline: 38.8% (95% CI: −0.9–62.9%) in the 25 months after the first dose of vaccine.
- There is an increased risk of hospitalized dengue and severe dengue in seronegative individuals from year 3 onwards during the 66-month observation period.
- In areas of 70% dengue seroprevalence, over a 5-year follow-up, for every 4 severe cases prevented in seropositives there would be 1 excess severe case in seronegatives per 1000 vaccinees; for every 7 hospitalizations prevented in seropositive vaccinees, there would be 1 excess hospitalization in seronegative vaccinees.

avait demandé et obtenu l'homologation du vaccin pour une utilisation chez les sujets de 9 ans et plus.

En juillet 2016, l'OMS a publié une note de synthèse présentant sa position sur l'utilisation du CYD-TDV sur la base des recommandations émises par le SAGE en avril 2016, ces dernières se fondant sur les données issues d'essais cliniques et d'une modélisation mathématique qui laissaient supposer que les avantages de la vaccination pour la santé publique étaient d'autant plus importants que la séropositivité à la dengue était élevée dans la tranche d'âge ciblée par la vaccination. Cette note de synthèse stipulait que i) les pays devraient envisager l'introduction du vaccin CYD-TDV contre la dengue uniquement dans les contextes géographiques où les données épidémiologiques indiquent une forte charge de morbidité de la dengue, ii) la séroprévalence de la dengue devrait être d'environ 70% ou plus afin d'optimiser l'impact de la vaccination sur la santé publique et iii) le vaccin n'était pas recommandé dans les contextes de séroprévalence inférieure à 50% dans la tranche d'âge visée par la vaccination. Bien qu'aucun signal de sécurité n'ait été observé à l'époque, le SAGE a noté que les données sur l'innocuité du vaccin dans les populations séronégatives étaient limitées et a recommandé que des études d'innocuité soient menées pour surveiller l'apparition de dengue sévère chez les personnes vaccinées au cours du temps, en particulier parmi les sujets séronégatifs.

Le 29 novembre 2017, Sanofi Pasteur a communiqué les résultats d'études supplémentaires réalisées pour mieux décrire le rapport bénéfice/risque chez les sujets séronégatifs, grâce à l'utilisation d'un nouveau test de recherche des anticorps dirigés contre l'antigène NS1, qui permet de distinguer la réponse en anticorps provoquée par le virus de la dengue de celle qui est induite par le vaccin. Le test a été effectué sur des échantillons de sang prélevés 13 mois après la vaccination afin de déduire rétrospectivement le statut sérologique du sujet au moment de la première vaccination.

Les nouvelles analyses des données de suivi à long terme de l'innocuité vaccinale parmi les participants aux essais cliniques ont indiqué que:

- La vaccination demeure globalement avantageuse à l'échelle de la population, mais la performance du vaccin est différente selon que les personnes vaccinées sont séropositives ou séronégatives;
- Dans les 25 mois suivant la première dose, l'efficacité du vaccin contre la dengue symptomatique virologiquement confirmée était plus élevée parmi les participants âgés de ≥9 ans initialement séropositifs (76%, IC à 95%: 63,9–84,0%), mais beaucoup plus faible chez les participants initialement séronégatifs (38,8%, IC à 95%: −0,9–62,9%);
- Chez les sujets séronégatifs, il existe un risque accru d'hospitalisation due à la dengue et de survenue d'une dengue sévère à compter de la 3e année pendant la période d'observation de 66 mois;
- Dans les zones où la séroprévalence de la dengue est de 70%, sur une période de suivi de 5 ans, on estime que pour 4 cas graves évités parmi les personnes séropositives, un excédent de 1 cas grave serait observé parmi les sujets séronégatifs pour 1000 personnes vaccinées; pour 7 hospitalisations évitées dans la population séropositive, il y aurait 1 hospitalisation excédentaire parmi les personnes séronégatives vaccinées.

These findings indicate that in high prevalence settings, the vaccine provides overall population benefit but an increased risk for seronegative individuals. SAGE considered 2 vaccination scenarios for countries considering the use of the dengue vaccine: Strategy 1, using the vaccine only in populations with high seroprevalence (>80%); Strategy 2, screening individuals for seropositivity prior to vaccination and vaccinating only those who were seropositive. In the discussion of these strategies, SAGE considered the feasibility of population seroprevalence studies and individual pre-vaccination screening, the heterogeneity of seroprevalence between and within countries, the number of people who could be eligible for vaccination under these scenarios, confidence in vaccination programmes, performance of tests for dengue antibody testing, ethical considerations, and communication issues.

SAGE concluded that for countries considering CYD-TDV vaccination as part of their dengue control programme, a pre-vaccination screening strategy, in which only dengue-seropositive persons are vaccinated, is the preferred option.

Screening tests could be used to identify persons who have had a previous dengue infection. Ideally, a test with the highest specificity should be used to minimize the inadvertent use of vaccine in seronegative persons. Two types of tests could be considered: serological assays such as dengue IgG ELISA, and rapid diagnostic tests (RDT). The ELISA assays do not provide point-of-care information on an individual's serostatus, and the currently available RDTs have not yet been validated for the purpose of screening for previous dengue infection. Nevertheless, either could be considered in high prevalence settings until better tests become available.

Given that no test will be 100% specific, some 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 less than 100%. Hence, the limitations of CYD-TDV will need to be clearly communicated to those offered vaccination.

Decisions about implementing a pre-vaccination screening strategy will require careful assessment at the country level, including sensitivity and specificity of a screening test, dengue hospitalization rates, and affordability of both CYD-TDV and the tests. 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.

The CYD-TDV vaccine is licensed for the indicated age range of 9–45 years. The optimal age group to be targeted is the age at which the incidence of severe dengue is the highest, and this can be ascertained from national and subnational routine hospital data.

Ces résultats montrent que dans les contextes de forte prévalence, le vaccin présente globalement des avantages pour la population, mais induit un risque accru pour les sujets séronégatifs. Le SAGE a examiné 2 scénarios de vaccination pour les pays qui envisagent d'utiliser le vaccin contre la dengue: la stratégie 1 consiste à administrer le vaccin uniquement dans les populations où la séroprévalence est élevée (>80%); la stratégie 2 consiste à effectuer un test de séropositivité individuel avant la vaccination et à vacciner uniquement les personnes dont les résultats indiquent qu'elles sont séropositives. Lors de l'examen de ces stratégies, le SAGE a tenu compte des éléments suivants: la faisabilité d'études de séroprévalence dans la population et de la réalisation de tests individuels avant la vaccination, l'hétérogénéité de la séroprévalence d'un pays à l'autre et à l'intérieur d'un même pays, le nombre de personnes susceptibles de remplir les conditions pour être vaccinées selon ces scénarios, la confiance à l'égard des programmes de vaccination, l'efficacité des tests de recherche des anticorps de la dengue, les considérations éthiques et les problèmes de communication.

Le SAGE a conclu que les pays envisageant la vaccination par le CYD-TDV dans le cadre de leur programme de lutte contre la dengue devraient privilégier la stratégie consistant à effectuer un test avant la vaccination et à vacciner uniquement les personnes séropositives.

Les tests pourraient être utilisés pour identifier les personnes précédemment infectées. Dans l'idéal, on utilisera un test doté de la plus grande spécificité possible pour éviter de vacciner par inadvertance des personnes séronégatives. Deux types de tests peuvent être envisagés: les tests sérologiques, comme le test ELISA de détection des IgG de la dengue, et les tests de diagnostic rapide. Avec le test ELISA, les informations sur le statut sérologique de la personne ne peuvent pas être obtenues sur le lieu des soins, tandis que les tests de diagnostic rapide actuellement disponibles n'ont pas encore été validés pour détecter une infection antérieure par le virus de la dengue. Néanmoins, tant qu'on ne dispose pas de meilleures options, on pourra envisager d'utiliser l'un ou l'autre de ces tests dans les contextes de forte prévalence.

Étant donné qu'aucun test n'a une spécificité de 100%, il est possible que certains sujets séronégatifs soient vaccinés suite à l'obtention d'un résultat faussement positif. En outre, bien que le vaccin soit très efficace contre la dengue chez les personnes séropositives, son efficacité reste inférieure à 100%. Les limites du vaccin CYD-TDV devront donc être clairement expliquées aux personnes à qui la vaccination est proposée.

La décision d'adopter une stratégie prévoyant la réalisation d'un test avant la vaccination exigera une évaluation attentive de la situation dans le pays, en tenant compte notamment de la sensibilité et de la spécificité des tests, du taux d'hospitalisation imputable à la dengue et du prix des vaccins CYD-TDV et des tests. La vaccination doit s'inscrire dans une stratégie intégrée de lutte contre la dengue, comprenant des activités efficaces et soutenues de lutte antivectorielle et la prestation d'excellents soins cliniques reposant sur des bases factuelles.

Le vaccin CYD-TDV est homologué pour un usage dans la tranche d'âge indiquée de 9 à 45 ans. La tranche d'âge optimale à cibler est celle dans laquelle l'incidence de la dengue sévère est la plus élevée, ce qui peut être déterminé à partir des données recueillies par les hôpitaux dans le cadre des soins de routine au niveau national et infranational.

In the absence of data on vaccine efficacy and safety with fewer than 3 doses, SAGE advised that CYD-TDV be used according to the indicated schedule as a 3-dose series, with the doses given 6 months apart.

SAGE emphasized that important research and implementation questions remain concerning CYD-TDV, in particular the need to develop a highly sensitive and specific RDT to determine serostatus, simplified immunization schedules, and assessment of the need for booster doses. An updated dengue vaccine WHO position paper on CYD-TDV will be published on September 2018.

Reports from advisory committees on immunization

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

IVIR-AC met in March 2018 and discussed the following topics: global research updates on rotavirus and HPV vaccines; global research on vaccine demand and acceptance; the malaria RTS,S policy decision-making framework and impact modeling; the measles mortality model and optimal intervals between measles SIAs; the WHO guide on standardization of economic evaluations of vaccines; the development of a Full Public Health Value Proposition; total system effectiveness; and standardization of vaccine delivery costing.

Expert Committee on Biological Standardization (ECBS)

The chair of ECBS informed SAGE on the work of the committee to develop WHO standards for regulatory evaluation of vaccines against Ebola, polio, pertussis, typhoid, and respiratory syncytial virus. The guidelines for the quality, safety and efficacy of Ebola vaccines were described as a new standard adopted by the ECBS in 2017.

Global Advisory Committee on Vaccine Safety (GACVS)

GACVS met in December 2017 and reported to SAGE on 4 topics: the safety of rotavirus vaccines in Africa; an evaluation of WHO causality assessment tools and accompanying methodology; the initiative to harmonize efforts to monitor safety vigilance of interventions during pregnancy; and the ongoing work to develop guidance for preventing and managing anxiety and stress reactions related to vaccination. Two additional topics, safety aspects of dengue and malaria vaccines, were reported in the *Weekly Epidemiological Record*[4] and presented during other sessions during this meeting.

Recent data from multi-country studies to assess the risk of intussusception after monovalent rotavirus vaccine did not show any association in a 7-country surveillance network, while a small risk following the second dose was seen in South Africa. These were less

En l'absence de données sur l'efficacité et l'innocuité du vaccin lorsque moins de 3 doses sont administrées, le SAGE a recommandé que le CYD-TDV soit utilisé selon le calendrier indiqué sous forme d'une série de 3 doses espacées de 6 mois chacune.

Le SAGE a souligné qu'il reste d'importantes questions de recherche et de mise en œuvre à résoudre concernant le vaccin CYD-TDV, en particulier la nécessité de mettre au point un test de diagnostic rapide hautement sensible et spécifique pour déterminer le statut sérologique, la possibilité de simplifier les calendriers de vaccination et l'évaluation de la nécessité des doses de rappel. L'OMS publiera une note de synthèse actualisée sur le vaccin CYD-TDV contre la dengue en septembre 2018.

Rapport des comités consultatifs sur la vaccination

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

L'IVIR-AC s'est réuni en mars 2018 et a abordé les sujets suivants: bilan de la recherche sur les vaccins antirotavirus et anti-PVH dans le monde; recherche sur la demande et l'acceptation des vaccins dans le monde; cadre de prise de décision politique et modélisation de l'impact du vaccin antipaludique RTS,S; modélisation de la mortalité rougeoleuse et intervalle optimal entre les AVS contre la rougeole; guide de l'OMS sur la standardisation des évaluations économiques des programmes de vaccination; élaboration d'une proposition de valeur complète en matière de santé publique; efficacité du système global; et standardisation du calcul des coûts de distribution des vaccins.

Comité d'experts de la standardisation biologique (ECBS)

Le président de l'ECBS a fait part au SAGE des travaux réalisés par le Comité pour élaborer des normes OMS d'évaluation réglementaire des vaccins contre la maladie à virus Ebola, la poliomyélite, la coqueluche, la fièvre typhoïde et le virus respiratoire syncytial. Les lignes directrices relatives à la qualité, à l'innocuité et à l'efficacité des vaccins contre le virus Ebola ont été décrites comme une nouvelle norme adoptée par l'ECBS en 2017.

Comité consultatif mondial pour la sécurité des vaccins (GACVS)

Le GACVS, qui s'est réuni en décembre 2017, a fait rapport au SAGE sur 4 sujets: l'innocuité des vaccins antirotavirus en Afrique; l'examen des outils OMS d'évaluation de la causalité et de la méthodologie correspondante; l'initiative visant à harmoniser les efforts de vigilance pour surveiller la sécurité des interventions pendant la grossesse; et les travaux en cours pour formuler des orientations concernant la prévention et la prise en charge des réactions d'anxiété et de stress liées à la vaccination. Deux autres sujets, relatifs à l'innocuité des vaccins contre le paludisme et contre la dengue, ont été traités dans le *Relevé épidémiologique hebdomadaire*[4] et présentés lors d'autres sessions de cette réunion.

De récentes études multipays visant à évaluer le risque d'invagination intestinale suite à l'administration d'un vaccin antirotavirus monovalent n'ont mis en évidence aucun lien entre ces événements dans un réseau de surveillance couvrant 7 pays, tandis qu'un risque faible a été observé après la deuxième dose

[4] See No 3, 2018, pp.17–32.

[4] Voir N° 3, 2018, pp.17–32.

than the risks identified in most studies previously reviewed by GACVS. Studies show vaccine impact with a 52–94% reduction in severe rotavirus illness.

With respect to monitoring the safety of interventions in pregnancy, there is growing interest in developing platforms to bridge ongoing efforts in maternal, reproductive and child health, in order to ensure greater harmonization and thus comparability of safety data in pregnancy. These will enable improved evaluation of the impact and outcomes of those interventions.

GACVS has convened an expert working group to explore stress-related reactions that have been reported to occur as clusters which have affected immunization programmes.

Measles and rubella

SAGE noted the substantial progress in the reduction of global measles incidence and mortality since 2000. However, concerns were expressed about the resurgence of measles in some areas, particularly in the European Region, and the measles outbreak in Venezuela that has put the elimination status of the Region of the Americas at risk.

SAGE reviewed preliminary modelled scenarios, designed to develop an investment case (IC) for measles and rubella eradication. The IC in development is planned as part of the response to the WHA resolution concerning GVAP 2017. A report will be provided to the 73rd WHA in 2020 on the epidemiology, resource requirements, and feasibility of measles and rubella eradication.

SAGE recommended that the Measles-Rubella WG should revise the key modelled scenarios to include a baseline scenario that reflects current vaccination efforts and disease in the countries, and a separate mortality reduction scenario, in addition to the "eradication as soon as possible" scenario. The WG was requested to develop additional eradication scenarios with different timelines and with different levels of achievement (e.g. elimination in all but a few countries and including the costs of reaching inaccessible locations and hard-to-reach populations). SAGE also highlighted the importance of the inclusion of total cost when a decision regarding a global eradication target is considered, including the standard surveillance cost for elimination. Inclusion of the contribution of the measles and rubella eradication effort towards the prevention of other vaccine-preventable diseases should also be considered. This IC model is currently under review by IVIR-AC and a revised version will be presented to SAGE for recommendations.

en Afrique du Sud. Ces risques étaient moins importants que ceux qui avaient été identifiés dans la plupart des études précédemment examinées par le GACVS. Des études ont démontré l'impact du vaccin, avec une réduction de 52% à 94% des cas de maladie grave à rotavirus.

S'agissant de la surveillance de la sécurité des interventions lors de la grossesse, un intérêt croissant est porté à la mise en place de plateformes faisant le lien entre les efforts entrepris dans les domaines de la santé maternelle, de la santé reproductive et de la santé de l'enfant en vue de favoriser une plus grande harmonisation, et donc une meilleure comparabilité, des données d'innocuité pendant la grossesse, ce qui permettra de mieux évaluer l'impact et les résultats de ces interventions.

Le GACVS a réuni un groupe d'experts chargé d'étudier les grappes de réactions liées au stress qui ont été signalées dans le cadre de la vaccination et qui ont eu une incidence sur les programmes de vaccination.

Rougeole et rubéole

Le SAGE a noté que des progrès considérables ont été réalisés dans la réduction de l'incidence et de la mortalité rougeoleuses dans le monde depuis 2000. Il a toutefois exprimé son inquiétude face à la résurgence de la rougeole dans certaines zones, en particulier dans la Région européenne, et face à l'épidémie de rougeole survenue au Venezuela, qui risque de compromettre la pérennité de l'élimination de la maladie dans la Région des Amériques.

Le SAGE a examiné des scénarios modélisés préliminaires devant servir de base à l'élaboration d'un argumentaire d'investissement en faveur de l'éradication de la rougeole et de la rubéole. La préparation de cet argumentaire est l'une des actions entreprises pour donner suite à la résolution de l'Assemblée mondiale de la Santé concernant le GVAP 2017. Un rapport sur l'épidémiologie, les besoins en ressources et la faisabilité de l'éradication de la rougeole et de la rubéole sera présenté à la 73e Assemblée mondiale de la Santé en 2020.

Le SAGE a recommandé au Groupe de travail sur la rougeole et la rubéole de réviser les principaux scénarios modélisés afin d'inclure un scénario de référence qui reflète la situation actuelle dans les pays, en termes de vaccination et de prévalence de la maladie, ainsi qu'un scénario distinct de réduction de la mortalité, en sus du scénario visant une «éradication dès que possible». Il a été demandé au Groupe de travail sur la rougeole et la rubéole d'élaborer d'autres scénarios d'éradication avec des calendriers différents et des niveaux de réalisation différents (par exemple, élimination dans tous les pays à l'exception de quelques-uns, et prise en compte des coûts associés à la couverture des endroits inaccessibles et des populations difficiles à atteindre). Le SAGE a également souligné qu'il est important de tenir compte du coût total, y compris du coût lié à la mise en œuvre d'une surveillance conforme aux exigences d'élimination, lors de toute prise de décision relative à une cible mondiale d'éradication. On envisagera en outre de faire état, dans l'argumentaire d'investissement, de la contribution apportée par les efforts d'éradication de la rougeole et de la rubéole à la prévention d'autres maladies évitables par la vaccination. Le modèle d'élaboration des argumentaires d'investissement est actuellement examiné par l'IVIR-AC et une version révisée sera présentée au SAGE pour recommandations.

SAGE reviewed the approach and methodology developed by the WG to provide guidance to all countries on methods for assessing population immunity through a review of available data sources and analytical methods and a description of their strengths and weaknesses, in order to estimate age-specific immunity gaps.

SAGE also reviewed the guidance tool for endemic countries on prioritizing measles and rubella control/elimination activities in order to increase population immunity, prevent outbreaks and achieve elimination. The approach proposed 4 endemic country categories that take into consideration the disease epidemiology, population immunity and capacity to carry out elimination strategies. Guidance was then provided within each category on how to best prioritize the control or elimination interventions/activities. SAGE agreed with the overall approach and highlighted the need to include subnational groups within countries when assessing and addressing immunity gaps, and the importance of including civil society organizations and community participation as important elements for successful interventions.

Full Public Health Value Proposition for Vaccines (FPHVP)

The remit of the work on immunization by WHO includes accelerating development of vaccines against priority pathogens, identified through its Product Development for Vaccines Advisory Committee, and supporting countries with policy recommendations on the introduction of vaccines when they become available. In addition, many of the vaccines in development are expected to be targeted towards specific populations, depending on the burden of disease and context-specific epidemiology. In resource-constrained settings, robust evidence will be needed to justify the inclusion of new vaccines in the context of other disease interventions. In this perspective, broader evaluation of the vaccine value beyond demonstration of the individual direct health benefits and related costs has been proposed. Such evaluation could include broader economic, societal and indirect impacts of vaccination at a population level. Consideration of these data and evidence requirements that inform policy recommendations, prior to undertaking Phase 3 clinical studies, could help to prioritize the vaccines that would have the greatest impact, and reduce delays between licensure and introduction as encountered with vaccines such as the RTS,S malaria vaccine.[5]

A conceptual framework of pathways between immunization and its proposed broader economic and social benefits has been developed, including methodologies and measures[6] to quantify the economic

[5] O'Brien K et al. Mind the gap: jumping from vaccine licensure to routine use. The Lancet. 2016;387: 1887–1889.

[6] Jit M et al. The broader economic impact of vaccination: reviewing and appraising the strength of evidence. BMC Med. 2015;13:209.

Le SAGE a examiné l'approche et la méthodologie mises au point par le Groupe de travail pour fournir à tous les pays des conseils sur les méthodes d'évaluation de l'immunité des populations par un examen des sources de données et des méthodes d'analyse disponibles et une description de leurs atouts et de leurs faiblesses afin d'estimer les déficits de l'immunité selon l'âge.

Le SAGE a également examiné l'outil d'orientation destiné à aider les pays d'endémie à définir les activités prioritaires de lutte et d'élimination de la rougeole et de la rubéole afin d'accroître l'immunité de la population, de prévenir les flambées épidémiques et d'atteindre le stade de l'élimination. Dans cette approche, il est proposé de classer les pays d'endémie en 4 catégories selon l'épidémiologie de la maladie, l'immunité de la population et la capacité du pays à appliquer les stratégies d'élimination. Pour chacune de ces catégories, des orientations ont été données concernant la marche à suivre pour établir l'ordre de priorité des activités et interventions de lutte ou d'élimination. Le SAGE a approuvé l'approche générale proposée et a souligné la nécessité d'inclure des groupes infranationaux du pays concerné lors de l'évaluation des déficits immunitaires et des activités destinées à les combler. Il a également indiqué que la participation des organisations de la société civile et des communautés est essentielle à la réussite des interventions.

Proposition de valeur complètes en matière de santé publique pour les vaccins

Dans le cadre de la mission qui lui incombe en matière de vaccination, l'OMS s'emploie à accélérer la mise au point de vaccins contre les agents pathogènes prioritaires, identifiés par son Comité consultatif sur le développement de produits pour les vaccins, et à soutenir les pays en formulant des recommandations politiques concernant l'introduction des vaccins devenus disponibles. En outre, de nombreux vaccins en cours de développement cibleront probablement des populations spécifiques, selon la charge de morbidité et la situation épidémiologique particulière du milieu concerné. En situation de ressources limitées, des preuves solides devront être apportées pour justifier l'introduction de nouveaux vaccins dans le cadre d'autres interventions de lutte contre les maladies. Dans cette perspective, il a été proposé d'adopter une approche plus générale d'évaluation de l'utilité des vaccins, au-delà de la seule démonstration de leurs avantages individuels directs pour la santé, et des coûts associés. Cette évaluation pourrait tenir compte de manière plus globale des conséquences économiques, sociétales et indirectes de la vaccination dans la population. La prise en compte de ces éléments et des données probantes destinées à orienter les recommandations politiques avant le début des études cliniques de phase 3 pourrait faciliter la hiérarchisation des vaccins susceptibles d'avoir l'impact le plus important et permettrait de réduire les délais entre l'homologation et l'introduction, comme ceux observés pour certains vaccins comme le vaccin antipaludique RTS,S.[5]

Un cadre conceptuel a été élaboré pour décrire les trajectoires entre la vaccination et les avantages économiques et sociaux qui en sont attendus, présentant notamment des méthodes et des mesures[6] permettant de quantifier les aspects écono-

[5] O'Brien K et al. Mind the gap: jumping from vaccine licensure to routine use. The Lancet. 2016;387: 1887– 1889.

[6] Jit M et al. The broader economic impact of vaccination: reviewing and appraising the strength of evidence. BMC Med. 2015;13:209.

elements.[7,8] This framework considers the population impact of vaccination and encompasses measures of community benefits against a range of outcomes, such as improvements in health equity, financial risk protection, reduction in long-term/ongoing disability and a decrease in the development of antibiotic resistance. WHO is building on these efforts to develop an approach for describing the Full Public Health Value Proposition (articulating both the individual and population benefits) for vaccines for which there is a clear public health need, but a lack of investment in developing vaccines for LMICs. This FPHVP approach was presented to SAGE for information and discussion.

As the candidate vaccines advance, 2 FPHVP objectives can be formulated. The early stage FPHVP is intended to strengthen disease burden estimates to better define the need, identify gaps that will inform the value from an LMIC perspective, and encourage investment by vaccine manufacturers and funders on a well-articulated public health priority. The late stage FPHVP (post-clinical proof of concept) includes an economic evaluation to more comprehensively define the potential impact of the vaccine, considering individual and population-based benefits, to inform country and global level decision-makers. WHO has termed the economic elements underpinning the FPHVP as the "global economic investment case."

There was agreement that a consistent, transparent, systematic and integrated approach, based on a common methodology and nomenclature/definitions, for evaluating the potential value of vaccines is needed to enable comparison between vaccines and candidates and across health-care interventions, and aid investment and policy decision-making at all levels. However, SAGE commented that the primary target audiences for the FPHVP are the public health stakeholders, and advised on reconsideration of respective terminology. Elements such as how new vaccines would address inequity require prominence, in line with WHO's Universal Health Coverage priorities set out in the GPW. Furthermore, SAGE members were keen to ensure that the needs of individual households are incorporated within any framework that is developed, alongside those of manufacturers and vaccine purchasers. ■

miques.[7,8] Ce cadre examine l'impact de la vaccination sur la population et permet de mesurer les avantages qu'elle procure au niveau communautaire au regard de divers critères, comme l'amélioration de l'équité en matière de santé, la protection contre les risques financiers, la réduction du handicap à long terme ou permanent et la diminution du risque d'apparition d'une résistance aux antibiotiques. L'OMS s'appuie sur ces efforts pour concevoir une approche de description de la proposition de valeur complète en matière de santé publique des vaccins (axée à la fois sur les avantages individuels et les avantages pour la population) lorsque la mise au point de vaccins pour les pays à revenu faible ou intermédiaire relève d'un besoin évident de santé publique, mais souffre d'un manque d'investissement. Cette approche a été présentée au SAGE pour information et discussion.

À mesure que progresse le développement des vaccins candidats, 2 objectifs relatifs à la proposition de valeur peuvent être formulés. La proposition de valeur applicable au stade précoce du développement vise à renforcer les estimations de la charge de morbidité afin de mieux cerner les besoins, d'identifier les lacunes qui contribueront à définir la valeur du vaccin du point de vue des pays à revenu faible ou intermédiaire, et d'encourager les fabricants et les bailleurs de fonds à consentir les investissements nécessaires, sur la base d'une priorité de santé publique clairement énoncée. La proposition de valeur applicable aux stades ultérieurs (études précliniques de validation de principe) comprend une évaluation économique visant à définir l'impact potentiel du vaccin de manière plus complète, en tenant compte des avantages individuels et des avantages pour la population, en vue de guider les décideurs aux niveaux national et mondial. L'OMS a adopté le terme «argumentaire d'investissement économique mondial» pour décrire les aspects économiques qui sous-tendent la proposition de valeur.

Il a été convenu que la valeur potentielle des vaccins doit être évaluée selon une approche cohérente, transparente, systématique et intégrée, fondée sur une méthodologie et une nomenclature/des définitions communes, pour permettre la comparaison entre les vaccins et les vaccins candidats, ainsi qu'entre les interventions sanitaires, et faciliter la prise de décision à tous les niveaux concernant les investissements et les politiques à mettre en œuvre. Cependant, le SAGE a observé que les principaux publics visés par les propositions de valeur sont les intervenants en santé publique et a préconisé une réévaluation des terminologies respectives employées. Certains aspects, notamment la manière dont on pourra remédier aux inégalités avec les nouveaux vaccins, doivent être mis en exergue, conformément aux priorités relatives à l'instauration de la couverture sanitaire universelle énoncées dans le programme général de travail de l'OMS. Par ailleurs, les membres du SAGE ont tenu à souligner que tout nouveau cadre devra inclure les besoins des ménages individuels, outre ceux des fabricants et des acheteurs de vaccins. ■

[7] Gessner BD et al. Estimating the full public health value of vaccination. Vaccine. 2017;35(46):6255–6263.

[8] Wilder-Smith A et al. The public health value of vaccines beyond efficacy: methods, measures and outcomes. BMC Med. 2017;15(1):138.

[7] Gessner BD et al. Estimating the full public health value of vaccination. Vaccine. 2017;35(46):6255–6263.

[8] Wilder-Smith A et al. The public health value of vaccines beyond efficacy: methods, measures and outcomes. BMC Med. 2017;15(1):138.

WHO web sites on infectious diseases – Sites internet de l'OMS sur les maladies infectieuses

Avian influenza	**http://www.who.int/csr/disease/avian_influenza/en/**	Grippe aviaire
Buruli ulcer	**http://www.who.int/buruli/en/**	Ulcère de Buruli
Child and adolescent health and development	**http://www.who.int/child_adolescent_health/en/**	Santé et développement des enfants et des adolescents
Cholera	**http://www.who.int/cholera/en/**	Choléra
Deliberate use of biological and chemical agents	**http://www.who.int/csr/delibepidemics/informationresources/en/**	Usage délibéré d'agents chimiques et biologiques
Dengue (DengueNet)	**http://apps.who.int/globalatlas/**	Dengue (DengueNet)
Epidemic and pandemic surveillance and response	**http://www.who.int/csr/en/**	Alerte et action en cas d'épidémie et de pandémie
Eradication/elimination programmes	**http://www.who.int/topics/infectious_diseases/en/**	Programmes d'éradication/élimination
Fact sheets on infectious diseases	**http://www.who.int/topics/infectious_diseases/factsheets/en/**	Aide-mémoires sur les maladies infectieuses
Filariasis	**http://www.filariasis.org**	Filariose
Geographical information systems (GIS)	**http://gamapserver.who.int/mapLibrary/**	Systèmes d'information géographique
Global atlas of infectious diseases	**http://apps.who.int/globalatlas/**	Atlas mondial des maladies infectieuses
Global Outbreak Alert and Response Network (GOARN)	**http://www.who.int/csr/outbreaknetwork/en/**	Réseau mondial d'alerte et d'action en cas d'épidémie (GOARN)
Health topics	**http://www.who.int/topics/en**	La santé de A à Z
Human African trypanosomiasis	**http://www.who.int/trypanosomiasis_african/en/**	Trypanosomiase humaine africaine
Influenza	**http://www.who.int/csr/disease/influenza/en/**	Grippe
Influenza network (FluNet)	**http://who.int/flunet**	Réseau grippe (FluNet)
International Health Regulations	**http://www.who.int/ihr/en/**	Règlement sanitaire international
International travel and health	**http://www.who.int/ith/en/**	Voyages internationaux et santé
Leishmaniasis	**http://www.who.int/leishmaniasis/en**	Leishmaniose
Leprosy	**http://www.who.int/lep/en**	Lèpre
Lymphatic filariasis	**http://www.who.int/lymphatic_filariasis/en/**	Filiariose lymphatique
Malaria	**http://www.who.int/malaria/en**	Paludisme
Neglected tropical diseases	**http://www.who.int/neglected_diseases/en/**	Maladies tropicales négligées
Outbreak news	**http://www.who.int/csr/don/en**	Flambées d'épidémies
Poliomyelitis	**http://www.polioeradication.org/casecount.asp**	Poliomyélite
Rabies	**http://www.who.int/rabies/en**	Rage
Global Foodborne Infections Network (GFN)	**http://www.who.int/gfn/en**	Réseau mondial d'infections d'origine alimentaire
Smallpox	**http://www.who.int/csr/disease/smallpox/en**	Variole
Schistosomiasis	**http://www.who.int/schistosomiasis/en/**	Schistosomiase
Soil-transmitted helminthiases	**http://www.who.int/intestinal_worms/en/**	Géohelminthiases
Tropical disease research	**http://www.who.int/tdr/**	Recherche sur les maladies tropicales
Tuberculosis	**http://www.who.int/tb/en** and/et **http://www.stoptb.org**	Tuberculose
Immunization, Vaccines and Biologicals	**http://www.who.int/immunization/en/**	Vaccination, Vaccins et Biologiques
Weekly Epidemiological Record	**http://www.who.int/wer/**	Relevé épidémiologique hebdomadaire
WHO Lyon Office for National Epidemic Preparedness and Response	**http://www.who.int/ihr/lyon/en/index.html**	Bureau OMS de Lyon pour la préparation et la réponse des pays aux épidémies
WHO Pesticide Evaluation Scheme (WHOPES)	**http://www.who.int/whopes/en**	Schéma OMS d'évaluation des pesticides (WHOPES)
WHO Mediterranean Centre for Vulnerability Reduction, Tunis	**http://wmc.who.int/**	Centre Méditerranéen de l'OMS pour la Réduction de la Vulnérabilité à Tunis (WMC)
Yellow fever	**http://www.who.int/csr/disease/yellowfev/en/**	Fièvre jaune

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 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. AFRO continues to work with countries on updating their pre service curriculum.
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. In 2017, for 2016 data, 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. In 2018, for 2017 141 countries reported subnational data, for a total of about 23,000 districts. Detailed analysis and reported data are available from http://www.who.int/immunization/monitoring_surveillance/data/subnational/en/
AEFI reporting	SAGE urged that efforts be pursued to enhance Adverse Events Following Immunization (AEFI) reporting worldwide.	Apr 2016	Ongoing	Progress with AEFI surveillance is sustained with 114 countries reporting at least 10 AEFI per 100,000 surviving infants during 2017 as compared to 45 in 2010 and 97 in 2016. In order to further analyze national capacity, more refined indicators related to serious AEFI, timeliness and completeness of reporting are now being developed and evaluated.
Analysis of national legal framework on immunization	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	Oct 2017	ongoing	The university of Dalhousie Canada is currently conducting a study to assess the impact of legislative frameworks on immunization. Fist results will be presented at DoV WG meeting in Aug 2018, if ready.
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 were part of this working group, but one member resigned. The terms of reference were split into 6 and a member was assigned as a lead each. Several teleconferences have been held, nine members participated in the "Data Partners Meeting" organized by EPI/WHO in October 2017 and the first face-to-face meeting took place in July 2018 (sharable report is available upon request). Work is ongoing. Recommendation (April 2018) to explore coordination with other WHO programmes collecting subnational data.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Decade of vaccines/GVAP	The SAGE working group should continuously review the Progress on GVAP and 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 met 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.
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	An assessment of global demand and supply for Diptheria 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 Linksbridge 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: • 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

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
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	WHO has established a DAT international working group to coordinate and allocate extremely limited DAT supplies. In 2018 WHO coordinated the procurement of DAT among different procurement agencies and partners. DAT was supplied to Yemen, Bangladesh, Indonesia, Venezuela and Haiti. Around 20,000 vials have been deployed between WHO, PAHO and MSF. DAT-WG is now looking for solutions to establish either procurement mechanism to make agreement in advance or a stockpile to meet the urgent or unexpected demand during outbreaks. WHO is now evaluating the quality of the available DAT WHO DAT-WG coordinates the group to look at the following areas of work: 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) Members of the coordinating group: MSF, UNICEF, ECDC, CDC, PEI, MHRA, EC, FDA, EMA, PHE, NIBSC
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 end of August 2018
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	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. 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. Regulatory evaluation of the vaccine is currently ongoing. 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.

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Full public health value of vaccines	SAGE requests update on progress and implementation of the concept, and on a more public health related terminology.	Apr 2018	Ongoing	On the recommendation of SAGE, the term value proposition has been removed and the new terminology for the concept is the 'Full public health value of vaccines (FPHVV)'. Efforts to socialize the concept are continuing, and the PFHVV was discussed at the 2018 PDVAC meeting. Efforts and collaborations to develop components of FPHVVs are underway for Herpes Simplex Virus, Group B strep and Group A strep vaccines.
Hepatitis A	Long-term protection from single or 2-dose schedules should be regularly monitored by countries and reviewed by SAGE.	Apr 2012	Ongoing	Post-market surveillance continues in Argentina and a detailed report on the recent epidemiological situation was provided to WHO in March 2017. The next active follow-up report will be requested ahead of the April 2018 SAGE meeting. 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 of hepatitis A virus (HAV) acute infection cases reported occurred in individuals over >10 years. All cases reported occurred in unvaccinated individuals. 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. 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. 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. (Update needed on single dose, such as data from Argentina)

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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	WER on status of global introduction and implementation of hepatitis B birth dose has been drafted and cleared; scheduled for publication in Feb 2018. 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. 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. 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. 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. 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.

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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	In 2017, it was approved to collect an additional variable on hepatitis B birth dose to distinguish birth dose vaccine adminstered within 24 hours (TIMELY) and any birth dose administered (TOTAL) as part of the WHO/UNICEF Joint Reporting Form (JRF). Previoulsy only timely birth dose was requested. 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. In Sept 2016, the European Regional Office (EURO) held a consultation to discuss establishing a regional verification mechanism. 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. 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 (GHHS) 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. In April 2016, WHA Endorsed the GHHS 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. 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. 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. 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. The EURO will consider a regional hepatitis B control goal as proposed by ETAGE. The Pan American Health Organization (PAHO) has resolved to eliminate hepatitis B virus transmission and is formulating a regional strategy. Documenting the "Impact of Hepatitis B Immunization: best practices for conducting a serosurvey" (WHO/IVB/11.08) was published in 2011 by the department of Immunization, Vaccines and Biologicals. In 2012, WHO HQ has published a framework for global action to control viral hepatitis (http://www.who.int/csr/disease/hepatitis/Framework/en/index.html).
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	As of August 2018, one Hepatitis B vaccine manufacturer, LG Chem, has obtained licensure approval from the Korean Ministry of Food and Drug Safety for their Hepatitis B vaccine product, Euvax B Injectable vaccine (single dose, thimerosal containing 0.5ml presentation) to be stored up to 37°C for 28 days and up to 45°C for 4 days. The latter parameters are compatible with Controlled Temperature Chain (CTC) requirements, however this product has yet to be WHO Pre-qualified. A second manufacturer, Biological E. Ltd, is actively testing its birth-dose Hepatitis B vaccine with a view to seeking a label variation for licensed and WHO Pre-qualified use in a 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.
Hexavalent IPV-based combination vaccines PQ and supply	tracking progress on Hexavalent IPV-based combination vaccines prequalification and supply	Oct 2017	ongoing	This work is ongoing through the Gavi market shaping team who is leading on collecting information on hexavalent supply as well as communication with manufacturers on potential future demand

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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 responses are starting . Several other approaches are being tested in translational research. WHO IVR organized a consultation on HIV vaccine development early 2018 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. A meeting report is under finalization.
HPV	The secretariat is developing a pathway, milestones and indicators towards that goal that will require careful consideration of the role of HPV vaccination, besides screening and care components. To guide WHO on this, it was agreed that a SAGE working group would be needed, with an initial reporting back to SAGE in October 2018. SAGE should consider new data in terms of cost-effectiveness, defining long- and interim- goals, identifying indicators for the elimination strategy as related to vaccination.	Jun 2018	Ongoing	
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	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. - 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 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 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. 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. 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 took place in the October 2017. The data presented and discussed did not indicated that the 2013 SAGE policy recommendation needs to be changed. 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.
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.

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Implementation Research	SAGE identified the conditions necessary for pertussis resurgence and the effective strategies for prevention of resurgence as important topics for modelling research.	Apr 2014	Ongoing	The June 2015 meeting of the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) meeting agreed on the plan for phase 1 of the comparison of pertussis models from Australia, England & Wales and the United States of America, which is meant to be a rapid assessment on the relative contributions of vaccine formulations, waning immunity, vaccine coverage and schedule to 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 or further opportunities to add pertussis markers (primarily PCR on respiratory specimens) to studies such as Gavi– or the BMGF– supported vaccine impact studies. There were concerns that the opportunistic process by which the 3 models were identified may not have included all relevant parameters or modelling approaches. The feasibility of taking into account other models and parameters identified through a literature review and/or open call should be assessed, focusing on the main results of the different models for phase 1, and if they are interested to include them in phase 2. 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.
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.
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/

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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	During the April 2016 SAGE meeting, SAGE members were 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. Based on pilot MOV assessments conducted in Chad and Malawi in 2015 (manuscript submitted for peer review) and Kenya in 2016 (draft manuscripts in preparation for submission to peer reviewed journal), WHO published a set of updated MOV guidance documents and field tools in Q3-2017. These include: a planning guide and the assessment methodology (including the MOV protocol, sample questionnaires and generic field tools). The intervention guidebook is currently under review and will be published in Q4-2018. WHO launched a MOV web page which contains links to all the available materials for easy access to countries and is regularly updated with country experiences, MOV related documents and publications. Having strengthened the capacity of AFRO to implement the MOV strategy (MOV assessments completed in: Chad, Malawi, Burkina Faso (led by partner AMP), Kenya, DRC, Nigeria, Mozambique (led by partner VillageReach) and Zimbabwe), collaboration is ongoing with SEARO (MOV assessment completed in Timor Leste 2016), EMRO (MOV assessment completed in Jordan (led by partner UNICEF) in 2017) and WPRO (MOV lite model completed in Cambodia (in collaboration with CDC) in 2017). 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 fifth partner coordination call took place on Apr. 13, 2018. In 2018, WHO priorities include supporting countries that have completed MOV assessments to implement and monitor actions to reduce MOV; evaluate and document the impact of these interventions on coverage and timeliness; and continue building capacity in regions and countries to support additional assessments and MOV reduction strategies. To date, WHO has provided support to AMP in Burkina Faso to implement MOV activities, which will commence in Q3-2018 and are also supporting the hiring of a consultant in Malawi to assist the country office and MoH in Malawi with MOV activities in Q3-2018. Through monitoring and evaluation, the impact of post-MOV assessment country intervention action plans will be assessed and reported back to SAGE at a future date. Through monitoring and evaluation, the impact of post-MOV assessment country intervention action plans will be assessed and reported back to SAGE at a future date.
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	In Q1 2018, UNICEF issued an update on IPV supply which provides the current understnading of IPV supply. this is available upon request.

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Lower middle-income countries: sustainable adoption and financing for new vaccines	SAGE requested that WHO facilitate the establishment of a partnership among all relevant stakeholders to consider: pooled procurement; tiered pricing; greater transparency of pricing; and exploring the role that UNICEF, the Pan American Health Organization and foundations can have in assisting these countries with procuring and financing vaccines.	Nov 2010	Ongoing	WHO 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. 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. 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. 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 accross 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. 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.

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Malaria Vaccine	SAGE requested continued review of the planning of the pilot implementations and to receive regular updates on the results.	Oct 2015	Ongoing	Progress continues on the Malaria vaccine implementation programme (MVIP). The National Regulatory Authorities in all three pilot countries (Ghana, Kenya and Malawi) have authorized the RTS,S vaccine for use in the pilot areas. Following a competitive bidding process, research consortia in each pilot country have been selected to lead the evaluation of the RTS,S vaccine introduction; contracts are being finalized. The first investigators' meeting was held in Ghana in July 2018, where all components of the evaluation were reviewed in detail, and timelines for evaluation readiness considered. Subsequently, timelines for vaccine introduction were reconsidered by the EPI programmes. RTS,S vaccine launch dates now aim for Q1 and Q2 2019. Preparations are underway for a Jan 10 announcement of the vaccine introduction in Malawi and a Q1 launch in Ghana and possibly Malawi or Kenya. Communication plans, including a crisis communication strategy, are in place or being finalized. Vaccine supply is ready for shipment. A competitive process to identify an external monitor is being completed and negotiations with a reference lab are underway. A dedicated consultant statistician and data manager have been contracted and are assisting with the development of the statistical analysis plan and data management platform, respectively. The hiring of dedicated staff in AFRO and the three pilot countries is progressing. The MVIP Programme Advisory Committee and Data Safety and Monitoring Board have met quarterly and have provided guidance to the programme. A working group for the Framework for Policy Decision has been constituted, including two SAGE members. An initial teleconference has been held with a meeting planned in December.
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	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. Also, IVR has supported two efforts evaluating the ethics of maternal immunization: 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 2) Verweij M, Lambach P, Ortiz JR, Reis A. Maternal Immunisation: Ethical Issues. In press at Lancet Infectious Diseases. Both publications advocate for the ethical imperative of clinical trials in pregnant women.
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) Service delivery of Maternal Tetanus Immunization and Antenatal Care in collaboration with the WHO Maternal Child and Adolescent Department ; 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, 1) assessment of vaccine confidence/hesitancy in pregnant women and health care workers.

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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 priorotize reserach areas in order to increase interets of donors to fund and of reserach institutions to carry out the needed research
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 and again additiona findings discussed in July 2018. The results of this work were presented to the IVAR-AC. IVIR_AC have created a sub working group that would continue to review the modelling work and provide feedback to the whole of the IVIR-AC. Additionla work is needed to validate the models and revise the recommendations. This work is not expected to be completed until 2019.
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 vaccine(MR) / micro-array patch (MAP) Working Group (WG) was set up and has had five conference calls. A face to face consultation with the MR-MAP WG, vaccine manufacturers, MAP developers and other stakeholders took place in April 2018. The outcomes and recommendations from this WG will be shared with SAGE. In addition, the MR-MAP TPP will be finalized and publicly available in the fall of 2018.
Measles rubella investment case	SAGE requests update on measles rubella investment case as per recommendations from April 2018 meeting	Apr 2018	Ongoing	The work on the measles and rubella invetsment case is ongoing. The model is being evaluated by IVIR-AC. The draft concept paper of the feasibility of measles and rubella eradication (which includes the investement case) will be discussed at the October 2018 SAGE
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 survillance and outbreak investigations in country.
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, 8 countries have launched their introduction at the age of 9 months (Sudan, July 2016; Mali, February 2017; Central African Republic, June 2017; Chad, July 2017; Niger, October 2017; Cote d'Ivoire, August 2018); or at the age of 18 months (Ghana, November 2016) or at the age of 15 months (Burkina Faso, March 2017), respectively. The remaining two countries intend to do so in 2018 (The Gambia, Nigeria). Another 3 countries (Guinea; Guinea Bissau; Togo) have applied to Gavi through its new country engagement framework for an introduction in 2019. Three additional countries have applied to Gavi to conduct their initial mass vaccination campaigns: Burundi and Kenya in Q4-2018 with the intention to enhance surveillance while waiting for availability of affordable multivalent vaccines to consider an introduction into their routine programme; and Eritrea in Q2-2019 with the intention to introduce the vaccine into their routine programme 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 September 2018 and January 2019.

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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? Recommendation to review lessons learned from EMRO
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	The investment case for countries that are yet to eliminate has been finalized and ready for printing. Work is ongoing for the investment case for the countries that have eliminated, as there is the need to incorporate findings from the post-validation missions that were conducted in Algeria, Timor Leste, Cameroon and Djibouti during 2018.
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	US CDC has recently gotten across to the MNTE Initative to discuss the possibility of adding TT as part of the multi-antigen assay to be conducted in Nigeria. Discussions are going on, but the progress is not as much as initially anticipated.
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	A regional workshop is planned for African countries, including those that have been validated to support them in developing their sustainability plans. The guidance document for sustaining MNTE and broader tetanus prevention is being finalized and is incorporating recommendations from the SAGE. MNTE was presented at the recent SEARO and WPRO TAGs, and is on the agenda of the next AFRO TAG all in an effort to sustain the advocacy. MNTE sustainability is included in the agendas of the two EPI Managers' meetings in the AFR scheduled to take place in Sep 2018
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	UNICEF programme and supply divisions through USF are following up with BMGF to secure this support under Total System Efefctiveness (TSE) initiative. In the absence of the TT pre-filled device, the programme is encouraging use of opportunities of accelerated activities and campaigns like Immunization and Child Health weeks and periodic intensification of routine immunization (PIRI) designed for hard to reach areas to also add on TT-containing vaccines.
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	Some progress has been achieved, but it is still challenging to get countries to allocate resources in support of MNTE activities. Nigeria has agreed to pay for the Td vaccine for its upcoming campaign in South South zone States, but operational funds had to be sourced externally. This is work in progress.

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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. A new menu option has been created on WHO website called 'Workforce' which will host all related document in this area of work including the framework document of staff functions and competencies.
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. A simplified evaluation tool was developed for NITAGs to assess themselves and should be piloted in Q4.
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 have launched activities to analyze available pneumococcal and meningitis surveillance data and a systematic literature review to describe known outbreaks. This and disease modeling will be used to devise a strategy for responding to pneumococcal outbreaks, since the existing data is sparse. We hope to discuss this at upcoming ICG meeting and African meningitis meeting in Q3 2018.
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). In China, WHO supports sIPV manufacturers to carry out clinical trials with fsIPV for in-label use.

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Polio	SAGE encouraged further engagement of WHO regional offices in regard to the polio legacy planningto ensure adequate technical support to countries.	Oct 2015	Ongoing	WHO Regional Offices from AFRO, EMRO and SEARO are an integral part of the polio transition planning exercise at the country level, providing guidance and 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, Regional Immunization Technical Advisory Group recommendations, discussions at the Regional Committees). In addition, the “Strategic Action Plan on Polio Transition”, which was presented to the World Health Assembly in May 2018 was prepared with substantive input from AFRO, EMRO and SEARO. The Strategic Action Plan focuses on functions that need to be sustained to keep the world polio-free, to strengthen immunization and to strengthen outbreak preparedness, detection and response capacity and 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 accelerate implementation of the WHO Global Action Plan for containment (GAPIII) 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	Phase I of GAPIII (Preparations for containment of poliovirus type 2 (PV2)): As of September 2018, countries have been informed that the 'Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses' is available and that GCC recommended its implementation by April 2019. Phase II of GAPIII (PV2 containment period): 29 countries reported the intention to retain PV2 materials (WPV2 or OPV2/Sabin2) in 81 designated poliovirus-essential facilities (PEFs). 22 of these countries have nominated a national authority for containment (NAC). Lately, two additional designated facilities, one in South Africa and one in Indonesia, have applied to engage in the containment certification process, bringing the total number to 3. However, so far only one CP has been delivered.
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). SAGE also requested reconsideration of terminology from fractional IPV to intradermal; explore if PEF safety monitoring can be linked to IH regulation (April 2018)	Oct 2016	Ongoing	IPV supply has imroved in Q3 2018 and all countries now have sufficient supply of IPV for routine immunization. Pre-qualification of Tropis jet needle-free injector was achieved in June 2018 and will be available for use in the polio program in Q3-Q4 2018. Discussions on change of terminology and IH procedures are ongoing.
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	The 'Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses’ (PIM Guidance) has been finalized and published on the GPEI website in April 2018. PIM Guidance implementation workshops have already been organized in 3 Regions, and action is already being taken to ensure the collection of facility data and compilation of national progress reports on preparations for poliovirus containment and completion of Phase I of GAPIII.
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 2018 Polio Working Group meeting, will be provided during the October 2018 SAGE meeting.
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 joined the Polio Eradication Department. South Africa and Indonesia have submitted to GCC the second and third certificate of participation (CP) in the containment certification activities. WHA adopted resolution WHA71.16 on containment in May 2018. A meeting between the Chairs of national authorities for containment (NACs) and GCC Containment Working Group (CWG) members to discuss progress, gaps and needs with containment certification activities is planned at WHO in October 2018.

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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	Documentation and dissemination of lessons learned from polio eradication is one of the three objectives of transition planning. Through different initiatives (e.g. GPEI History Project,Johns Hopkins Curriculum Project, Multimedia Project, documentation of polio lessons-learned at the country level) contributions of frontline workers involved in polio eradication efforts are being captured. These projects involve 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.
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	This has been completed and the item may be archived.
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 the previous update, the PPCs for new tuberculosis and Group A streptococcus vaccines have been finalized and published on the PDVAC website. The PPC for Herpes Simplex Virus vaccine, and the first target product profile for a product in combination with a new delivery technology (MR vaccine with microarray patch) is near finalization.
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

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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	The Regulation and other health Technologies (RHT) aims to strengthen regulatory preparedness for public health emergencies through: • Strengthening of regulatory procedures for risk-based evaluations during public health emergencies (PHEs) • Reinforcing RHTs capacity to support regulatory preparedness for PHEs • Assist countries in adapting their regulatory requirements for PHEs and using networks for expedited assessments during PHEs The scope and activities for WHO regulatory work includes support for WHO's R&D Blueprint, development of technical guidelines and standards, Regulatory Systems Strengthening, Emergency Use Assessment and Listing (EUAL), Safety monitoring and ensuring communication and coordination with different stakeholders. RHT has mapped regulatory provisions for emergency clinical trial and marketing authorization in 40 countries In November 2017, RHT organised a tabletop exercise on regulatory preparedness in a simulated emergency setting. Several activities under the norms and standards have been implemented/planned as follows: • Publication of the Guidelines on the quality, safety and efficacy of Ebola vaccines endorsed by ECBS in May 2018 and implementation workshop is planned in 2019. • Discussion of the Guidelines of Nucleic acid based vaccines of importance for priority pathogens for PHE during the ECBS meeting October 2018. • A meeting of collaborative centers networks of vaccines for standardization of priority pathogens. Following Ebola outbreaks in DRC, RHT convened a meeting with regulators of the AVAREF in June 2018 to review and discuss key regulatory considerations to facilitate implementation of EUAL for Ebola vaccine. additional work is still ongoing. Regarding the Emergency Use Assessment and Listing (EUAL) procedure, the WHO Prequalification Team took note of recommendations made during a public consultation in May 2017 and also by SAGE and initiated revision of the EUAL. The main principles of the revision includes: • a pre-emergency phase to concentrate most of the assessment activities and allow a rapid decision when the emergency is declared and a post deployment monitoring phase • Involvement of NRAs responsible for oversight of the products and NRAs of potentially affected countries at different stages of the procedure The document will be shared with external stakeholders. WHO has continued working with CEPI, which support product development and CT phases 1 and 2 for vaccines for emerging pathogens, with as priorities Lassa fever, MERS and Nipah. WHO ensures liaison with CEPI via a Biostandard and Assay Working Group co-chaired by WHO and CEPI and via specific Task Forces for the 3 prioritized diseases. This work addresses in particular the need to coordinate between different donors and partners. CEPI funding should accelerate the development of reference standards and reference materials for vaccines in a two-stage approach with intern standards with fast-track development paving the way to the future adoption of WHO official standards. CEPI will also support a better coordination of the collection of clinical samples for emerging diseases, which should facilitate the development of products and standards

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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	WHO and NIBSC have been working on the plan for dissemination of the outcomes of the ECBS deliberations since the ECBS 2017 meeting. Workshops/ consultations on typhoid conjugate vaccines and RSV vaccines have been organized to explain the relevance of recently adopted WHO standards to the broader immunization community in 2018 and 2019. Publication of the articles on these topics as well as on a broader range of vaccine standards in relevant journals for immunization community is planned in 2019 and 2020.
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	The Essential Medicines and Health Products (EMP) department is holding an informal consultation of experts on "Guidelines on the quality, safety and efficacy of human Respiratory Syncytial Virus vaccines" in September 2018, which should lead to published guidelines for manufacturers by the end of the year. The EMP department has created a standard for a microneutralization assay, and is currently working on standardization assays for RSV antibodies. A Phase 3 trial of the Novavax RSV F protein 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. In contrast, Novavax announced that a planned informational analysis in December 2017 of a Phase 3 trial in late 2nd/early 3rd trimester pregnant women, using the same vaccine, was favorable, supporting trial continuation, with a planned interim analysis in Q1 2019, which could be the final analysis depending on the results. Other candidate RSV vaccines including pre-fusion F protein vaccines, gene-based vector vaccines and live, attenuated vaccines are in phase I and II clinical trials. Regarding long-acting mAbs, one product (MEDI8897) will complete phase IIb trial in late 2018, planning to undertake a phase III study in normal term infants in 2019. The WHO prequalification (PQ) department has begun a pilot for PQ of similar biotherapeutic products for the anticancer mAbs, rituximab and trastuzumab, as the test cases for PQ of mAbs for LMICs; the results of which could lead to a pathway for PQ of RSV mAbs in the future. 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. With funding support from the Gates foundation, WHO is supporting systematic reviews, impact modelling, and an expert consultation on evaluation of the long-term impact of early RSV infection on subsequent wheeze/asthma, with the objective of contributing to policy-related decisions regarding RSV vaccines/mAbs.
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, in collaboration with UNICEF. The guidance document "Establishing and strengthening immunization in the second year of life: Practices for vaccination beyond infancy" has now been published and is available online in English, French and Portuguese (http://www.who.int/immunization/documents/WHO_IVB_ISBN9789241513678/en/). 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.

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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. The Regulation and other health Technologies RHT is developing mechanisms to ensure timely deployment in countries of smallpox vaccines through development of a procedure that provides acceptable assurance of the quality, safety and efficacy of smallpox vaccines, providing technical assistance to WHO member states in building capacities for the import, registration and emergency use of smallpox vaccine and developing the capacity in member states to monitor, oversee, the safety of the vaccines for emergency use. A procedure for assessment of smallpox vaccine was developed as well as a safety monitoring guidelines. WHO is also mapping regulatory provisions for emergency use of medical countermeasures.
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	Review of the evidence for characterization of BCG strains for vaccine production is being conducted and will be reported in 2019.
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. In 2017, 131 (70%) of Member States reported existence of a NITAG with a formal legislative or administrative basis. In 2017, there were 98 Member States with a NITAG that met all six process indicators, which includes 66 low- and middle-income countries. This is a 58% increase compared to 2010 (and 16% since 2016), when only 41 countries reported having a NITAG meeting all six process indicators. These figures are included in the global report on a yearly basis. A specific NITAG session was held at the April 2017 SAGE meeting. NITAG side meeting are organized back to back to SAGE meetings.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
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 throguh 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 Linksbridge 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 Linksbridge 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. MI4A undertook its first market study on global availability of HPV vaccines to inform the WHO Call for Action on ELimination of Cervical Cancer

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Surveillance	SAGE endorsed the recommendations of the ad hoc TAG for improving the quality of the IB-VPD surveillance network and urged that the objectives of this network be more clearly defined, that collaboration with other surveillance systems and laboratory networks (i.e. the polio/measles laboratory networks) be continued, and that, where feasible, activities be linked with other programmes enhancing country capacity, including implementation of the International Health Regulations. SAGE urged greater attention to integration of data systems, which would facilitate real-time analysis and performance monitoring. SAGE also noted the opportunities for integration by building upon the enhanced capacity developed by these networks to conduct surveillance for other diseases using a similar case-definition and personnel trained in applying and adhering to rigorous surveillance protocols. Both networks should continue to share experiences with the polio surveillance network. Integration efforts must be strategically designed in ways that are logical and synergistic.	Nov 2013	Ongoing	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.

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	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. 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: - 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. This indicator aims to measure access to vaccines, including the newly available or underutilized vaccines, at the national level over the life course. Indicator was reported for DTP3, MCV2 and PCV3 in February 2018 and will be part of next SDG report.

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	WHO IVR, with the support from an TB vaccine expert working group, with further advise from PDVAC, continues to progress its activities on TB vaccine development. Several tuberculosis efficacy trial results are awaited in the coming months. H4/IC31 is an adjuvanted recombinant protein under development by Sanofi Pasteur, SSI and Aeras. A Phase II prevention of infection study in adolescents (Phase II) showed no significant protection against infection induced by H4/IC31. In the same trial, a secondary analysis showed indication that BCG revaccination induced moderate protection against sustained infection. Possible next steps following this observation are being discussed. 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 imminently. Secondary endpoints include safety and immunogenicity. 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. 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. Upon PDVAC recommendation, WHO has developed guidance on preferred product characteristics for TB vaccines, through a thorough consensus building consultation process including a vast stakeholder meeting organized late 2017 with support from the Bill and Melinda Gates Foundation. The document is now publically available through the WHO IVR website: http://www.who.int/immunization/research/development/tuberculosis/en/.
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	Work is ongoing in a number of areas to respond to this request: 1) Publication of the "Missed Opportunities for Vaccination" guide and related projects in a number of countries (see item 284). 2) Publication in 2016 of a companion document to the Global Vaccine Action Plan (GVAP) focusing on Routine Immunization entitled "Global Routine Immunization Strategies and Practices" (GRISP). 3) Publication of a range of resources to support demand and acceptance of vaccination, including health worker training materials on conversations with hesitant parents/caregivers, and addressing concerns regarding multiple injections and pain. 4) Coordination with regions on scaling up efforts to generate demand and acceptance, and to address hesitancy. This includes the 'Tailoring Immunization Programmes' approach, based on the original guide from EURO, which is increasingly being applied in countries worldwide.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccine coverage	SAGE recommended that WHO explore alternative survey methods to improve the precision, reduce the cost and improve the usefulness of survey results to national and local immunization programmes.	Nov 2011	Ongoing	To improve the 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 and published in 2018, see http://www.who.int/immunization/documents/who_ivb_18.09/en/. 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 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. In June-July 2018, a repeat of module A3, on survey analysis and interpretation was done. The French version of the distance-based Survey Scholar is planned for Q4 2018 to Q2 2019.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
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.
Vaccine coverage	WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage.	Nov 2011	Ongoing	Currently, WHO is developing global guidelines on conducting serosurvey studies on measles and rubella 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 and in Bhutan 2017; this latter 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. Also, give several advances in field of diagnostics mainly, the current draft is being revised in 2018 and is to be rolled out as a tool to evaluate the immune status of the target or targeted population.
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. At the March 2018 IVIR-AC meeting a proposal was presented for a WHO Guidance document on the standardization of delivery costing of vaccines to facilitate comparison of delivery costs across vaccines and to improve the quality of these costing tools/studies. Currently a Typhoid Costing Tool is under development to help countries to plan and costs the roll out of TC vaccines.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
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. There is now 1FTE at WHO HQ focused on this area, and a number of initiatives are now scaling up, both in terms of guidance being published on the WHO Vaccine Hesitancy web page, as well as jointly coordinated initiatives with UNICEF and CDC. 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 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. In June 2018, Martins et al. published 8 year follow-up immunogencity data from a YF vaccine dose finding study in military personal, with very encouraging results. Fractional dose was extensively used during 2018 campaigns in Brazil, which will allow to gather more data on programmatic aspects and safety.
Yellow fever routine immunization and surveillance	Update needed on efforts to strengthen YF surveillance and routine immunization in context of EYE strategy	Apr 2018	Ongoing	

MEETING REPORT

REGIONAL IMMUNIZATION TECHNICAL ADVISORY GROUP (RITAG)

KIGALI, RWANDA
29TH AND 30TH JUNE, 2018

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ACRONYMS

ADI	*Addis Ababa Declaration on Immunization in Africa*
AFRO	*African Regional Office*
AFP	*Acute flaccid paralysis*
AGE	*Acute Gastroenteritis*
ANC	Ante-natal care
AVAREF	*African Vaccine Regulatory Forum*
BMGF	*Bill and Melinda Gates Foundation*
bOPV	*Bivalent oral polio vaccine*
CDC	*US Centers for Disease Control and Prevention*
cMYP	Comprehensive multiyear plans for immunization
CRS	Congenital Rubella Syndrome
CSF	Cerebrospinal Fluid
CSO	Civil society organizations
CTC	Controlled Temperature Chain
cVDPV	*Circulating vaccine-derived poliovirus*
DHF	*Dengue Hemorrhagic Fevers*
DHS	Demographic and Health Surveys
DOPV	Directly Observed Polio Vaccination
DQS	Data quality self-assessment
DQWG	Data Quality Working Group
DTP	Diphtheria-tetanus-pertussis [vaccine]
EPI	Expanded Programme on Immunization
EYE	Elimination of Yellow Fever Epidemics
FRH	Family and Reproductive Health
Gavi	Global Alliance for Vaccines & Immunization
GIS	Geographic Information systems
GPEI	*Global Polio Eradication Initiative*
GPS	Geospatial positioning system
GVAP	Global Vaccine Action Plan
HPV	Human Papilloma Virus Vaccine
HR	High Risk
HSS	Health systems strengthening
ICC	Inter-Agency Coordinating Committee
IDSR	Integrated Disease Surveillance & Response
IMCI	Integrated Management of Childhood Illness
LMIC	Low and middle income countries
LQA	Lot Quality Assurance
MCIA	Ministerial Conference on Immunization in Africa
MCH	Maternal and Child Health
MCV	Measles-containing vaccine
MCV1	First dose of MCV
MCV2	Second dose of MCV
MNT	maternal and neonatal tetanus
MOF	Ministry of Finance
MOH	Ministry of Health
mOPV	*Monovalent oral polio vaccine*
MOV	Missed Opportunity for Vaccination
MR	Measles-rubella [vaccine]
MSF	Médecins sans Frontiers
NGO	*Non-governmental organization*
NIDs	*National Immunization Days*
NITAG	*National Immunization Technical Advisory Group*
NNT	*Neonatal tetanus*
NRA	*National Regulatory Authority*
OPV	*Oral polio vaccine*
PAB	Protection at birth
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PCV	Pneumococcal conjugate vaccine
PID	Pneumococcal invasive disease
PIVI	Partnership for Influenza Vaccine Introduction
RCV	Rubella-containing vaccine
RED	Reaching Every District Approach
RITAG	Regional Immunization Technical Advisory Group
RV	Rotavirus Vaccine
SAGE	Strategic Advisory Group of Experts on immunization
SIAs	Supplementary Immunization Activities
tOPV	*Trivalent oral polio vaccine*
RITAG	Task force for Immunization
TBA	Traditional Birth Attendants
TT	Tetanus toxoid
VCMs	*V*olunteer community mobilizers
VHF	*Viral Hemorrhagic Fevers*

JRF	The WHO UNICEF Joint Reporting Form	*VPD*	*Vaccine Preventable Disease*
		YF	*Yellow Fever*
UNICEF	United Nations Children's Fund	*WHA*	*World Health Assembly*
LGA	*Local Government Area*	WHO	World Health Organization
		WPV	*Wild poliovirus*

EXECUTIVE SUMMARY

The Regional Immunization Technical Advisory Group (RITAG) met in Kigali Conference Centre, Kigali, Rwanda from 29th to 30th June 2017 for its first ordinary meeting of the year. Dr Felicitas Zawaira, Director, Family and Reproductive Health, WHO AFRO, welcomed the participants on behalf of the Regional Director, Dr Matshidiso Moeti. She also declared the meeting open. Present at the opening was the Honorable Minister for Health, Rwanda, the WHO Country Representative for Rwanda and representatives of other UN agencies and immunization partners in Rwanda. In the subsequent sessions were immunization partners and donors as well as representatives of civil society organizations, immunization staff from the countries and various levels of WHO (ISTs, Regional Office and Immunization and Polio Directors from HQ).

The primary goals of the meeting were to update the RITAG members on progress made in the programme, current priorities as well as levels of achievement of the recommendations from the previous RITAG meetings and to seek their advice and guidance on current specific challenges and programme plans and activities. Some of the recent priority areas in immunization in the African Region were discussed in sessions of the meeting after the brief presentations made by the secretariat. In these sessions, the progress made was summarized, challenges highlighted and the RITAG members given the opportunity to discuss and to provide advice. At the end, a number of key recommendations were made.

Recommendations

TYPHOID:

Preamble

The global estimates of typhoid fever burden are very high with South/South East Asia and Sub-Sahara Africa bearing the highest disease burden including deaths. Studies have shown that children are disproportionally affected with a peak incidence between 5 and 15 years of age. Risk of dying is highest among children reaching up to 20% where antimicrobial resistance (AMR) to S. Typhi exists or where antibiotics are not available. The risk factors for this disease include lack of safe water, inadequate sanitation and hygiene especially among food handlers and overcrowding. In addition to affected communities, at risk groups include health care workers and laboratory staff. WHO recommends that typhoid vaccination should be implemented in the context of other control strategies including improved access to safe water, adequate sanitation and appropriate personal and food hygiene.

Emergence of AMR to S. Typhi is a security threat with resistance to ampicillin, chloramphenicol, cotrimoxazole, fluoroquinolones, cephalosporins having been reported in Sub Sahara Africa thus requiring serious consideration of additional interventions such as typhoid vaccination.

RITAG, in providing the recommendations below, considered also the following;

- the magnitude of typhoid and other enteric fevers in the African region where the burden of disease is one of the highest
- the WHO/SAGE position and recommendations on the typhoid vaccine and vaccination
- the GAVI board decision to provide support

RITAG Recommendations

1. WHO AFRO to prioritise the development of a comprehensive multi-sectoral plan for control of typhoid and other water-borne/faeco-oral diseases (including safe water and sanitation).

2. Countries to implement comprehensive, multi-sectoral approaches to typhoid control including food safety, provision of safe water, promotion of improved hygiene and sanitation especially among food handlers.

3. For countries with data indicating a high disease burden or a high burden of AMR:
    a. Introduction of TCV 0.5ml, single dose, intramuscular into the routine immunization programme along with measles vaccine at 9 months or in the second year of life, with possibility of catch-up campaigns up to 15 years.
        i. Countries should consider sub-national introductions in the highest risk areas with or without catch-up campaigns.
        ii. Post TCV introduction, countries should strengthen post-marketing surveillance monitoring and safety in special groups, such as malnourished children.

4. For countries with inadequate data/potentially large disease burdens
    a. To prioritize strengthening surveillance and research on disease burden (including but not limited to data on geographical distribution, drug resistance, and risk factors) to make the case for vaccine introduction.
    b. WHO AFRO should support the use of the WHO surveillance standards for typhoid fever and other invasive salmonella diseases (press here) to generate better quality data on disease burden and antimicrobial resistance.

5. In outbreak situations
    a. The use of vaccination in response to confirmed outbreaks of typhoid fever

6. In emergency situations
    a. Countries to prioritize provision of safe water and promotion of improved hygiene and sanitation especially among food handlers. Typhoid vaccination may be considered within the framework of implementation research. Countries are encouraged to use the "WHO framework for decision making in the use of vaccines in humanitarian settings" as a guide for risk assessment.

7. Evidence gaps/Research
    a. WHO AFRO to guide and support priority research on TCV to generate evidence:
        i. of vaccine effectiveness and impact in Africa including mathematical modelling and cost effectiveness analyses
        ii. on safety and immunogenicity in special populations such as malnourished children, immunocompromised individuals and co-administration with other vaccines
        iii. on use of typhoid vaccines for outbreak control and assess the effectiveness of preventive and reactive vaccination campaigns including duration of protection and need for revaccination for outbreak control and emergency settings

8. RITAG will follow up on results of ongoing impact studies in Malawi, Nepal and Bangladesh when they become available and may review these recommendations should the need arise.

INFLUENZA:

Preamble

Influenza occurs globally with an annual attack rate estimated at 5-10% in adults and 20-30% in children. Seasonal epidemics occur mainly during winter in temperate climates and year-round in tropical regions. The mortality rate of seasonal flu in sub-Saharan Africa of 2.8 -16.5/100 000 is similar to that in other regions. Influenza A viruses may also cause worldwide pandemics at intervals of 10 - 40 years. The last pandemic occurred in 2009.

Influenza disease is not considered a priority by most African countries. Only three countries have a policy for influenza vaccination. Less than one percent of global seasonal influenza vaccines produced is used in Africa.

Although many countries may depend on regional/sub-regional data to assess the overall epidemiological situation, individual national decisions on influenza vaccine use will be determined by national capacity and resources. Country-specific information about risk groups, disease burden and cost-effectiveness are important for national policy makers and health programme planners to make informed decisions.

For countries considering the initiation or expansion of programmes for seasonal influenza vaccination, WHO recommends that pregnant women should have the highest priority. Additional risk groups to be considered for vaccination are children aged 6–59 months, the elderly (>65 years), individuals with specific chronic medical conditions (such as HIV, asthma, and chronic heart or lung diseases), and health-care workers.

Influenza surveillance platforms are critical for monitoring and communicating the impact of introducing seasonal influenza vaccination. In the AFRO region, 31 countries currently have capacity for influenza PCR surveillance.

Strengthening of seasonal influenza vaccination programmes may assist in programmatic preparedness for pandemic vaccine introduction and should be considered by countries.

The Partnership on Influenza Vaccine Introduction (PIVI) is a public-private programme supporting the introduction sustainable, routine, seasonal influenza vaccination programmes in low- and middle-income countries.

RITAG Recommendations:

Noting the 2012 WHO/SAGE recommendation on Seasonal Influenza vaccination, RITAG recommends that AFRO countries who:

1. Are not using the current Pandemic Influenza Preparedness framework, should consider adopting this approach to frame their response to the threat of pandemic influenza.

2. Have introduced the seasonal influenza vaccine, should also use the opportunity to prepare programmatically for pandemic influenza.

3. Have introduced or are considering the introduction of seasonal influenza vaccine should prioritize the vaccination of pregnant women. Extension to additional high-risk groups such as HIV positive individuals is encouraged and should be based on local evidence where available and priority setting.

4. Have local epidemiologic data on influenza but have not introduced seasonal influenza vaccine should be supported by WHO to analyze the data, and use local data to advocate and communicate the need for the vaccine to policy-makers.

5. Are currently not collecting epidemiologic data on influenza should consider standardized data collection on seasonal influenza within the context of an integrated surveillance system.

General

6. Noting that NITAG strengthening for influenza vaccine introduction is being offered in some countries, we encourage this initiative to extend their support to NITAGs in a holistic manner beyond influenza vaccine alone to overall strengthening of NITAG's capacity to efficiently support other vaccine introductions.

7. WHO should ensure effective community engagement as part of influenza vaccine introduction and as an integral component of managing future outbreak response.

Possible Research Questions

8. How can service delivery of influenza vaccine in difficult to reach high risk groups, e.g., the elderly, best be managed?

9. How can vaccine hesitancy in health care workers be overcome?

EBOLA

Preamble

Disease outbreaks are occurring more frequently in the region and constitute a major public health problem requiring a major emergency response from countries with the support of WHO and partners. During the large outbreak of ebola in west Africa, efforts were made to develop and to test vaccines and therapies against the disease. One of the candidate vaccines, rVSV, was successfully tested in a phase II clinical trial in Guinea using a ring vaccination design. In the recent outbreak in Equateur Province of the DRC, the same vaccine was deployed under the SAGE recommendation of experimental compassionate use. Given that neighboring countries, especially those at risk, have requested the use of the vaccine and noting the operational challenges associated with its use, RITAG recommends the following:

RITAG Recommendations

WHO/AFRO to:

1. Using the current Pandemic Influenza Preparedness framework, develop regional response procedures and guidelines for oversight and use of vaccines and therapies in the event of Ebola outbreaks. Similar procedures and guidelines to be developed for Chikungunya, Lassa, Marburg, etc.

2. Assist high risk AFR countries to develop national regulatory preparedness response plans that includes timely requests for Ebola vaccines and WHO emergency funds. Priority should be given to endemic countries, and second priority for countries neighbouring endemic countries.

3. Compile and analyze lessons from recent outbreaks (West Africa, DRC) in order to develop guidance concerning:
    - regulatory preparedness for vaccine use utilising the African Vaccine Regulatory Forum (AVAREF);
    - community involvement and response;
    - implementing containment vaccination;
    - on-going vaccine safety monitoring.

4. Encourage countries where vaccine has been deployed to use residual stocks before expiry to vaccinate more HCWs and incorporate them fully into the clinical protocol.

5. Explore ways to strengthen AVAREF both technically and with additional resources to expand its capacity to provide increased support to NRAs and national Ethics Committees throughout the AFR region.

6. Communicate with industry the urgent need to secure licensure (and eventually seek WHO prequalification) of the Ebola candidate vaccines for which clinical data are available.

POLIO

Preamble:

Wild poliovirus remains endemic in three countries – Afghanistan, Pakistan and Nigeria. Until poliovirus transmission is interrupted in these countries, all countries remain at risk of importation of polio, especially vulnerable countries with weak public health and immunization services. In Africa the latest wild poliovirus (WPV) case was reported in August 2016 in north eastern state of Borno in Nigeria. Access to the Lake Chad region and the islands in Lake Chad remain a concern despite some inroads being made by the Nigerian military. The tOPV-bOPV switch was carried out in the region from April-May 2016. Unfortunately, after this switch, circulating vaccine derived poliovirus type 2 (cVDPV2) cases have been reported in Nigeria from the environment in 2016 for which monovalent OPV type 2 (mOPV2) was used for the response. In 2017, DR Congo reported 35 cVDPV cases from 3 provinces. By 10 September 2018, DR Congo reported 17 cVDPV2 cases in 5 provinces while Nigeria reported 8 cases in 3 states. From environmental surveillance, 34 cVDPV2s where detected in Nigeria as well as one cVDPV2 detection in Kenya. In responding to these cVDPV2 cases in these countries, mOPV2 has been used. The poor quality of the response campaigns in DR Congo and low routine

immunization coverage has contributed towards the continuous spread of the outbreak since early 2017. It is important to note that these polio outbreaks and responses are occurring at a time when polio ramp down is being implemented and transition plans are being finalized. Having presented the above context, the RITAG formulated the following recommendations:

Country specific recommendations:

The RITAG has noted with great concern the geographically diverse outbreaks of cVDPV that are ongoing in **DR Congo**, the lack of quality in SIAs, and lack of financing for some response activities. The RITAG further noted the weakness of the RI and the surveillance systems in the country. The RITAG therefore request:

1. The WHO/AFRO RD to consider whether high level intervention (RD to President) could strengthen country commitment toward quality outbreak response.

2. The WHO/AFRO RD to advocate for stronger partners coordination, to ensure timely release of funds by both partners and government for outbreak response activities including strengthening RI.

3. The Country to improve the quality of the outbreak response (scope, microplanning, implementation and monitoring).

4. WHO to consider whether operational research might assist the country in understanding why multiple cVDPV outbreaks are occurring in the region.

Lake Chad Region:

5. Noting the weakness of surveillance and immunization coverage in the Lake Chad region, Nigeria should be asked about timelines for access to all islands in Lake Chad on the Nigeria side.

GPEI extension plan (2020-2022) and Transition plans:

At the global level GPEI is applying for funds to cover transitional activities from 2020 – 2022. The 7 priority countries, except Nigeria, have completed polio transition planning. However, the implementation requires clear guidance on next steps, and the commitment of governments to the required activities and to co-funding before raising fund from donors.

1. Frame both the Extension Planning and Transition plans within the context of RI strengthening and integrated PHC services.

2. Develop a high-level advocacy programme driven by the WHO Regional Director to mobilize country and donor resources, and a communication strategy informed by all stakeholders including CSOs on what ending polio means.

3. Ensure that transition plans focus on RI and VPD surveillance as well as essential polio functions.

4. Guide and advocate to the 6 countries that have completed their polio transition planning to ensure that the plan has senior level oversight in the MoH and beyond and is implemented with a clear commitment of phased in domestic resources within the next six months.

5. Present an update of the implementation of transition plans using the monitoring dashboard to every RITAG meeting to monitor progress and make recommendations that address bottlenecks.

OPERATIONAL RESEARCH

Preamble:

Research is increasingly assuming position of centrality in the delivery of public health interventions globally. However, in the African Region there have been low research activities in immunization due to a number of constraints, including low research interests and capacity. Consequently, the RITAG called for a Strategic Framework for Research on Immunization (SFRI) in the African Region that will provide immunization stakeholders with guidance to facilitate scientifically rigorous, coordinated research that addresses immunization priorities of the African countries.

A draft SFRI was presented, discussed and endorsed with the following recommendations:

WHO AFRO to:

1. Promote immunization research capacity strengthening in the African Region.
2. Promote linkage between research institutions, the AFRO office and immunization programmes in the African Region, and through this activity keep an audit of ongoing and completed research undertaken in the region.
3. Advocate for adequate immunization research financing in the African Region.
4. Encourage partners and governments to organize biennial conferences on immunization research in Africa to:

    - Celebrate immunization research in Africa;
    - Share and exchange research findings and ideas;
    - Facilitate collaboration among researchers;
    - Stimulate immunization research among young researchers: and
    - Attract potential donor interested in funding research in Africa

1.0 BACKGROUND

This is the first of the two scheduled regular meetings of the Regional Technical Advisory Group (RITAG) on immunization in the African Region in 2018. The goal of this meeting was to appraise the performance of the immunization programme since the last meeting in December 2017, which held in Johannesburg South Africa. Consequently, the status of implementation of the action points from the last meeting was among the item scheduled to be reviewed along with the review of other programme implementation activities. The level of progress and challenges were also marked for review with suggestions given for remedial actions where necessary.

Specifically, the meeting was called to among others things apprise RITAG members on level of successes in implementation of the recommendations from the last meeting. The broad topics discussed include polio eradication and endgame strategy in the African Region. This has been a standing agenda item for the RITAG in the recent past, given the timeline for the eradication of polio in the Region. Other topic discussed included vaccines issues for influenza, typhoid and Ebola. The RITAG also received the final version of the strategic framework for research on immunization in the African Region. This was first presented to the RITAG in the December 2017 meeting, where suggestions were made for its finalization. The RITAG endorsed it for use after this presentation.

This report presents a detailed account of the meeting and its key achievements.

2.0 OPENING CEREMONIES

Dr Felicitas Zawaira, Director, FRH, WHO/AFRO

Dr Zawaira welcome remarks on behalf of Dr Matshidiso Moeti, WHO Regional Director for Africa. In her welcome remarks, Dr Zawaira highlighted the immeasurable value that immunization brings to children, families, communities and economies stating that, by vaccinating children, we go beyond saving lives – we also protect their education, return precious time and money to their families, a make critical investments in future prosperity.

She emphasized that immunization is an important building block of strong primary health care and universal health coverage and that if Africa curbs 4 major vaccine preventable diseases by 2030, we will avert more than 167 million cases of disease and generate US$58 billion in economic benefits.

Dr Zawaira also informed participants that the *Business case for WHO immunization activities on the African continent 2018-2030* was recently launched in May 2018 at the World Health Assembly in Geneva, which maps out how WHO will better support countries to strengthen their national immunization programmes.

In her closing statement, Dr Zawaira urged immunization stakeholders to continue to strengthen linkages between immunization funding and national priorities, and formulate policies that support immunization and health system development. She also advised RITAG members to place emphasis on integration of activities to support the overall strengthening of the health system which, in the long-run, will sustain regional immunization targets.

Introductory Remarks by Helen Rees, RITAG Chair

In her introductory remarks, Professor Rees welcomed RITAG members and immunization stakeholders to the RITAG meeting and thanked everyone for taking time to attend the RITAG meeting – especially given the meeting took place over the weekend to accommodate the Global Immunization Meeting.

Prof Helen Rees, Chair of RITAG

Professor Rees emphasized the importance of ensuring the RITAG remains beneficial to the Region and requested RITAG members to review past SAGE recommendations and ensure to interpret them to be significant to the WHO African Region. She also requested RITAG members to play an active role in being regional immunization advocates under the umbrella of the Global Health Security Agenda and Universal Health Coverage.

Professor Rees highlighted key outcomes of the recently concluded Global Immunization Meeting which focused on post-2020 immunization priorities, with the theme of navigating transitions – particularly polio and Gavi transitions. She expressed the importance

of emphasizing the success of the immunization programme to date and linking this success to protecting children, families and communities under the Global Health Security Agenda.

In her closing remarks, Professor Rees walked participants through the 2-day RITAG agenda stating: the need to strengthen influenza surveillance in the African region as well as NITAG capacities for influenza vaccines decision-making; steps that need to be taken to ensure countries are readily prepared to introduce the typhoid-conjugate vaccine; the remaining risks within the region to attain polio eradication status; and learn of the Ebola vaccine candidates under clinical development and the outbreak experience of using rVSV ZEBOV in ring vaccinations in Guinea and DRCongo.

Opening Remarks by Minister of Health, Rwanda

The Minister opened the meeting by welcoming all participants to Rwanda on behalf of the Government of Rwanda. She emphasized the importance of taking an integrated multi-sectoral approach to immunization stating that strengthening the routine immunization programme will bolster the overall health system and accelerate progress towards Universal Health Coverage.

Honourable Minister of Health, Rwanda

The Minister highlighted 3 key factors that have continued to Rwanda attaining and sustaining their immunization coverage level – namely: strong political commitment for all levels of government; the fundamental role that community health workers play in attaining health development goals; and using mobile technology to attain public health targets – including immunization. All three factors assisted the Government of Rwanda in sustaining their immunization coverage to over 95%, assisted in successfully introducing new vaccines into their routine immunization programme; and reducing the overall burden of vaccine-preventable diseases in Rwanda.

The Minister concluded her opening remarks by urging all immunization stakeholders to redouble efforts to attain universal immunization coverage by developing a sustainable immunization programme in each country.

Dr Richard Mihigo, Coordinator, IVD Programme, WHO/AFRO

On his part, Dr Richard Mihigo took participants through the programme of work for the two days. He noted that the work will extend into Saturday. At this point, he acknowledged the tremendous sense of responsibility on the part of the RITAG members and their commitment to the immunization programme in the African Region

He expressed his hope that with this commitment on the part of the RITAG members and the Secretariat, the meeting objectives will be reached as planned.

Participants at the June 2018 RITAG Meeting in Kigali, Rwanda

3.0 TECHNICAL SESSIONS

3.1 Overview

The meeting assessed the epidemiology of selected vaccines preventable diseases and the capacity of the immunization programme in the African Region to delivering products and services to protect the populations of Africa, and indeed the world against these diseases. It also provided opportunities to discuss challenges and seek expert orientation, from the RITAG members, on how to better deliver on WHO mandate to the people of the region and the world. Of particular interest were broad issues like polio eradication and endgame strategy in the African Region as well as building resilient vaccine preventable disease surveillance in the African Region. Others issues focused vaccines for influenza, typhoid and Ebola. The meeting also received and endorsed the strategic framework for research on immunization in the African Region. about immunization coverage and introduction of the human papillomavirus vaccine (HPV) in the African Region.

A total of 16 technical presentations were made. One of these, on the status of implementation of RITAG recommendations was for information while 15 were made for RITAG decision and recommendations. The presentations provided participants with the necessary background information on the status of immunization and key vaccine preventable diseases (VPDs) in the African Region. Some of the presentations were from colleagues from the WHO/HQ which were on plans to improve on issues concerning VPD, globally, including the African Region as well as colleagues from WHO Regional Emergencies.

The presentations were followed with discussions leading to actionable recommendations. The presentations, highlights of subsequent discussions and the recommendations are summarized below.

3.2 Information

Update on Status of implementation of RITAG Recommendations

Dr Masresha Balcha, WHO/AFRO

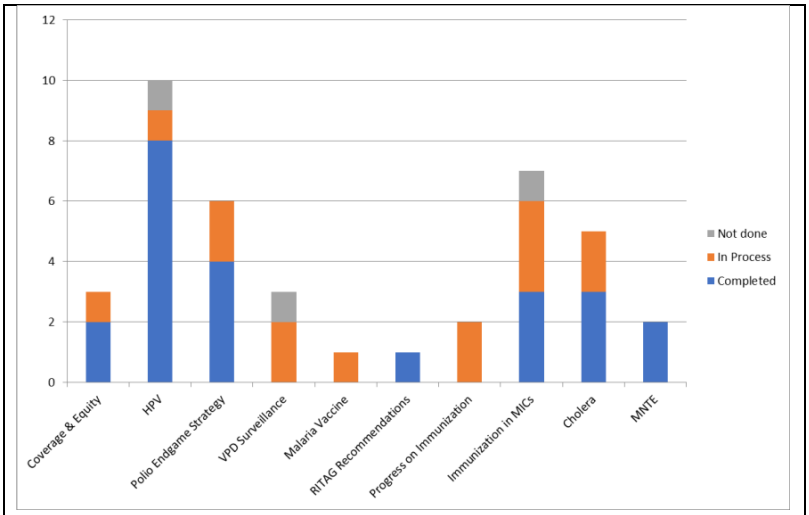


Figure 1: Status of implementation of RITAG recommendations from December 2017

There were 42 actions in 10 domains (see Figure 1). Of these, 25 were fully achieved. Another 14 were in progress, being actions to be taken on a continuous basis. Three other actions were not done at these. The three unimplemented actions are in the areas of VPD surveillance, HPV and MICs. Specifically, for HPV, The WHO recommendation for 3 doses of HPV vaccine for HIV infected girls should be implemented has not started. However, discussions started between Global Fund and Gavi to implement the 3 dose schedule for HIV positive girls. On VPD surveillance, WHO/AFRO is yet to convene a consultative platform to discuss future VPD surveillance priorities and funding needs with diverse stakeholders. However, this has been scheduled for October – November 2018, once the investment case is in an advanced stage. And on immunization and vaccine access in the Middle Income Countries (MICs), the recommended consultative study to explore the potential of pooled vaccine procurement; and identify and address potential barriers to the development of such mechanisms and potential solutions is yet to be implemented.

Discussing this, RITAG members commended the steps taken in the implementation of the recommendation. They noted that it is almost feasible to quantify the activities and measure progress. However, it was still suggested that RITAG members make recommendation with identifiable and measurable indicators for future assessment.

3.3 For Discussion and Decision

3.3.1 Influenza vaccines

Influenza burden and surveillance in the WHO African Region

Belinda Herring, WHO/WHE

Influenza occurs globally with an annual attack rate estimated at 5-10% in adults and 20-30% in children. Seasonal epidemics occur mainly during winter in temperate climates and year-round in tropical regions. The mortality rate of seasonal flu in sub-Saharan Africa of 2.8 -16.5/100 000 is similar to that in other regions. Influenza A viruses may also cause worldwide pandemics at intervals of 10 - 40 years. The last pandemic occurred in 2009.

The WHO Pandemic Influenza Preparedness Framework is an international arrangement that aims to improve global pandemic influenza preparedness and response. The Framework brings together Member States, industry, civil society, member states and other stakeholders.

Delivery strategies for influenza vaccines

Joachim Hombach, WHO/HQ

Influenza vaccine introduction and routine use remains an important component of influenza pandemic preparedness. Unfortunately, influenza disease is not considered a priority by most African countries. The use of influenza vaccine is highly biased to three regions, and reflects availability of national policies. Only three countries have a policy for influenza vaccination. Less than one percent of global seasonal influenza vaccine produced is used in Africa. As of 2015, only 115 of 194 countries had influenza vaccine introduced into their national immunization programs. The Seasonal influenza vaccine dose distribution (2015) is more than 250 per 1000 population in the Americas but less than 10 per 1000 in Africa.

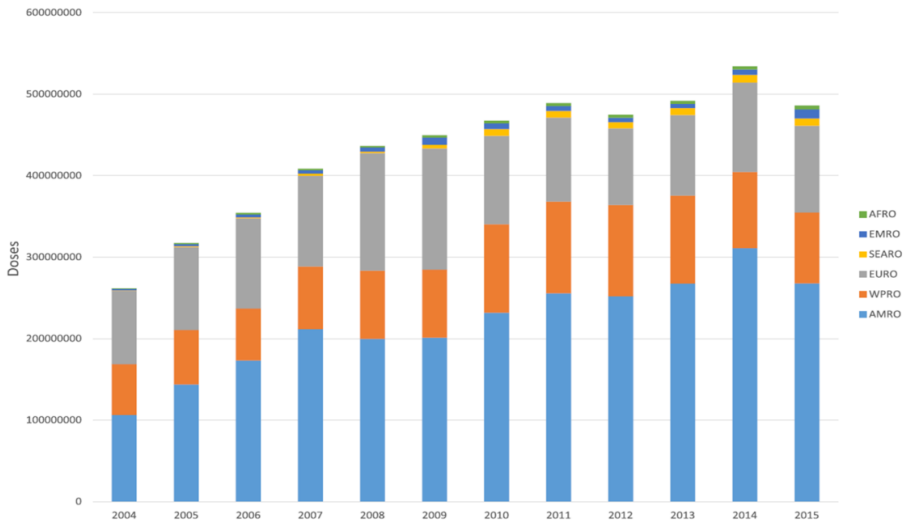


Figure 2: Vaccine doses distributed by WHO regiona 2004-2015
Source: A Palache et al, Vaccine 2017

WHO recommends that pregnant women should have the highest priority in countries considering the initiation or expansion of programmes for seasonal influenza vaccination,. Additional risk groups to be considered for vaccination are children aged 6–59 months, the elderly (>65 years), individuals with specific chronic medical conditions (such as HIV, asthma, and chronic heart or lung diseases), and health-care workers. Risk groups for influenza in low- and middle-income countries are less well defined.

The vaccination of specific risk population, especially pregnant women and HCWs seem to offer particular benefits with regards to vaccine efficacy and feasibility of delivery. Maternal influenza immunization project of WHO has provided a set of tools and guidance's to specifically support vaccine introduction in low resource settings. Evaluations following the introduction of influenza vaccine helped identify challenges including: the need for clarifying the roles and responsibilities of all the actors involved in the planning and management of influenza vaccination; the need for appropriately defining target denominators, for triangulating coverage data with the number of vaccine doses distributed and for including vaccine doses administered in the private sector; and the need to strengthen AEFI surveillance mechanisms

Influenza surveillance platforms are critical for monitoring and communicating the impact of introducing seasonal influenza vaccination. In the AFRO region, 31 countries currently have capacity for influenza PCR surveillance.

Strengthening NITAG capacities for influenza vaccines decision-making

Blanche Anya - AFRO

Detailed information was provided on the 3 countries (Mauritius, South Africa and Cote d'Ivoire) that reported having policies on Influenza vaccination, as well as on the training conducted in Cote d'Ivoire to strengthen capacity of their NITAG. The Partnership for Influenza Vaccine Introduction (PIVI) was presented as an opportunity to strengthen NITAG in Cote d'Ivoire and to support KAP studies in 3 countries (Cote d'Ivoire, Kenya and Uganda) to assess acceptability of the influenza vaccines.

During the discussion, RITAG members noted the huge gap in the uptake of influenza vaccines in the continent, there is a need for more advocacies and for the RITAG to prioritize its uptake in the African Region. The strategy for prioritization should be agreed upon (regional vs country by country prioritization). They requested to understand better the burden of the disease to make the case and through implementation of integrated surveillance around IDSR.

RITAG appreciated the opportunity of the PIVI to strengthen NITAG, however, they noted this was a missed opportunity if the NITAG capacity building activities conducted by PIVI was focused on the single influenza disease and recommended a more holistic approach taking into account other diseases, among others.

3.3.2 TYPHOID

Global & regional typhoid fever disease burden

Kashmira Date, CDC

This highlighted the causes of Typhoid and Paratyphoid (Enteric) fevers whose diagnosis is by bacterial culture with the gold standard being bone marrow culture but not feasible in most settings. Currently, blood culture is the primary diagnostic standard and Widal test, although used in several settings, is not a recommended diagnostic measure. The presentation also highlighted the global burden of typhoid fever as well as various studies in Africa that have underscored the high disease burden of Typhoid in the region.

Year	Global	Sub-Saharan Africa
1986	12.5 million	-
2004	21.65 million typhoid cases 5.41 million paratyphoid cases 216,500 typhoid deaths	409,000 typhoid cases 102,000 paratyphoid cases 4,100 typhoid deaths
2010	Adjusted Estimates 11.9 million typhoid cases, 129,000 typhoid deaths	Adjusted Estimates 3.1 million typhoid cases 33,500 typhoid deaths
2014	17.8 million cases in LMICs Incidence: 283/100,000/yr	7.2 million cases Incidence: 762/100,000/yr
2016	15.5 million cases of typhoid and paratyphoid 153,400 deaths	1.8 million cases of typhoid and paratyphoid 21,500 deaths

Figure 3: Global versus Africa – Enteric Fever Disease Burden Estimates, 1986-2016

Typhoid conjugate vaccines: updated recommendations and policy implications

Adwoa Bentsi-Enchill, WHO/HQ

This presentation gave a background of the various licensed typhoid vaccines and the recently WHO pre-qualified Vi-TT typhoid conjugate vaccine (Typbar-TCV™) manufactured by Bharat Biotech, India. WHO recommendations for the use of typhoid conjugate vaccine, published in a WHO Position Paper in March 2018, include the recommendation for primary vaccination with a single IM dose for infants and children from 6 months of age and adults up to 45 years in typhoid endemic regions. Routine programmatic use at 9 months of age, or in the 2nd year of life is feasible given that co-administration of Typbar-TCV with measles and MMR has shown non-interference of anti-Vi IgG and anti-measles IgG. Catch up vaccination to 15 years of age is also recommended when feasible and supported by epidemiological data.

Figure 4: Vi-TT (Typhar – TCV™ by Bharat Biotech)

The introduction of TCV is to be prioritized in countries with the highest burden of typhoid disease or a high burden of antimicrobial resistant *Salmonella* Typhi. Vaccination has also been recommended in response to confirmed outbreaks and in the context of an outbreak response countries should consider introduction/strengthening of routine immunization.

Update on considerations for TCV introduction and Gavi support to eligible countries ***Pascal Bijleveld, Gavi***

Figure 5: One product that received WHO Prequalification
Source BMGF/Sam Reinders; Bharat Biotech Ltd

The Gavi Board approved the opening of a funding window for typhoid conjugate vaccines in December 2017. Given the heterogeneous nature of typhoid, countries will have the option to choose the most feasible vaccination strategy. However, Gavi will provide support for 1 dose delivered in the routine immunization programme and a one-time single dose catch-up of children up to 15 years of age. Gavi will also finance relevant grants to ensure successful implementation (Vaccine Introduction Grant and operational costs). Gavi will not finance a vaccination strategy based only on catch-up and a routine immunization strategy must be pursued at minimum.

It is also important to note that countries have an option to pursue a risk-based (sub-national) introduction; however, this should be carefully evaluated on risks / benefits and supported by epidemiological, operational and other considerations as per the WHO Position Paper..

Country preparedness for typhoid conjugate vaccines

Aziza Mwisongo, PATH

The Typhoid Vaccine Acceleration Consortium (TyVAC) is led by the Center for Vaccine Development at the University Of Maryland School Of Medicine, the Oxford Vaccine Group at the University of Oxford, and PATH and funded by the Bill & Melinda Gates Foundation.

TyVAC is working to;

- Identify countries for possible early introduction of TCVs in Africa.
- Support existing country decision-making and program preparation processes to secure a positive policy decision.
- Support preparation activities for TCV introduction following policy decision

Figure 6: TyVAC's multidisciplinary strategy to combat typhoid

During the discussion that followed, RITAG members underscored the importance of availability of blood-culture based surveillance data and country-specific burden data prior to vaccine introduction.

3.3.3 Immunization Research

Strategic framework for research on immunization in the WHO African region: Report from the RITAG Working Group

Joseph C. Okeibunor, WHO/AFRO

The presenter gave a brief recap of the development of the framework. A significant point was that following the presentation of the draft framework in December 2017, the RITAG made a number of recommendations. Furthermore, he also noted that a RITAG WORK Group was set up to finalize the framework.


Figure 7: RITAG Working Group on Completion of the SFRI

He proceeded to enumerate the comments and recommendations of the RITAG on the Framework during its December 2017 meeting in Johannesburg, South Africa.

He also showed the steps taken by the RITAG Working Group on the SFRI to address the comments and recommendations in the revised version. Every concern raised by the RITAG was carefully addressed and the group futher introduced new elements to improve on the usefulness of the document.

Proposed recommendation on the SFRI from the RITAG working group

Rose Kambarami, RITAG Member

The presenter called for the endorsement of the Strategic framework, with its three thematic areas of priority researches, in view of the efforts for the working group to effectively address the concerns of the RITAG. She also highlighted the further improvements made on the SFRI as well as recommendations for the consideration of the RITAG members. These recommendations from the RITAG working group on the SFRI were group under two main area, namely research financing and coordination. On research financing, she noted that countries should, in addition to complying with the Abuja, Algiers and Bamako declarations on research funding, explore other financing mechanisms for research. It also called for strong partnership to address and fund research priorities.

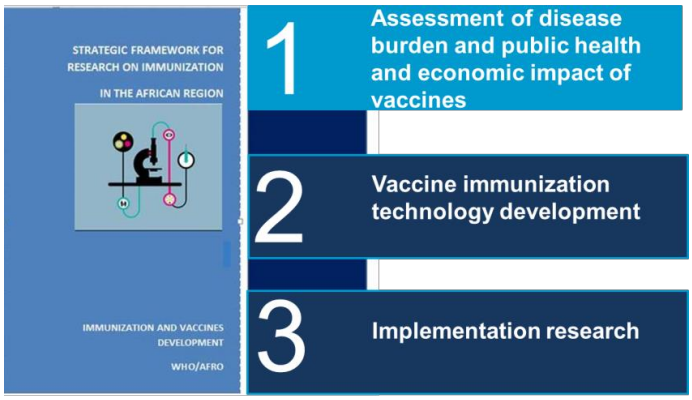


Figure 8: The three thematic areas of research in the SFRI

With regards, to research coordination, she noted that the working group recommended the following:

- Clearing house for immunization research in the African Region
- Immunization Research Committee
- Biennial meeting on immunization research in Africa
    - Celebrating immunization research in Africa;
    - Exchanging ideas;
    - Facilitating collaboration among researchers; and
    - Attracting potential donor interested in funding research in Africa

Following the discussing both presentations, the RITAG requested for a clearer formulation of the Clearing House concept for easy implementation. The RITAG also advised that rather than having another committee just for immunization research, the Regional Director should be encouraged to ensure that the existing advisory committee on research on the Region give sufficient attention to immunization research. It also stressed the need for WHO to advocate to partners and funders to take on the responsibility of organizing the biennial meeting on immunization in Africa. It finally endorsed the SFRI and recommended for its wide circulation.

3.3.4 Ebola Vaccines

Ebola vaccine candidate under clinical development and current SAGE recommendation for the use of rVSV, Ana-Maria Henao-Restrepo, WHO/HQ

The presentation discussed the development of the vaccine, and the details on the clinical trial that is on-going. The results add weight to the interim assessment that rVSV-ZEBOV offers substantial protection against Ebola virus disease EVD), with no cases among vaccinated individuals from day 10 after vaccination in both randomised and non-randomised clusters.

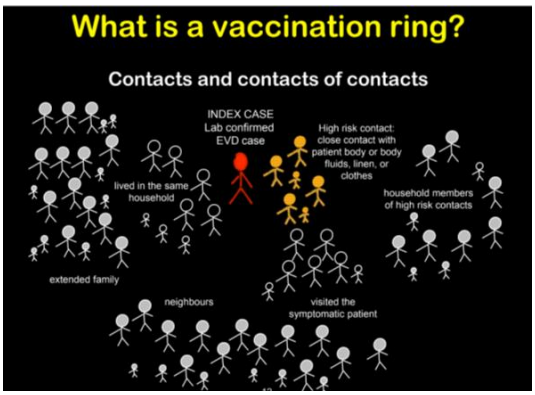


Figure 9: Demonstration on ring vaccination against EVD

Regulatory pathway preparedness for Ebola vaccine

B Akanmori- AFRO/AFRO

The use of the EUAL procedure Product development has become complex driven by situations where there are no counter measures for disease situations. Clinical trials of the vaccines performed much better than those of therapeutics. Pre-qualification (PQ) of products is used to ensure that licensed products are assessed for suitability, safety and efficacy.

The normal regulatory pathway for vaccines shows that risk-benefit assessment is done prior to licensures. National registration by government then assures that importation by country can be done. In some cases the normal pathway is not taken given the situation on ground. WHO developed the emergency use assessment listing (EUAL) to address the gap. One of the criteria to use EUAL is that there is public health emergency of emergency of international concern or country declared emergency. However, some principles discussed in the use of EULA include the following:

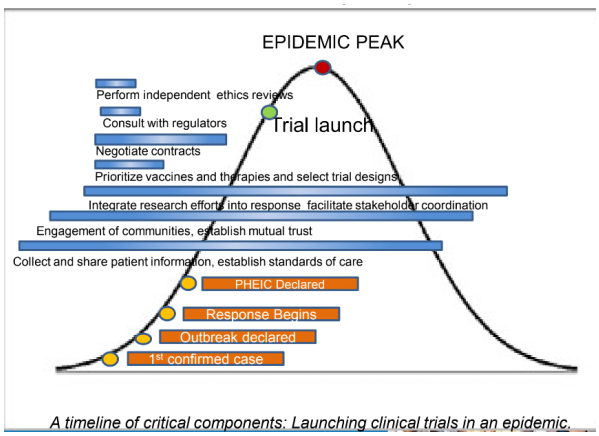


Figure 10: Clinaitrials in Ebola epidemic: Timelines of critical components 2014-2015

- EUAL is not prequalification , but rather a procedure to assess and list products in development (or registered for a different use) for public health emergencies
- Listing under EUAL based on eligibility criteria; a set of quality, safety and efficacy data ; benefit-risk assessment
- Inclusion in the EUAL should not compromise the clinical development of the product

The validity of an emergency EUAL in the context of a public health emergency will generally be for 12 months, following which all decisions for an emergency use listing will be reassessed.

The AVAREF discussed the EUAL and national regulatory frameworks and agreed on the revision of EUAL to adequately address experimental products , and agreed on the need for AVAREF to support countries to utilize outcome of EUAL for implementation of rVSV in public health emergencies.

Ring vaccination with rVSV ZEBOV

Alejandro Costa, WHO/HQ

Trials were conducted in Guinea, one of the countries most affected by an outbreak of Ebola that ended this year, show it offers 100% protection. The vaccine is now being fast-tracked for regulatory approval. Merck has made 300,000 doses of the rVSV-ZEBOV vaccine available for use should Ebola strike. The trial took place in Equateur and Kinshasa provinces in DR Congo. Preliminary results show that 1673 were vaccinated, including first line health workers, contact, and contacts of contacts. Participants were monitored for adverse event for 30 minutes. Challenges include regulatory and ethical approvals. There were also issues in communication, daily reporting of data.

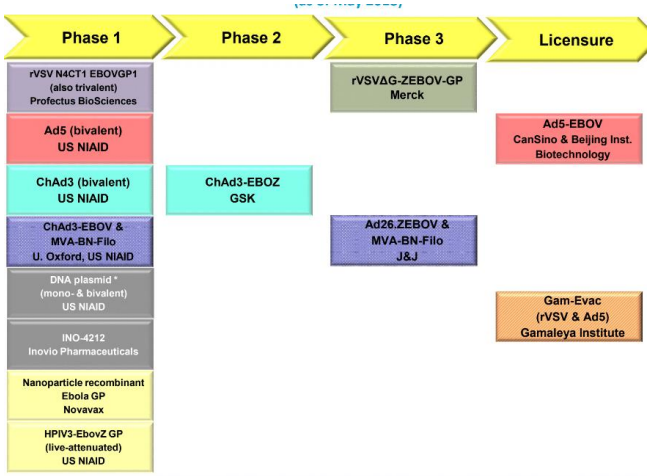


Figure 11: Candidate Ebola vaccines in clinical development (as of May 2018)

Discussions that followed focused essentially on four key issues. These included the PIP framework, which the RITAG considered ripe for review with a view to including issues on Ebola outbreaks. Other had to do with the level of assistance given to countries to develop their respective response plans for vaccines and ways AVAREF could be strengthened to support regulatory authorities in countries. Members noted the need to make recommendations that will make countries to in a perpetual state of readiness.

3.3.5 Polio Eradication and End-Game Strategy

Polio eradication in the African Region: updates and way forward

Ticha Johnson, WHO/AFRO

The Polio Endgame Strategy (2013-18) has the following objectives: Poliovirus detection and interruption; Immunization systems strengthening and introduction of inactivated polio vaccine (IPV); Containment/certification and Transition planning are used to measure progress towards certification of eradication and closure of the program.

As of June 2018, the Polio endemic countries are Afghanistan, Pakistan and Nigeria (with 11 WPV in Afghanistan and Pakistan in the calendar year). In the African Region, Nigeria reported 16 cVDPVs. Outside of Nigeria, 22 cVDPVs (2017-2018) were reported and response was done using mOPV2 in Lake Chad, HOA and DRC.

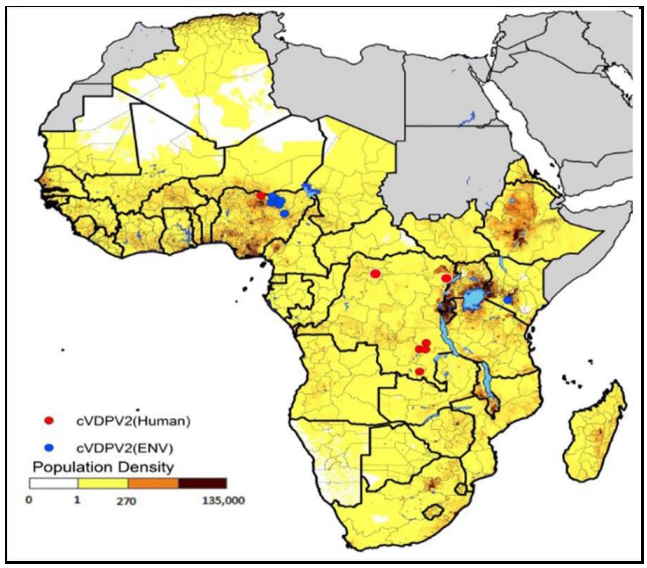


Figure 12: Distribution of cVDPV cases Jan-June 2018

Source: AFP and Environmental Surveillance

There are still sub-national surveillance and immunity gaps in some parts of the region (particularly in Southern and east Africa subregion). Other challenges include insecurity; gaps in Government ownership/support; High staff turnover and Staff accountability. The challenges in Lake Chad basin, HOA and DRC deal with competing outbreaks (Ebola, measles, cholera); Insecurity; Hard to reach areas / logistics; Micro planning, Mobile populations and Refusals. However, the confounding factor specifically in DRC is weak surveillance system, low population immunity from type 2; Low IPV Coverage; Continued use of mOPV type 2.

In order to alleviate surveillance and response challenges, the WHO African Region has initiated GIS and mobile technology based innovations and accountability frameworks. These are now mandatory for all member states as implementation has been linked with country technical and financial support. These innovations include AVADAR Sierra-Leone, Liberia, Nigeria and DRC; ISS Mandatory in all countries; eSURV in Chad in 2108 and Environmental surveillance to supplement the traditional AFP surveillance in identified 22 high risk countries.

cVDPV outbreak in DRCongo – Lessons learnt

MOH DR Congo

The DRC has had several outbreaks due to the importation of WPV type 1 from 2006 – 2010 and a case of cVDPV2 in Kabondo area in 2009. In May 2017, 2 confirmed separate outbreaks of cVDPV2 were detected in the Kunda (Maniema Province) and Butumba (Haut-Lomami Province) areas. In February 2018, DRC declared polio of Public health national emergency, following the notifications of 2 cVDPV in Tanganyika and HK. Five mOPV2 SIAs rounds were planned, but the SIAs were not of high quality, particularly with challenges of access to HTR, risking spreading of cVDPV2 to other countries.

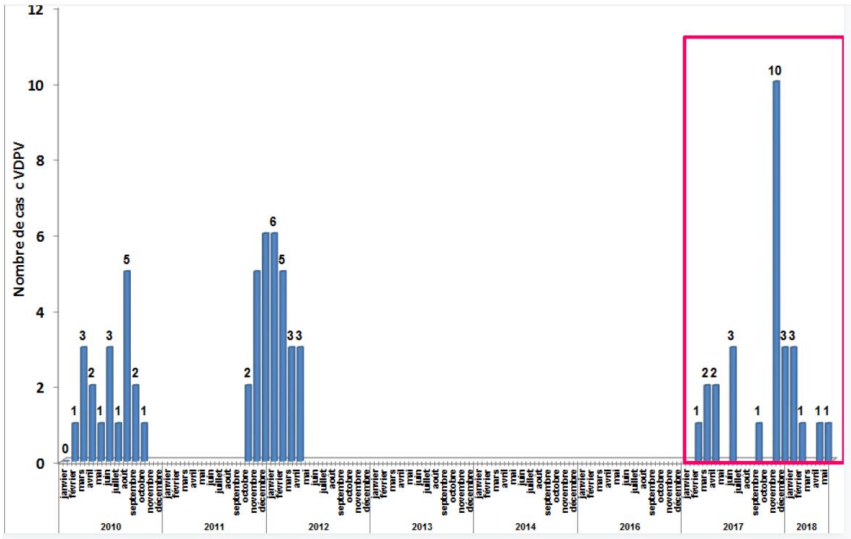
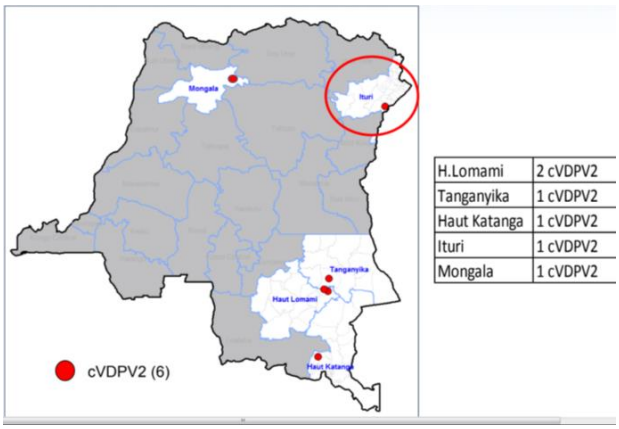


Figure 13: History of notifications of cVDPV2 cases in the DRC (1Jan-28 June, 2018)

With satellite mapping, over 100 villages were identified. There are remaining logistical challenges including natural obstacles as well as roads in bad condition; limited geographic accessibility; areas of insecurity; ongoing Ebola outbreak in Equateur Province ; and the the ongoing polio program ramp down which affected DR Congo in 2017 which in turn decreased capacity for response and surveillance.



H.Lomami	2 cVDPV2
Tanganyika	1 cVDPV2
Haut Katanga	1 cVDPV2
Ituri	1 cVDPV2
Mongala	1 cVDPV2

Figure 14: Localization of cVDPV2 cases in DRC, 2018

The priority is to interrupt the cVDPV2 transmission in the country; to Strengthen AFP and environmental surveillance and laboratory monitoring; to strengthen cross-border activities and; strengthening routine immunization using IPV.

Polio Transition planning: Update

Ebru Ekeman, WHO HQ

Polio Transition and development of plan focused on 16 countries with large polio infrastructure. While Nigeria, South Sudan and Somalia are yet to develop plan, 6 other countries have finalized plans of which 5 were endorsed by the respective ICCs. The challenge is to adequately finance and implement the plans (commitments from countries and expectation from donors) as the fragile counties like Somalia, S Sudan and DRC have very little domestic funding to enable critical functions are implemented.

The WHO Global framework for transition defines the needs and has three components: Sustain polio free status with all functions to continue; strengthening support to RI and VPD surveillance. The estimated cost and financing options have also been defined. For surveillance, lab, core functions and Technical Assistance, the cost is estimated to be about US$ 667 million for 5 years. The African region portion has been reflected in the WHO business case for the African Continent. These funds are expected to be covered by GPEI until certification by 2022; bilateral funding and advocacy for domestic funding; any remaining Gap to be mobilized by WHO within the new GPW framework. Within this context, the main pillars are Immunization systems; new comprehensive VPD surveillance Partnership (avoiding dependence of VPD on Polio funding and fragmentations of VPD surveillance); streamlining of polio essential functions into immunization. Thus in conclusion there is a need to manage the transition so that critical functions are maintained.

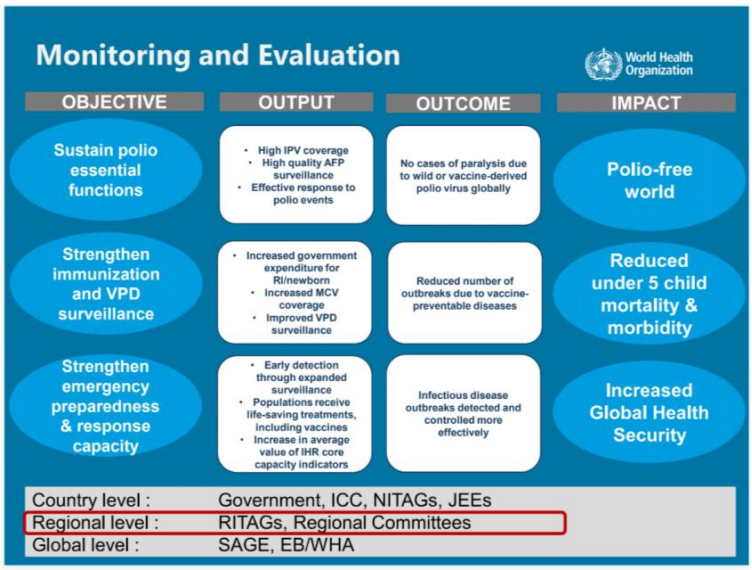


Figure 15: Process for monitoring and evaluating the polio transition framework

During the meeting briefing was provided by audio call by DR Michel Zafran (Polio Director/HQ) and DR Pascal Mkanda (PEP/RO) on challenges in the region particularly in the Lake Chad Basin. In the just concluded Lake Chad meeting, issues were raised with regards to how to reach the hard-to-reach areas. The progress on access to these areas was noted, since all islands were accessed and are doing immunization and surveillance activities. However, some islands in Cameroon territory were not reached. The activities are done by the military. It is thought that surveillance is good but when looking closely, there are some transmissions missed indicating gaps in quality of SIAs. One of the major concerns is also that vaccine management is not accounted for as expected. Operations of outbreak response goes for 18 months and it is reasonable for countries to take over ownership as the program cannot continue as such there is a need to look at how quickly to transition responsibility/ownership back to countries. In addition there anxiety in DRC as there is not enough engagement by the country to stop transmission though there is a promise to do so.

The subsequent discussion included the need to continue to meet funding for critical functions post certification in 2022. For priority countries, WHO will try to help to maintain essential functions to continue till certification and beyond. Other issues raised included the Polio program support to RI, Polio asset mapping, advocacy needs, environmental surveillance , mobile and cross border strategies in DR Congo. It was clarified that transition plans are not WHO plans and they are developed by Government with WHO and UNICEF support. Advocacy for the transition plan advocacy was done at WHA and also at grass root level through WRs. There is a need for transition to be linked with Gavi post-2020 strategy and with accountability and country financing. In the case of DR Congo, the need to strengthen Routine immunization was reiterated along with the need to intensify communication around cVDPV and for countries with no polio cases. Developing an advocacy strategy and engaging of civil society is important.

ANNEX: RITAG Meeting Agenda

Regional Immunization Technical Advisory Group (RITAG) Meeting			
Kigali, Rwanda - 29 & 30 June 2018			
Programme of Work (as of 27 June 2018)			
Friday, 29 June 2018			
Time	**Session**	**Presenter**	**RITAG Lead(s)**
07:30-08h30	Closed-Door Breakfast Session with RITAG Members		
08:00-09:00	Registration		
SESSION 1: OPENING SESSION			
09:00 - 09:10	Welcome remarks	Felicitas Zawaira, WHO	n/a
09:10 - 09:20	Introductory remarks	Helen Rees, RITAG Chair	
09:20 - 09:30	Opening remarks	MoH/Rwanda	
09:30 - 10:30	Update on status of implementation of RITAG recommendations	Balcha Masresha, WHO	
10:30 - 11:00	Group Photo + Refreshment Break		
SESSION 2: INFLUENZA VACCINES			
11:00-13:00	(1) Influenza burden and surveillance in the WHO African Region	Belinda Herring, WHO	Clarisse Loe Loumou, Haroon Saloojee + Folake Olayinka
	(2) Delivery strategies for influenza vaccines	Joachim Hombach, WHO	
	(3) Strengthening NITAG capacities for influenza vaccines decision-making	Blanche Anya, WHO	
13:00 - 14:00	*Lunch*		
SESSION 3: TYPHOID VACCINES			
14:00 - 16:00	(1) Global & regional typhoid fever disease burden	Kashmira Date, CDC	Mohamed-Mahmoud Hacen & Rose Kambarani
	(2) Typhoid conjugate vaccines: updated recommendations and policy implications	Adwoa Bentsi-Enchill, WHO	
	(3) Update on considerations for TCV inroduction and Gavi support to eligible countries	Pascal Bijleveld, Gavi	
	(4) Country preparedness for typhoid conjugate vaccines	Aziza Mwisongo, PATH	
16:00 - 16:15	*Refreshment Break*		
SESSION 4: IMMUNIZATION RESEARCH			
16:15-17:30	(1) Strategic framework for research on immunization in the WHO African region: Report from the RITAG Working Group	Joseph Okeibunor, WHO	Robb Linkins & Ekoe Tetanye
	(2) Proposed recommendation from the RITAG working group	Rose Kambarani, RITAG Member	
17:30	Wrap-Up Day 1	RITAG Chair	
19:00	*Cocktail reception*		
Saturday, 30 June 2018			
Time	**Session**	**Presenter**	**RITAG Lead(s)**
07:30 - 08:45	Closed-Door Breakfast Session with RITAG Members		
SESSION 5: EBOLA VACCINES			
09:00-11:00	(1) Ebola vaccine candidates under clinical development, and current SAGE recommendations for the use of rVSV ZEBOV unlicensed vaccine for Ebola outbreak control	Ana-Maria Henao-Restrepo, WHO	Bill Brieger & Robin Biellik
	(2) Regulatory pathway for Ebola vaccine: the use of the EUAL procedure	Dicky Akanmori, WHO	
	(3) Ring vaccination with rVSV ZEBOV - Guinea & DRCongo outbreak experiences	Alejandro Costa, WHO	
11:00 -11:30	*Refreshment Break*		
SESSION 6: POLIO ERADICATION & END-GAME STRATEGY			
11:30 - 13:30	(1) Polio eradication in the African Region: updates and way forward	Ticha Johnson, WHO	Ephrem Lemango
	(2) cVDPV outbreak in DRCongo - lessons learnt	MoH/DRCongo	
	(3) Polio transition planning update	Ebru Ekeman, WHO	
13:30 - 14:30	*Lunch*		
SESSION 7: DRAFTING RITAG RECOMMENDATIONS (CLOSED DOOR SESSION)*			
14:30 - 16:00	RITAG members to draft recommendations	n/a	All RITAG Members
SESSION 8: WRAP-UP & WAY FORWARD			
16:00 - 16:30	Reporting back at plenary on RITAG draft recommendations	RITAG Chair	n/a
16:30 - 17:00	Setting agenda & dates for next RITAG meeting	RITAG Chair	n/a
17:00	Wrap-up & closure		

ad hoc

TAG Meeting

July 2018

Fourth ad hoc Meeting of the Technical Advisory Group (TAG) on Vaccine-preventable Diseases

10 July 2018
Washington, DC
United States of America

Pan American Health Organization

World Health Organization
REGIONAL OFFICE FOR THE Americas

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Regional advisor on immunization,
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Unit Chief, Comprehensive Family Immunization
PAHO/WHO
Washington, DC, United States

* Not present at the meeting

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Introduction

On 10 July 2018, PAHO convened an extraordinary meeting of its Technical Advisory Group (TAG) on Vaccine-preventable Diseases to discuss the grave situation concerning measles in the Americas and the implementation of recommendations from PAHO's TAG made in March 2018. As of 30 June 2018, measles transmission in Venezuela has been ongoing for over one year. Therefore, endemic transmission of measles is considered to have been reestablished in Venezuela. This situation calls for regional action and an urgent public health response to achieve and sustain the elimination of measles, rubella and congenital rubella syndrome in the Americas. There is also a pressing need for clear guidance on the requirements for the re-verification of measles elimination for countries that have reestablished endemic transmission. This guidance should be part of a new regional framework aiming to regulate the post-verification phase.

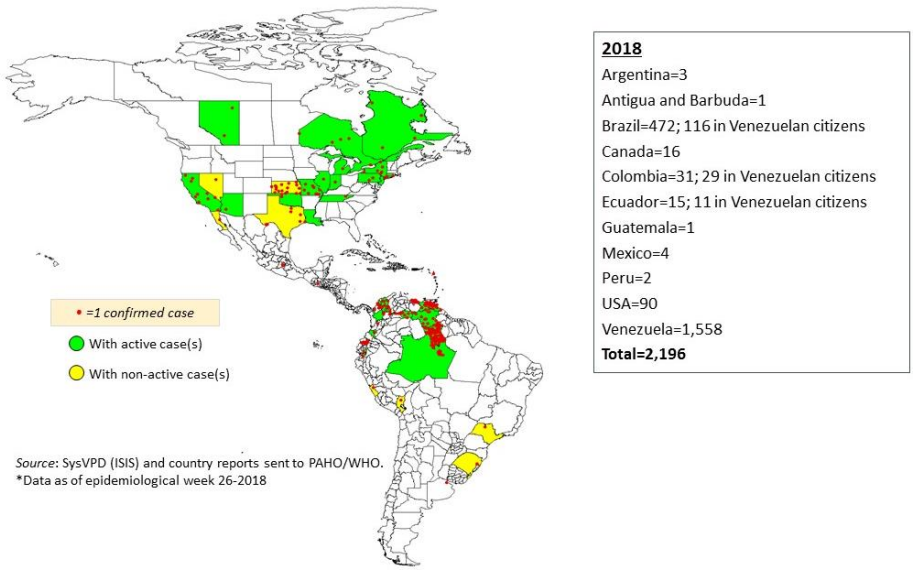
Additionally, an update was provided to TAG members on the status of yellow fever, polio, and diphtheria, which were also addressed during the previous ad hoc meeting.

Update on the Epidemiological Measles Situation and Implications for Measles Elimination in the Americas

Epidemiological Situation

From 1 January to 30 June 2018, a total of 2,196 measles cases were confirmed in the Region of the Americas. Measles outbreaks are ongoing in six countries: Brazil (n=472); Canada (n=16); Colombia (n=34); Ecuador (n=15); United States (n=90) and Venezuela (n=1,558) **(Figure 1)**. Eleven countries have reported measles outbreaks in 2018 compared to only four countries in 2017.

Figure 1. Ongoing (active) and past (non-active/interrupted) outbreaks in the Americas, 2018



In **Venezuela**, measles has spread to 21 of the 23 states and to the Capital District, also known as the federal district. Between epidemiological week (EW) 26 of 2017, when the first confirmation of a measles case occurred in the state of Bolivar, and EW 22 of 2018, 2,285 confirmed measles cases were reported in Venezuela: 727 (32%) in 2017 and 1,558 (68%) in 2018 (**Figure 1**). The Capital District (Caracas) reported 59% of the confirmed cases in 2018, followed closely by Delta Amacuro, the second most affected state. The highest proportion of cases occurred among children under five years of age followed by children six−15 years of age. At the national level, 35 deaths were reported, 33 (94%) were from the state of Delta Amacuro, where cases have been reported since EW 33 of 2017. Additional deaths in Delta Amacuro are under investigation. Delta Amacuro borders Guyana and 25% of its population consists of indigenous Warao communities. Other local sources of information indicate that the Yanomami communities in the municipality of Alto Orinoco and the state of Amazonas, which border Roraima in Brazil, have also been affected by measles. It is important to highlight that Delta Amacuro is a remote area of 40,200 km^2 located in the Orinoco Delta. Most of its indigenous populations live in isolated areas only accessible by hours-long water transport. This situation has increased the costs of implementing control measures for measles, malaria and other disease outbreaks. The lack of electricity, which affects 80% of Amazonas, poses an additional challenge to disease containment efforts.

The risk of spread within and outside Venezuela remains very high due to the continuous movement of population across the borders with Brazil and Guyana, as well as other factors, including the delayed implementation of control measures, absence of a national health alert, inadequate surveillance and case investigation, low capacity for isolation and case management. Additionally, insufficient vaccination coverage levels among certain birth cohorts have resulted in large pockets of susceptible populations. The ongoing outbreak in Venezuela represents a threat to the other countries of the Americas. Most of PAHO's Member States (30/35) reported their last endemic case before the year 2000, i.e. over 18 years ago.

On 22 June 2018, Venezuela's Ministry of Health expressed its willingness to intensify vaccination campaigns in the states with the highest proportion of measles cases and expand efforts nationwide, targeting children six months to 15 years of age. Special tactics and strategies will be implemented to reduce measles virus exportation to neighboring countries while achieving a homogeneous coverage of ≥95%. Although PAHO has been providing the Minister of Health with political, technical, financial and logistic support since the beginning of the measles outbreak, endemic transmission has been re-established in Venezuela since 30 June 2018, which corresponds to 12 months of continuous measles virus circulation.

Since the beginning of the outbreak in Venezuela, the measles cases identified in Colombia, Brazil and Ecuador have been confirmed to belong to the same genotype and clade as the cases previously detected in Venezuela. No measles cases have been confirmed in Guyana to date. The country has enhanced its measles and rubella surveillance and vaccination efforts as part of preparedness and response, including the areas bordering Venezuela and Brazil. With support from the PAHO office in Guyana, the country recruited additional staff to perform daily surveillance, conduct mop-up vaccination for those living in border communities and vaccinate individuals coming from Venezuela. Guyana also put provisions in place for the timely shipment of samples by courier service to the Caribbean Public Health Agency (CARPHA).

In Brazil, 472 measles cases have been confirmed since February 2018, a period of five months. The outbreak continues, with an increasing number of confirmed cases in Roraima (n=200) and Amazonas (n=265). At least 1,864 suspected cases are under investigation; 88% of which have been reported in Amazonas. Additionally, one highly suspected measles case was reported in the state of Rondônia, which borders southern Amazonas. Of 465 confirmed measles cases with available data on age, the highest proportion of cases (47%) occurred among children less than five years of age. 345 of the 472 (72%) confirmed cases were Brazilian citizens. Therefore, Brazil is at high risk of measles virus spread to the other federal states if more aggressive control measures are not taken, especially in Roraima and Amazonas. **Table 1** summarizes the measles epidemiological situation by federal state in Brazil, as of EW 26 2018.

Table 1. Distribution of Confirmed Measles Cases by Federal State in Brazil, 2018

Federal State	No. of Confirmed Cases (%)	Outbreak-related?
Amazonas	265 (56)	Yes, an outbreak in Venezuela; genotype D8
Roraima	200 (42)	Yes, an outbreak in Venezuela; genotype D8
Rio Grande do Sul	5 (1)	Yes, an outbreak in Venezuela; pending genotype
Rio Grande do Sul	1 (0.2)	No, an isolated case with travel history to Europe; genotype B3.

São Paulo	1 (0.2)	No, an isolated case with travel history to Lebanon; genotype D8.
Total	**472 (100)**	

In **Colombia,** between EW 11 and 26 2018, 34 measles cases were confirmed; 22 (65%) were imported from Venezuela, i.e. were individuals who crossed the Venezuela-Colombia border prior to or during their communicable period, seven (21%) were Venezuelan secondary cases residing in Colombia for at least four months with unknown vaccination history, two (6%) were Colombian citizens and three (9%) had no information on nationality. Thirteen of 32 (41%) departments reported confirmed cases. The Departments of Norte De Santander and Sucre reported the highest proportion of cases (48%). Moreover, a high proportion of the confirmed cases (74%) were young children less than five years of age.

In **Ecuador**, between EW 13 and 23 2018, 15 measles cases were confirmed. The cases were reported in Quito (eleven cases; 73% of the cases), Tulcán, located in the border area with Colombia (two cases), Riobamba (one case), and Cuenca (one case). Six (40%) of the cases were epidemiologically linked to the cases previously identified in Quito's southern sector. Eleven (73%) of the cases were male. The age of cases ranged from four months to 44 years. Eleven (73%) of the cases were imported from Venezuela. The genotypes of the viruses are being identified.

PAHO Response

The main actions taken by PAHO have been directed at supporting Venezuela, Brazil, Colombia and Ecuador. This was done through high-level political advocacy with the countries' Ministers of Health and Presidents, training in rapid public health response, deploying international consultants to support field activities, providing laboratory reagents, vaccines and other supplies, and mobilizing resources to cover operational costs of vaccination activities. The specific actions included:

- High-level advocacy and a face-to-face meeting between PAHO's Director and Venezuelan President Nicolás Maduro to discuss the emergency on 12-13 June 2018.
- PAHO/WHO presented an update on the situation in Venezuela and the neighboring Member States, as well as a plan to maintain an effective technical cooperation agenda during the 162nd session of the Executive Committee held in Washington, DC in June 2018. The Executive Committee urged Venezuela to urgently develop and implement a plan of action to stop measles and diphtheria transmission and recommended that all countries invest in and prioritize vaccination coverage reaching at least 95% in all municipalities and communities, as well as address outbreaks of vaccine-preventable diseases.
- Four PAHO regional advisors in immunization have been repeatedly deployed to support Venezuela, Guatemala, Haiti, Ecuador and Brazil since September 2017 for technical assistance and to maintain visibility of the epidemiological alerts at the highest political level.
- The PAHO regional immunization team closely monitors the current measles and diphtheria outbreaks through regular meetings and communication with the country immunization focal points.
- Strong advocacy for resource mobilization with the Measles and Rubella Initiative resulted in the donation of 2.7 million doses of measles-rubella-containing vaccines to support implementation of the vaccination plan in Venezuela. Negotiations with strategic partners are ongoing to mobilize additional financial resources for Venezuela and to cover expenses from the scheduled nationwide campaign.

- Two sub-regional workshops on rapid responses to measles outbreaks were conducted in 2017 with participation from all Spanish-speaking countries in the Region. A similar sub-regional training is programmed for the English-speaking Caribbean countries in October 2018. Ten equivalent national workshops were funded in Central and South America.
- PAHO's Comprehensive Family Immunization Unit (IM) has mobilized funds to finance the Plan of Action for the sustainability of measles and rubella elimination in many countries, raising more than USD $500,000.
- IM has mobilized additional funding (approximately USD $150,000) to support vaccination and surveillance activities in countries neighboring Venezuela, such as Colombia and Brazil.
- PAHO is working on four new technical resources that should be available in the next two months for use at the country level including 1) a *risk assessment tool for measles and rubella outbreaks*; 2) a *manual for measles/rubella outbreaks rapid response*; 3) a *case study for measles/rubella outbreak response training* and 4) a *manual for rapid monitoring of vaccination coverage*.

Regional Framework for the Post-Verification of Measles Elimination Era
In 2016, the International Expert Committee for Documenting and Verifying Measles, Rubella, and Congenital Rubella declared the Region of the Americas free of measles. During the same year, the Americas reported 93 confirmed measles cases, none of which represented endemic transmission, with a regional incidence of 0.07 cases per million people, the lowest rate ever recorded. During the 29th Pan American Sanitary Conference in September 2017, the Ministers of Health approved a Plan of Action for the sustainability of measles, rubella, and congenital rubella syndrome (CRS) elimination, for the period 2018-2023, with the purpose of protecting this important public health gain.

While it was hoped that this achievement would be sustained, a measles outbreak has been ongoing since July 2017 in Venezuela. This outbreak has lasted more than twelve months and has resulted in the re-establishment of endemic transmission in the country.

In the ***"Plan of Action for the documentation and verification of the measles and rubella elimination"*** published in 2011, the geographical unit for the documentation of the interruption of endemic transmission was defined as the entire Region instead of individual countries. All PAHO Member States made considerable efforts to document and verify the interruption of endemic transmission of measles and rubella viruses in their territories during 2011−2016.

Global Framework for the Post-Verification of Measles Elimination Era
In 2017, SAGE endorsed WHO's update of the four categories used to classify countries as they progress towards measles and rubella elimination:

1) **Endemic**: Countries with continuous transmission of the 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:** Countries where there is an absence of endemic transmission for ≥12 months but <36 months in the presence of a high-quality surveillance system.
3) **Eliminated and verified:** Countries that have had no endemic transmission for ≥36 months.
4) **Re-established endemic transmission post-verification:** Countries that have evidence indicating the presence of a chain of transmission of a virus strain that continues uninterruptedly for ≥12 months in a defined geographical area (region or country) following previous verification of elimination.

Countries with re-established endemic transmission post-verification would need to demonstrate again that they have no endemic transmission for ≥36 months in the presence of a high-quality surveillance system to be classified as measles-free and consequently verified as such.

To address this important topic, TAG recommended in March 2018 during an ad hoc meeting, to convene an expert group for the sustainability of measles, rubella and CRS elimination in the Region of the Americas with two main objectives:

1. Monitoring the sustainability of the elimination of measles, rubella, and CRS in the Region through its fulfillment of the objectives and indicators outlined in the regional plan of action for sustainability;
2. Developing or updating a regional framework for the Americas, to monitor the absence of endemic measles transmission in the Americas, as well as actions to take in the event of the re-establishment of endemic transmission.

The terms of reference of this expert group were presented to PAHO's Director and the proposed members are pending official designation. The immediate issues that the expert group will address include:

1. If the endemic transmission is re-established in one country, does the entire Region lose its measles, rubella or CRS elimination status?
2. If endemic measles or rubella transmission in a country or in the Region is re-established, what should be the criteria and process for the re-verification of measles, rubella or CRS elimination?

The PAHO secretariat proposed three scenarios to initiate discussions on the topic:

1. Scenario 1: If one country in the Americas loses its status as free of endemic measles following ≥12 months of ongoing virus transmission, **the 35 Member States of the Americas would lose their status as well.** In this situation, the Americas **would follow the guidelines of the "Plan of Action for the documentation and verification of measles, rubella and CRS elimination in the Region of the Americas" developed in 2011**.

2. Scenario 2: If one country in the Americas loses its status as free of endemic measles following ≥12 months of ongoing transmission (e.g. Venezuela), this country will be classified as a country that "**Re-established endemic transmission post-verification," according to the new WHO global framework.** To be re-verified, the affected country would have to demonstrate that transmission was interrupted for at least three years following the last known endemic case, in the presence of high-quality surveillance. The remaining 34 Member States of the Americas would maintain their status of elimination-verified. However, the Region could no longer be considered free of measles.

3. Scenario 3: If more than one country has reestablished endemic transmission with the same or a different virus genotype, the whole Region would lose its verification status. To be re-verified, all Member States would need to demonstrate interruption of endemic measles transmission for a period of at least three years following the last known endemic case, in the presence of high-quality surveillance. In this case, **a new regional framework** would be developed to further provide guidance on the re-verification process.

The table below summarizes the proposed scenarios:

	Scenario 1	**Scenario 2**	**Scenario 3**
Country	Re-establishment of endemic measles transmission in one country	Re-establishment of endemic measles transmission in one country	Re-establishment of endemic measles transmission in more than one country
Region	All 35 Member States of the Region would lose the elimination status	The remaining 34 (non-affected) Member States of the Region would maintain the elimination status	All 35 Member States of the Region would lose the elimination status
Action	The **entire Region** would undergo re-verification as per the 2011 **Plan of Action**	The **affected country** would undergo re-verification, at least 3 years following the last endemic case	The entire Region would undergo re-verification following a **new regional framework**

Conclusion

In view of the re-establishment of measles endemic transmission in Venezuela since 30 June 2018, the Region of the Americas is no longer considered free of measles. To provide guidance on the requirements and process for measles elimination re-verification, TAG reviewed the three scenarios proposed by the PAHO secretariat and opted for scenario two. Nevertheless, TAG emphasized that there should be regional action, including careful monitoring of vaccination coverage, as well as thorough risk assessment.

TAG agreed that the expert group should examine the question with more depth and define the elements of the re-verification process under scenario two. TAG urged the expert group to convene its first meeting promptly to begin adapting or developing a framework for the re-verification of measles elimination. TAG members agreed that the essential criteria of the 2011 Plan of Action shall be maintained, including the interruption of endemic measles for at least three years following the last known confirmed case, the presence of high-quality surveillance and the absence of endemic measles virus strains evidenced through viral surveillance. The PAHO secretariat shall organize high-level country visits of the expert group to high-risk countries, such as Venezuela and Brazil, to advocate for urgent public health action.

In the coming months, PAHO will focus its technical cooperation on high priority countries, i.e. those with ongoing outbreaks, to ensure optimal implementation of control measures. Focus will then be shifted to countries receiving significant migration influx from Venezuela, to reinforce surveillance and vaccination, and finally to countries with no measles cases, to sustain high vaccination coverage and measles elimination.

Recommendations

- TAG reiterates its previous recommendation to the Venezuelan health authorities, to act decisively to control the current epidemic and prevent further exportation of the measles virus to other countries in the Region. There is an urgent need to achieve high and homogeneous vaccination coverage levels among populations younger than 15 years of age, as well as to intensify outbreak control measures in high-risk municipalities, those located in border areas, and among indigenous communities (e.g. Warao, Yanomami and Wayuu populations).

- TAG urges Brazil to respond decisively and efficiently to the current measles outbreak to interrupt measles virus transmission and its spread to other parts of the country and to the rest of the Region. There is a serious risk of the re-establishment of endemic transmission in Brazil within seven months if a more aggressive response is not implemented immediately.
- Given the threats to measles elimination in the Americas, TAG urges countries/territories to reinforce measles and rubella surveillance, intensify vaccination activities to achieve coverage levels greater than 95% with two doses of the measles-rubella containing vaccines among all children under five years of age and respond rapidly to imported cases. Countries must urgently implement the Plan of Action for the Sustainability of Measles and Rubella Elimination endorsed by PAHO Member States in September 2017.
- TAG reminded countries of the importance of vaccinating at-risk populations that do not have proof of vaccination, such as health personnel, airports, tourism and transportation staff, and migration services, among others.

Update on the Ongoing Diphtheria Outbreaks in the Americas

Two major diphtheria outbreaks have been reported in Haiti and Venezuela in recent years **(Table 1)**, as well as other outbreaks associated with Venezuelan cases in Colombia, Brazil and the Dominican Republic. In both Haiti and Venezuela, the routine immunization coverage for DPT3 and boosters have been consistently below 95%, falling short of the goal set for the Region to reach coverage levels of 95% nationally and sub-nationally. These low coverage levels have resulted in an increase in the number of susceptible children and adults.

Table 2. Characteristics of the Recent Diphtheria Outbreaks in Haiti and Venezuela

	Haiti	**Venezuela**
Beginning of the outbreak	EW 50, 2014	EW 26, 2016
Number of confirmed cases since the beginning of the outbreak	170 (as of EW 25, 2018)	1019 (as of EW 16, 2018)
Most affected age group	<10 years of age	5-15 years of age
Routine vaccination coverage (WHO UNICEF Joint Report Form 2017)	DPT3: 72% DPT4: 32%	DPT3: 84% DPT4: 38%

In **Haiti,** the diphtheria outbreak began in December 2014 (EW 50), and until EW 25 of 2018, 555 probable cases (170 confirmed, 37 under investigation, and 283 discarded), and 79 deaths (31 confirmed cases, 34 under investigation, and 14 discarded cases) had been notified. The estimated case fatality rate for 2018 was 6%. In 2015 and 2017, a higher proportion of females than males were affected by the disease (57% and 60%, respectively). Also, the proportion of cases among children less than ten years of age was higher than among older children. Nine of the ten departments have been affected to date; seven have reported confirmed and probable cases, and two have only reported probable cases.

As part of the outbreak control measures, the Ministry of Health planned three rounds of vaccination campaigns targeting children 1-14 years of age in 44 communes of nine departments. The pentavalent vaccine was used to vaccinate children aged 1-6 years, and the Td vaccine for children 1-15 years of age. The first phase of the first round of the campaign was conducted from 11-15 March 2018 in eight states (29 communes); and the second phase was conducted from 8 to 12 April 2018, in 15 communes of the West Department. Administrative coverage reached 98% in the first eight departments and 81% in the West Department. Independent monitoring was conducted, estimating coverage levels at 87% in the nine departments and 85% in the West Department. Since the end of the first phase of the campaign, the number of reported diphtheria cases and deaths has decreased. The dates for the implementation of the two remaining rounds have not been confirmed.

In **Venezuela**, the diphtheria outbreak that began in July 2016 (EW 26) continues. Since the beginning of the outbreak until EW 16 of 2018, a total of 1,716 suspected diphtheria cases have been reported (324 cases in 2016, 1,040 in 2017 and 352 in 2018); 1,086 (63%) of the suspected cases were confirmed by laboratory (n=350) or epidemiological link (n=736) and 160 died (17 in 2016, 103 in 2017, and 40 in 2018). The cumulative case fatality rate is 14.7%. In 2016, cases were reported in 5/23 states (Anzoátegui, Bolívar, Delta Amacuro, Monagas and Sucre), while in 2017, confirmed cases were reported in 22/23 states, as well as in the Capital District. In 2018, 9/23 states reported confirmed cases in all age groups; however, the highest incidence rate occurred among children aged 5-15 years. The vaccination campaign is in

progress, targeting children aged two months to six years with the pentavalent vaccine, and 7-15 years with the Td vaccine.

In **Colombia**, five cases of diphtheria have been confirmed in 2018, aged from 3-27 years. Three of the cases were Venezuelan citizens, and two did not have information on nationality. Two cases were not vaccinated, and three cases had unknown vaccination history. All cases were male. One of the five cases died.

In **Brazil**, 42 suspected cases were reported in 14/26 states in 2017; five (12%) were confirmed in four states: Acre (1), Minas Gerais (2), Roraima (one fatal case, imported from Venezuela) and São Paulo (1). The remaining 37 were discarded by national authorities. In 2018, Brazil reported eleven suspected cases of diphtheria between EW 1 and EW 20, but no cases have been confirmed to date.

In the **Dominican Republic**, three suspected diphtheria cases were reported in 2017; one was confirmed for diphtheria and two were discarded based on clinical criteria for one case and laboratory results for the other case. No fatalities were reported. No cases have been reported in 2018.

National health authorities of neighboring countries have intensified epidemiological surveillance, investigations and vaccination to prevent importation of diphtheria cases from the affected countries.

PAHO's Revolving Fund has supported countries in the Region to ensure the supply of diphtheria antitoxin in a constrained global market. Haiti and Venezuela have received diphtheria antitoxin annually over the past 3 years; while Colombia, the Dominican Republic and Panama have procured it to replenish their national strategic stocks. The Revolving Fund currently has a supply agreement with only one manufacturer located in India, that is expected to cover the anticipated needs of the Region for 2018 and 2019.

Regional Update on Polio

Vaccination Coverage

Prior to 2016, the regional polio-3 vaccination coverage had ranged between from 90%-94% for over 20 years. In 2016, polio-3 vaccination coverage dropped to 87%, the lowest it had been in the previous two decades. Preliminary data from 2017, not including data from Uruguay and El Salvador, showed polio-3 coverage to be 88.4%. At the sub-national level, vaccination coverage levels were not homogeneous. Many municipalities in the Region have coverage levels <80%.

Surveillance Update

The quality of acute flaccid paralysis (AFP) surveillance in the Region is suboptimal. In the past 52 weeks (EW 26 2017-EW 26 2018), the Region has met the goal to report at least one AFP case per 100,000 children under 15 years old and to investigate ≥80% of AFP cases within 48 hours but has failed to achieve ≥80% of adequate stool samples collection from cases. Only four countries have met all three indicators over the last 52 weeks: Bolivia, Mexico, Nicaragua and Paraguay.

Fractional Use of the Inactivated Poliovirus Vaccine (fIPV)

In April 2017, the TAG recommended that all countries be prepared to respond to a shortage of the inactivated polio vaccine (IPV) and that countries (n=16) that administer more than 100,000 doses of IPV per year begin to prepare immediately for the implementation of fIPV vaccination. Of the 16 countries recommended to switch to fIPV, nine (56%) have already started training health workers (Ecuador, Cuba, Colombia, Dominican Republic, El Salvador, Guatemala, Nicaragua, Panama and Paraguay). Two countries have completed training at all levels and have started to implement fIPV as part of their routine programs: Ecuador (as of 1 January 2018) and Cuba (as of 1 May 2018).

In June 2018, members of PAHO's Comprehensive Family Immunization (IM) and Communications (CMU) units visited several locations in Ecuador to document the country's experience with preparing, implementing and supervising the use of fIPV. The lessons learned from Ecuador could benefit other countries in the Region and the world in their fIPV preparations. PAHO is preparing a technical report and a video explaining the preparation and implementation processes in Ecuador that will be made available to all countries in September 2018. The best practices identified included:

- Using quality cascade-style training of health care workers;
- Swaddling the child in blankets at the time of fIPV administration to help limit his/her movement and increase the chances of using the technique adequately and of a bleb forming;
- Administering fIPV in outreach settings;
- Achieving good acceptability of the new administration technique among parents;
- Reinforcing health care worker communication, a catalyst for increasing parents' acceptability and their understanding of the child's evolution and care immediately post-vaccination.

Vaccine Availability

The availability of IPV remains limited; however, no country in the Region has faced stock-outs to date. IM and PAHO's Revolving Fund continue to work closely with all countries to monitor IPV stocks. The Revolving Fund has continued negotiations with the supplier of IPV10, resulting in a favorable supply agreement for 2018 and 2019. An update was provided on IPV supply during the 162nd Session of the Executive Committee.

Risk Analysis

Until polio is eradicated everywhere, all countries remain at risk of poliovirus importation. In July 2017, PAHO presented a regional risk assessment to TAG endorsing the methodology and encouraged Member States to conduct annual subnational risk assessments. To align with some of the global risk assessment indicators, PAHO updated its regional risk assessment, repeating it in July 2018. Preliminary results showed that four countries were at very high risk (Dominican Republic, Guatemala, Haiti and Venezuela), five countries were at high risk (Argentina, Bolivia, Ecuador, Peru and Suriname), 15 countries were at medium risk (Anguilla, Antigua and Barbuda, Belize, Bermuda, Brazil, Colombia, Curacao, El Salvador, Guyana, Jamaica, Mexico, Panama, Paraguay, Trinidad and Tobago and the Virgin Islands), and the remaining 19 countries were at low risk (Aruba, Bahamas, Barbados, Canada, Cayman Islands, Chile, Costa Rica, Cuba, Dominica, Grenada, Honduras, Nicaragua, Saint Kitts, Saint Lucia, Saint Vincent, Sint Maarten, Turks and Caicos, United States, Uruguay).

It is worth noting that following improvements in vaccination coverage levels and surveillance performance, Brazil was reclassified from high risk to medium risk in this risk assessment update. Additionally, following TAG recommendations, PAHO developed a tool for countries to conduct their own national risk assessments down to the district/municipal level. PAHO is currently developing the tool further to include automated mapping of the risk areas. This tool will be presented to the countries during the 6th Regional Polio Meeting in December 2018.

Sabin 3 Isolation in Venezuela

In May 2018, Venezuela reported a case of acute flaccid paralysis (AFP) in a 34-month-old child with no vaccination history against polio residing in a community with low vaccination coverage in Delta Amacuro. The case was reported through the national surveillance system. A stool sample was collected from the child, following surveillance guidelines, and the national laboratory isolated Sabin type 3 poliovirus. The virus isolate was then sent to the global specialized laboratory (US CDC, Atlanta), which confirmed the national laboratory results. The virus isolate was the same form of the Sabin type 3 virus found in the oral polio vaccine; meaning the virus had not mutated and was neither a wild poliovirus (WPV) nor a vaccine-derived poliovirus (VDPV). Thorough field investigations did not identify additional AFP cases or case clusters suggestive of WPV or VDPV circulation. To classify the case, in accordance with polio surveillance guidelines, a clinical evaluation was conducted on 28 June 2018, 60 days following the onset of AFP, to determine the presence of residual paralysis. The results of the investigation were inconclusive, and the neurologist requested another evaluation be done on 2 July 2018. PAHO has not yet received the results of the evaluation. Although this case was not due to WPV or VDPV poliovirus, any state or district in the Region with low polio-3 vaccination coverage is at risk of the emergence of a VDPV or importation of WPV and should strive to improve polio vaccination coverage and strengthen surveillance.

Investigation of Immunodeficiency-related VDPV1 (iVDPV1) in Colombia

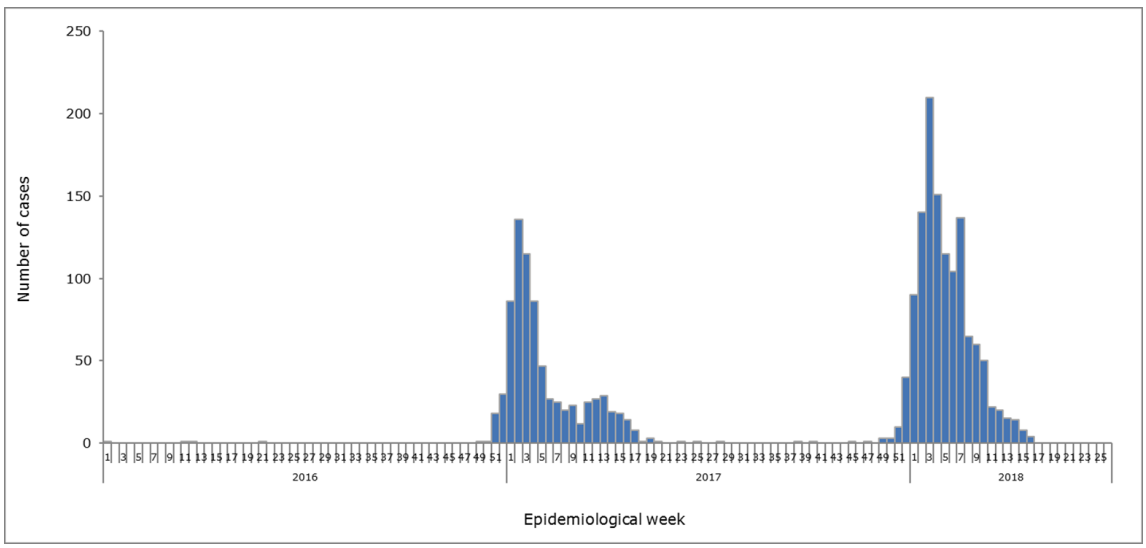
A suspected iVDPV1 case is currently under investigation in Colombia. An 11-month-old child with suspected severe primary immunodeficiency developed AFP on 1 March 2018 and VDPV poliovirus type 1 was subsequently isolated from the child. PAHO/WHO continues to evaluate the epidemiological situation and support the strengthening of surveillance and vaccination in the country.

PAHO/WHO is coordinating with partners of the Global Polio Eradication Initiative to obtain the antiviral Pocapavir. The child will be included in a treatment trial on the efficacy, safety and pharmacokinetics of Pocapavir. Cases of iVDPV are extremely rare and there has been no documentation of associated secondary spread of iVDPV to date. Colombia's national polio vaccination coverage is estimated at 91%, thus, the risk of further VDPV spread remains very low.

Update on the Yellow Fever Epidemiological Situation in Brazil

From July 2017 to 16 May 2018, the State of Minas Gerais confirmed 520 cases of yellow fever, including 177 (34%) deaths. During the same period, the State of São Paulo reported 516 yellow fever confirmed cases, including 163 (32%) deaths. From 1 January to 24 May 2018, the State of Rio de Janeiro reported 265 yellow fever confirmed cases including 84 (32%) deaths in 23 of 91 (25%) municipalities. From 1 January to 16 May 2018, the state of Espirito Santo reported six yellow fever confirmed cases, including one death (17%). From July 2017 to 16 May, the Federal District reported only one yellow fever fatal case. Yellow fever transmission has occurred through sylvatic vectors either in rural settings or in localized peri-urban areas. No yellow fever transmission by Aedes aegypti has been confirmed to date. There has been a steady decrease in the number of human and animal yellow fever cases reported in Brazil since the end of February 2018 **(Figure 2)**.

Figure 2. Distribution of confirmed yellow fever cases by epidemiological week (EW). Brazil, 2016–2018



Yellow fever season in Brazil typically occurs from December to May of every year. For 2018-2019, epidemiological and environmental analyses suggest that the yellow fever virus could spread to the South, reaching the states of Parana, Santa Catarina and Rio Grande do Sul. The virus is also expected to move towards the Southwest through sylvatic corridors currently running from the state of São Paulo, through the Parana River basin on the way to eastern Paraguay and northern Argentina and to the Northeast, potentially reaching the states of Sergipe, Alagoas, Pernambuco, Paraiba and Rio Grande do Norte.

On 20 March 2018, the Ministry of Health announced the expansion of yellow fever vaccination to the entire country, including 1,586 new municipalities in the Southeast, South and Northeast regions, increasing the population to be vaccinated by 77.5 million individuals. Vaccination of these new populations will be done gradually until April 2019. This preventive measure aims to protect the entire population against the disease in case the areas of virus circulation geographically expand, as observed during the 2017 outbreak. Based on official reports, the total number of doses applied (fractional or full doses) in Rio de Janeiro, during the mass vaccination campaign that took place from 25 January to 5 May 2018, was 2,073,151. With 8,395,098 doses administered in the state, prior to the campaign, the total number of vaccine doses administered to date was 10,464,249, covering 65% of the target population.

In São Paulo, the total number of doses applied (fractional and full doses) during the campaign running January-May 2018, was 5,529,017. Considering the 13,300,000 individuals vaccinated prior to the campaign, the cumulative vaccination coverage for the population of São Paulo was 60%. In addition to the states of Rio de Janeiro, São Paulo, and Bahia, which will continue to vaccinate using a fractional dose, the states in the South (Paraná, Santa Catarina and Rio Grande do Sul) will begin vaccinating with a standard dose in July 2018, followed by standard dose vaccination in the Northeast Region (Piauí in January 2019; Alagoas and Sergipe in February 2019; Paraiba and Pernambuco in March 2019; and Ceará and Rio Grande do Norte in April 2019). Accordingly, by April 2019, 1,586 new municipalities will be included as areas with vaccine recommendations, covering 100% of the national territory.

In Minas Gerais, the cumulative vaccination coverage (2003-2018) was estimated at 95%. Unlike the states of Rio de Janeiro, São Paulo and Bahia, Minas Gerais did have recommendations for yellow fever vaccination of its residents and incoming travelers; however, an estimated 691,450 individuals remain unvaccinated, especially those 15−59 years of age. This age group was particularly affected during the last large yellow fever epidemic in Brazil in 2017. Among the 853 municipalities of Minas Gerais, 142 (15%) did not reach a coverage level of 80%. Another 283 (33%) municipalities reported coverage levels between 80% and 95%. More than half of the cities in Minas Gerais reached coverage levels ≥95%.

No shortage of yellow fever vaccine or syringes is expected to perturb vaccination plans for the states of São Paulo, Rio de Janeiro and Bahia. On 30 January 2018, the national yellow fever vaccine stockpile consisted of 17.9 million full doses. Twenty million syringes should be received shortly, allowing the national authorities to carry on with the vaccination activities.

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South-East Asia Regional Immunization Technical Advisory Group (SEAR-ITAG)

Report of the Ninth Meeting

New Delhi, India, 17 to 20 July 2018

World Health Organization
Regional Office for South-East Asia

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Contents

Acronyms

AEFI adverse event following immunization

AES acute encephalitis syndrome

AFP acute flaccid paralysis

AMP assessment, mitigation and performance

AMR antimicrobial resistance

ASEAN Association of Southeast Asia Nations

AVSSR Association of Southeast Asia Nations Vaccine Security and Self-Reliance

bOPV bivalent oral poliovirus vaccine

CCS containment certification scheme

CCEOP cold chain equipment optimization platform

CRS congenital rubella syndrome

cVDPV circulating vaccine-derived poliovirus

DTP diphtheria-tetanus-pertussis vaccine

DTP1 first dose of diphtheria-tetanus-pertussis vaccine

DTP3 third dose of diphtheria-tetanus-pertussis vaccine

DHIS district health information software

EAPRO (UNICEF's) East Asia and Pacific Regional Office

EPI Expanded Programme on Immunization

ES environmental surveillance

FIC fully-immunized child

GAPIII 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

Gavi Gavi, the Vaccine Alliance

GDP Good Distribution Practices

GLO Global Learning Opportunities

GPEI Global Polio Eradicaiton Initiative

GRISP Global Routine Immunization Strategies and Practices

HbsAg hepatitis B surface antigen

HepB	hepatitis B vaccine
HepB3	third dose of hepatitis B vaccine
HepB-BD	hepatitis B vaccine birth dose
HPV	human papilloma virus
HR	human resources
ID	intradermal
IEAG	India Expert Advisory Group
IPV	inactivated poliovirus vaccine
ITAG	Immunization Technical Advisory Group
IVD	Immunization and Vaccine Development Unit
JE	Japanese encephalitis
JRF	Joint Reporting Form
LBs	live births
LMICs	lower--middle-income countries
MACs	multiple age cohorts
MCV	measles containing vaccine
MCV1	first dose of measles containing vaccine
MCV2	second dose of measles containing vaccine
MNTE	maternal and neonatal tetanus elimination
MoH	ministry of health
MOV	missed opportunities for vaccination
MR	measles rubella vaccine
MTR	midterm review
NAC	national authority for containment
NCCPE	national certification committee for polio eradication
NCTF	national containment task force
NIP	national immunization programme
NITAG	national immunization technical advisory group
NRA	national regulatory authority
NT	neonatal tetanus
NVC	national verification committee (for the elimination of measles and rubella/CRS control)

OPV	oral poliovirus vaccine
OPV2	type 2 OPV
OPV3	third dose of oral poliovirus vaccine
PCS	(polio) Post Certificatio Strategy
PCV	pneumococcal conjugate vaccine
PEF	poliovirus essential facilities
Penta	pentavalent vaccine
PIE	post introduction evaluation
POCT	point-of-care testing (for measles)
PQ	(WHO) prequalified
QA	quality assurance
ROSA	(UNICEF's) Regional Office for South Asia
RCCPE	Regional Commission for the Certification of Poliomyelitis Eradication
RCV	rubella containing vaccine
RI	routine immunization
RPLN	Regional Poliovirus Laboratory Network
RRL	Regional Reference Laboratory
RV	rotavirus vaccine
SAGE	(WHO's) Strategic Advisory Group of Experts on Immunization
SEA	South-East Asia
SEA-RCCPE	SEA Regional Certification Commission for Polio Eradication
SEAR-ITAG	South-East Asia Regional Immunization Technical Advisory Group
SEARN	South-East Asia Regulatory Network
SEAR-VAP	South-East Asia Regional Vaccine Action Plan
SIAs	supplementary immunization activities
Td	tetanus-diphtheria vaccine
TT	tetanus toxoid
TT2+	more than two doses of tetanus toxoid containing vaccine among pregnant women
TTCV	tetanus-toxoid--containing vaccine
tOPV	trivalent oral poliovirus vaccine
UN	United Nations

UNICEF United Nations Children's Fund

US CDC United States Centers for Disease Control and Prevention

VAEIMS Vaccine Adverse Events Information Management System

V3P (WHO's) Vaccine Product, Price and Procurement Web Platform

VPD vaccine-preventable disease

WCBA women of childbearing age

WHA World Health Assembly

WHO World Health Organization

WPV wild poliovirus

Introduction

The Ninth Meeting of the World Health Organization's (WHO's) South-East Asia Regional Immunization Technical Advisory Group (SEAR-ITAG) was held from 17 to 20 July 2018 in New Delhi, the Republic of India (India). The SEAR-ITAG (referred to hereafter as the ITAG) is a Regional technical expert group, established by WHO's Regional Director for South-East Asia to provide advice on all aspects of immunization, vaccines and vaccine-preventable-disease (VPD) prevention, control, elimination and eradication. It comprises experts from such disciplines as programme management, communicable disease and VPD control, virology, epidemiology and immunization. National Expanded Programme on Immunization (EPI) managers, national surveillance focal points, representatives of national immunization technical advisory groups (NITAGs) and partner agencies participate in the ITAG's annual meeting.

The terms of reference of the ITAG are to:

- review Regional and Member State policies, strategies and plans for the control, elimination and/or eradication of VPDs, in particular polio eradication, measles elimination, rubella and congenital rubella syndrome (CRS) control, and the acceleration of Japanese encephalitis (JE) and hepatitis B control;
- provide guidance on the setting of Regional priorities for immunization and vaccines;
- make recommendations on the framework for development of national immunization policies as well as operational aspects of these policies' implementation; and provide a framework for and approaches to periodic evaluation and strengthening of routine immunization (RI) services and systems;
- advise Member States on appropriate choices of new vaccines and recommend optimal strategies and provide technical guidance for the introduction of these vaccines and for the monitoring and impact evaluation of new vaccines once they are introduced into national immunization programmes (NIPs);
- promote and provide technical guidance for the implementation of high-quality VPD surveillance, including high-quality laboratory networks to support VPD surveillance;
- advise Member States on regulatory requirements to ensure quality and safety of vaccines used in NIPs;
- provide guidance on public-private partnerships in immunization and vaccines; and
- identify and advise on appropriate implementation of research topics in immunization and vaccines and review the conduct and results of such research projects.

The meeting began with an opening address by Dr Poonam Khetrapal Singh, WHO Regional Director for South-East Asia, read, on her behalf, by Dr Pem Namgyal, Director, Programme Management, WHO South-East Asia Region (see Annex 1 for the address of the Regional Director). The meeting was chaired by Professor Gagandeep Kang. The other members of the ITAG include Professor Sanath Lamabadusuriya, Dr

Robb Linkins, Dr Charung Muangchana, Dr Yasho Vardhan Pradhan, Dr Antonia Retno Tyas Utami, Professor Mohammad Shahidullah and Professor Saw Win.

The other meeting participants included:

- representatives from NITAGs from 11 countries of the South-East Asia (SEA) Region of WHO,
- representatives and technical experts from WHO headquarters and the WHO Regional Office for SEA,
- the chairperson and two members of WHO's Strategic Advisory Group of Experts on Immunization (SAGE),
- the chairperson of the SEA Regional Certification Commission for Polio Eradication (SEA-RCCPE),
- national EPI managers and surveillance focal points from ministries of health of the 11 countries of WHO's SEA Region,
- representatives and technical experts from the United Nations Children's Fund (UNICEF) headquarters and from UNICEF's Regional Office for South Asia (ROSA) and its East Asia and Pacific Regional Office (EAPRO),
- representatives from the United States Centers for Disease Control and Prevention (US CDC),
- immunization and VPD surveillance focal points from 11 WHO Country Offices in WHO's SEA Region,
- immunization focal points from UNICEF Country Offices,
- representatives of regional and global partners, donors and stakeholders in immunization and vaccines, including Gavi, the Vaccine Alliance (Gavi), PATH and Rotary International (see Annex 2 for the agenda of the meeting and Annex 3 for the full list of participants).

Objectives

The objectives of this meeting were to:

- review progress in performance of NIPs relative to the strategic goals outlined in the South-East Asia Regional Vaccine Action Plan (SEAR-VAP);
- review progress in implementation of the recommendations of the eighth SEAR-ITAG meeting held in June 2017; and
- identify priority actions for 2018 to 2019 to achieve the milestones and goals outlined in the SEAR-VAP.

Organization of the meeting

The meeting was organized over a period of four days and included four components:

- a review of country progress reports as submitted by NITAGs;

- an overview of the SEAR-VAP goals, goal by goal, with country examples for each;
- informational sessions on newer areas of work (e.g., rabies, cholera, typhoid, and influenza vaccines) as well as an update from the recent SAGE meeting;
- group work on how to improve immunization performance through use of the Global Routine Immunization Strategies and Practices (GRISP).

1.1 Methodology for the review of NITAG country progress reports

Both in preparation for and during the meeting, significant time and effort were dedicated to developing methodology for the review of NITAG country progress reports, as these reviews were the major focus of the ITAG meeting.

Prior to the meeting:

- Eight weeks prior to the ninth ITAG meeting, a country-tailored template for annual reporting on progress in meeting SEAR-VAP goals was developed and shared with all NITAGs in the Region.
- The annual progress reports, based on the template mentioned above, were submitted to the SEAR-ITAG (through WHO's Regional Office for SEA) by 10 NITAGs by the end of June 2018. India's report was submitted one week after the ITAG meeting. WHO's Regional Office for SEA and Country Offices provided technical support to all NITAGs as required.
- For each country report, two ITAG members were assigned as reviewers (Annex 3). The ITAG members were provided with a checklist to guide their review of countries' progress in implementing the recommendations from the eighth ITAG meeting and any newer initiatives and in achieving the SEAR-VAP goals.

During the meeting:

- The country progress reports and the reviewers' reports were provided to all ITAG members.
- Each NITAG representative presented a progress report on the country which he or she represented, following the review template shared prior to the meeting.
- Comments on the progress report were provided by the ITAG members and partners.

1. Conclusions and recommendations

1.2 Diphtheria in the SEA Region:

The ITAG notes that the reported incidence of diphtheria in the Region has increased from 1.46 per million population in 2015 to 3.56 per million population in 2017 and that two large diphtheria outbreaks occurred in the Region in 2017 and 2018. There were 3608 probable cases and 241 laboratory-confirmed

cases in the diphtheria outbreak that occurred among the migrants from the Republic of the Union of Myanmar (Myanmar) residing in the temporary settlements in Cox's Bazar, the People's Republic of Bangladesh (Bangladesh). Nearly 68% of these cases were under 15 years of age while only 25.9 % had been vaccinated against diphtheria. Another diphtheria outbreak occurred in the Republic of Indonesia (Indonesia) with 954 clinically compatible cases and a case fatality rate of 3.9%. A total of 70% of the cases were under 15 years of age. India reported 5293 diphtheria cases in 2017. Of these, 1505 cases were from states that conduct case-based surveillance. Sixty-one percent of cases were aged less than 10 years and 67% of cases had not received any vaccination against diphtheria. The reported incidence of diphtheria in the Federal Democratic Republic of Nepal (Nepal) was 25.44 per million population in 2017. In addition to three doses of pentavalent (Penta)/diphtheria-tetanus-pertussis vaccine (DTP) given during infancy, the Kingdom of Bhutan (Bhutan), India, Indonesia, the Democratic Socialist Republic of Sri Lanka (Sri Lanka), the Kingdom of Thailand (Thailand) and the Democratic Republic of Timor-Leste (Timor-Leste) provide three to four booster doses against diphtheria.

The ITAG reviewed the diphtheria incidence and outbreaks in the Region and the number of doses included in the immunization schedules of the countries and notes that the increase in diphtheria cases in the Region is due to persistent immunity gaps as well as policy barriers preventing provision of an adequate number of booster doses. The ITAG appreciates the efforts being made by countries to control diphtheria transmission, especially in India, Indonesia and among migrants in Bangladesh.

The ITAG recommends that countries:

- should achieve high coverage with the third dose of DTP (DTP3) and minimize drop-out between the first dose of DTP (DTP1) and DTP3 at all subnational levels;
- introduce three booster doses of diphtheria-toxoid-containing vaccine as well as conducting catch-up vaccination for children and adults, as dictated by the country epidemiology, in accordance with the revised WHO position paper on diphtheria;
- switch from tetanus toxoid (TT) to tetanus-diphtheria (Td) vaccine as soon as possible, if still using TT;
- establish case-based surveillance for diphtheria and update national guidelines on diphtheria surveillance and outbreaks, in line with the Regional and global surveillance guidelines for VPDs;
- review national laboratory needs for diphtheria diagnostics based on diphtheria epidemiology in the country;
- conduct contact tracing and chemoprophylaxis of suspected and probable diphtheria cases as a mandatory part of clinical-case-management protocols, and outbreak investigations and management;

The SEAR ITAG also recommends that the SEA Regional Office should strengthen coordination with global mechanisms for supply of diphtheria antitoxin to countries in the Region.

1.3 SEAR-VAP

1.3.1 General comments

Based on the deliberations during the ninth meeting, the SEAR ITAG:

- is pleased with the overall progress made in the Region to achieve the goals of the SEAR-VAP;
- commends the ministries of health of all 11 countries of the Region for their commitment to implement strategies targeted to achieve the goals of the SEAR-VAP;
- recognizes the critical role of NITAGs in monitoring progress and guiding actions to overcome the various challenges that exist at national and subnational levels in each country, and to achieve the goals of the SEAR-VAP;
- congratulates the partners for providing strategic support to countries of the Region; and
- notes that challenges and risks remain and that concerted efforts will be required to overcome these if all goals outlined in the SEAR-VAP are to be met.

1.3.2 NITAGs

The SEAR-ITAG notes that all countries in the SEA Region have established NITAGs that provide technical support and monitoring oversight to the NIPs. It also notes that the NITAGs have begun monitoring progress towards the SEAR-VAP goals in most countries and are also providing appropriate guidance to NIPs. It is pleased at the quality of the annual reports prepared by the NITAGs of the 10 countries that have submitted their reports and at the role being played by the NITAGs in monitoring progress towards the immunization goals. The SEAR-ITAG recognizes and highlights that the role of NITAGs remains critical for further progress. The ITAG notes that India's NITAG had yet to submit the country report and recommends that the report for 2017 be submitted by 31 July 2018. It also recommends that India should ensure that, in subsequent years, the country report be shared prior to the ITAG meeting to enable appropriate review and presentation at the meeting.

1.3.3 Progress in meeting SEAR VAP goals

The SEAR-VAP describes a set of goals and objectives for immunization and control of VPDs for the period 2016-2020. It has eight goals, as follows

- GOAL 1: Routine immunization (RI) systems and services are strengthened
- GOAL 2: Measles is eliminated and rubella/CRS controlled
- GOAL 3: Polio-free status is maintained
- GOAL 4: Elimination of maternal and neonatal tetanus is sustained
- GOAL 5: Control of JE is accelerated
- GOAL 6: Control of hepatitis B is accelerated

- GOAL 7: Introduction of new vaccines and related technologies is accelerated
- GOAL 8: Access to high-quality vaccines is ensured

Following a detailed review of performance, the ITAG made its conclusions and provided recommendations for each of the eight goals of the SEAR-VAP.

The conclusions and recommendations of the ITAG for each goal are summarized below.

1.3.3.1 Goal 1. RI systems and services are strengthened

Strengthening the RI systems and services is the overarching goal of the SEAR-VAP 2016-2020. The key targets to achieve are that:

- by 2015 all countries have ≥90% national coverage and ≥80% coverage in every district or equivalent with DTP3;
- by 2020 all countries have ≥90% national coverage and ≥80% coverage in every district or equivalent for all vaccines in national programmes, unless otherwise recommended.

As per WHO/UNICEF estimates, Bangladesh, Bhutan, the Democratic People's Republic of Korea (DPR Korea), the Republic of Maldives (Maldives), Nepal, Sri Lanka and Thailand have achieved 90% or more national coverage with DTP3 in 2017. Of these, Maldives and Sri Lanka have achieved 90% coverage for all vaccines given during infancy and the remaining five countries have achieved 90% coverage for all vaccines except inactivated poliovirus vaccine (IPV). Myanmar has achieved 89% DTP3 coverage while India has achieved 88%, Indonesia 79% and Timor-Leste 76% coverage for DTP3.

As per the 2017 national reports, all districts have achieved more than 80% DTP3 coverage in Bangladesh, Bhutan, DPR Korea, Maldives, Sri Lanka and Timor-Leste. From 2000 to 2017, DTP3 coverage in the SEA Region increased from 64% to 88%. However, an estimated 4.4 million children in the SEA Region do not receive DTP3. Of these, 3.1 million are in India and 1 million are in Indonesia.

All countries in the Region have committed to immunization through legislation or a legal framework that upholds immunization as a priority. All countries have developed a comprehensive national multiyear immunization plan and, in line with this, have developed microplans to improve immunization coverage in all districts or equivalent administrative levels.

Countries in the Region have followed up on the recommendations to improve immunization coverage in urban areas, implementing the recommendations of EPI and VPD surveillance reviews and coverage evaluation surveys and conducting data quality assessments and developing data quality improvement plans. With these efforts, urban immunization coverage is maintained above 90% in Bhutan, DPR Korea, Maldives, Sri Lanka and Timor-Leste. However, evaluated urban coverage is less than 80% in many cities of Bangladesh, India, Indonesia, Myanmar and Nepal. Myanmar conducted a data quality assessment exercise in 2017 and a data quality implementation plan has been initiated in the country. Sri Lanka has an ongoing mechanism for data quality assessment through district-level EPI reviews and initiating actions to correct identified gaps. Bhutan, DPR Korea and Timor-Leste have data quality assessments planned in 2018 and 2019.

Countries have developed innovative approaches such as the Intensified Mission Indradhanush in India, Fully Immunized District Initiative in Nepal, community registration and additional outreach clinics in Timor-Leste, and the high-risk district approach in Indonesia. These approaches have not only strengthened RI services but have also increased the access of the general population to the health system.

ITAG conclusions

- The ITAG notes that, while four countries in the Region have achieved more than 90% DTP3 coverage in all districts, there are considerable gaps at national and subnational levels in the remaining seven countries, resulting in increased incidence of diphtheria, pertussis, and measles.
- The ITAG observes that countries have initiated implementation of recommendations made in 2017 to improve urban immunization coverage.
- The ITAG is pleased that follow-up action on the recommendations of EPI and surveillance reviews and coverage evaluation surveys is being taken in Bangladesh, Bhutan, DPR Korea, Myanmar, Sri Lanka and Maldives.
- The ITAG notes that the EPI and VPD surveillance reviews and the joint appraisals coordinated by Gavi have been conducted back-to-back in some countries and that the findings of the EPI and VPD surveillance reviews and coverage surveys have been extensively discussed during the joint appraisals.
- The ITAG observes that the three components of the recommendations made during its meeting in 2017 (understanding subnational vaccine hesitancy, conducting subnational assessments and developing communication strategies) have been implemented variably in different countries.
- The ITAG notes that efforts have been made by some countries (for example, Myanmar and Sri Lanka) to improve quality of data, and that there is an urgent need to do the same in other countries.

ITAG recommendations

ITAG recommendations for all countries

- NIPs should review ongoing initiatives to improve immunization coverage and implement country-tailored approaches to improve immunization coverage in all districts using well-tested strategies (such as prioritization of districts for interventions; identification of gaps and reasons for children not being fully vaccinated; reviews of and efforts to improve microplans; tracking and reaching missed children; birth registries; data quality improvement; monitoring and supervision).
- Annual district-level immunization reviews should be conducted in priority districts, facilitated by the national programme manager and monitored by NITAG members.
- Strategies to overcome immunization gaps in low coverage areas and populations should be identified and implemented; these strategies should be reported to the SEAR ITAG through the NITAGs;

- NITAGs should monitor implementation of urban immunization coverage activities. especially in Bangladesh, India, Indonesia, Myanmar and Nepal.
- The ITAG reiterates the need for a meticulous follow-up of the recommendations made during the EPI and surveillance reviews and coverage evaluation surveys.
- The practice of conducting EPI review and Gavi joint appraisal back-to-back needs to be continued in forthcoming EPI reviews.
- The ITAG 2017 recommendation on demand generation and vaccine hesitancy needs to be fully implemented with support from UNICEF and WHO.
- Country-specific communication plans to improve confidence in vaccines and increase demand for vaccines, including crisis communication strategies, need to be developed. These plans should be shared with the SEAR ITAG, through NITAGs, during its next meeting.
- The ITAG reiterates the importance of conducting data quality assessments in countries that have not done so in the last three years. Based on the results of these assessments, data quality improvement plans should be developed and implemented; when these data quality assessments are conducted, countries should analyse both immunization and surveillance data for discordance.;

ITAG recommendations for specific countries

- Bangladesh: The ITAG recommends that the urban immunization plan be implemented urgently, and progress reported during the next meeting of the SEAR ITAG.
- DPR Korea: The ITAG recommends that the NITAG should monitor the full implementation of the recommendations of the recently conducted EPI and VPD surveillance review and a report of implementation be shared with the SEAR ITAG during its next meeting.
- India: The ITAG recommends that India's NITAG annually review the impact of targeted measures to enhance RI coverage (such as Mission Indradhanush, Intensified Mission Indradhanush, and the urban health mission) and that the findings of these reviews be presented to the SEAR ITAG during its next meeting. It also recommends an emphasis on analysis of VPD surveillance data in conjunction with reported vaccination coverage.
- Indonesia: The ITAG expresses concerns regarding the ongoing diphtheria outbreaks in Indonesia, which are indicative of low DTP3 coverage. The ITAG recommends that the NITAG engage with the national programme to ensure an analysis of the reasons for persistently low RI coverage and to ensure that an RI strengthening plan be urgently developed and implemented. The NITAG should report back to the SEAR ITAG in 2019 on specific measures taken in this regard. The ITAG also notes with concern the surveillance performance for VPDs and recommends that the NIP work closely with the national surveillance programme to ensure that surveillance performance is enhanced to meet the standards set for the Region as per the Regional VPD surveillance guide.

- Nepal: The ITAG notes the policy regarding age of vaccination which results in children who have missed being vaccinated in accordance with the EPI schedule not receiving any vaccination if they report to any health facility after 23 months of age. The ITAG recommends that the NITAG work with the NIP to advocate removal of this barrier and ensure that all children receive routine vaccination at first contact after a missed scheduled vaccination. The NITAGs should report back, in 2019, on the policy barriers that have been overcome. The ITAG reiterates the ITAG 2017 recommendation of conducting a comprehensive evaluation of '*fully-immunized districts' strategy*' with a focus on districts with suboptimal coverage. The ITAG would appreciate a report on this in 2019.
- Timor-Leste: The ITAG recommends that an analysis of the reasons for sub-optimal RI coverage be conducted and a plan to strengthen RI be prepared urgently.

1.3.3.2 Goal 2. Measles is eliminated, and rubella/CRS controlled

The WHO Regional Committee for the SEA Region, during its Sixty-sixth session in September 2013, adopted a resolution to eliminate measles and control rubella/CRS in the Region by 2020. Reaching the measles elimination and rubella/CRS control goal by 2020 requires all countries to:

- achieve and maintain at least 95% coverage with two doses of measles-and-rubella- containing vaccine (MRCV) through routine and/or supplementary immunization;
- have well-performing case-based measles and rubella/CRS surveillance systems supported by a measles and rubella laboratory network certified as proficient by WHO; and
- strengthen support from and linkages with other health initiatives and efforts at health systems strengthening to achieve the strategic objectives.

Two countries-Bhutan and Maldives-have been verified as having eliminated endemic measles. No measles cases have been reported in Timor-Leste or DPR Korea for more than 24 months. The remaining countries in the Region are still endemic for measles, rubella and CRS. Measles deaths in the SEA Region have been estimated to have been reduced by 73% from 2000 to 2016. All countries in the Region have introduced two doses of measles-containing vaccine (MCV) and eight countries have already introduced rubella-containing vaccine (RCV) in their RI schedules.

The Regional coverage of first dose of measles-containing vaccine (MCV1) has stagnated between 84% and 87% for the last five years and five countries have reported coverage of more than 95% at national level. The Regional coverage of the second dose of measles containing vaccine (MCV2) has increased to 77% in 2017 compared to 59% in 2014. The coverage of RCV delivered through RI was reported at 21% for the Region in 2017 compared to 13% in 2014. All countries in the Region are conducting case-based surveillance for measles and rubella, with India and Indonesia still expanding their measles and rubella case-based surveillance systems. The measles and rubella surveillance performance indicators are gradually improving, with the non-measles non- rubella discard rate, a proxy for the sensitivity of surveillance, at 0.71 in 2017 as compared to 0.41 in 2016. This is much below the target of 2 per 100 000 population, indicating that the sensitivity of the surveillance system remains relatively poor. Five (45%) of 11 countries have achieved the target non-measles-non-rubella discard rate of 2 per 100 000 population

in 2017 compared to three countries in 2016. CRS surveillance is conducted in all countries - in eight as sentinel site surveillance and in three as part of integrated disease surveillance.

A midterm review (MTR) of the progress in implementing the *Strategic Plan for Measles Elimination and Rubella and Congenital Rubella Syndrome Control in the South-East Asia Region 2014-2020* was organized in 2017. The review concluded that the basic strategies articulated in the Strategic Plan are sound and that the programme has gathered momentum in the Region, with two countries verified as having eliminated measles and two rapidly progressing towards elimination. However, measles elimination and rubella/CRS control are not on track to achieve the ambitious goals set by the Region by 2020 and WHO and Member States will have to shift gears to achieve the Regional goals on time. The review also concluded that this will require capitalizing on the existing high degree of in-country political willingness and the enthusiasm of the programme managers. Major investments are necessary and quite some distance shall have to be covered in a relatively short time if Regional goals are to be met as per the declared timeline.

The review also made specific recommendations in the areas of surveillance and immunization for countries of the Region to accelerate progress towards the Regional goal of measles elimination and rubella/CRS control by 2020. Some of the specific recommendations drawn from the midterm review (MTR)[1] that were highly appreciated by the ITAG are as follows:

"1. Ensuring optimal case-based surveillance: A top priority for achieving goals of the Strategic Plan is to enhance integrated case-based, laboratory-supported surveillance for measles and rubella.

1.1. Enhance integrated case-based, laboratory-supported surveillance for measles and rubella in Member States. Member States should shift to fever-rash surveillance to increase the sensitivity.

1.2. Continue monitoring the immunity gaps for both measles and rubella at national and subnational level including adult population.

1.3. SEARO establishes fortnightly or monthly country support meetings at the regional office to review surveillance data to identify weakness, silent areas and interventions; 3-4 countries can be analyzed in depth during every meeting.

1.4. Release of Surveillance Guide for Vaccine-Preventable Diseases on integrated measles and rubella case-based surveillance, serum sample collection strategies to avoid overwhelming laboratories and prioritizing samples for genotypes.

[1] *Midterm review of the strategic plan for measles elimination and rubella/CRS control in South-East Asia Region: 2014-2020 (under publication)*

1.5. *Ensure coordination between field and laboratory with assignment of an EPID number to each suspected case for tracking and final classification*

1.6. *Improve cases classification to determine cases attributable to program failure versus vaccine failure.*

1.7. *Initiate weekly review meetings within the Ministry of Health along with implementing partners using surveillance data for action at national/subnational levels*

2. *Improving immunization coverage and reducing immunity gap: Augmented efforts are needed in the region and individual member countries to improve and maintain population immunity against measles and rubella.*

2.1. *There is a need to undertake multi-dimensional diagnostics of immunization systems within every Member State to assess the current state of health of the routine immunization services and undertake a tailored approach towards strengthening. This will accelerate the achievement of measles and rubella goals. To assess the current state of health of the routine immunization services*

2.1.1. *Regional office works with the countries for developing a tailored approach towards system strengthening*

2.1.2. *Ensure high-quality SIAs: Readiness planning, high risk mapping, rapid coverage monitoring with special attention for high risk regions, districts with poor coverage, and urban poor*

2.2. *Encourage all member states to bring legislation regarding school entry/school level checks for immunization*

2.3. *Use of 2nd year of child platform for catchup immunization including those who have missed MCV; ensure children who miss MCV-2 are immunized even beyond the expected time and age schedules*

2.4. *MCV-2 should be adopted as a marker of mapping SDG progress, which is also expected to result in a healthy competition that will benefit the MR goals.*

2.5. *Adopt immunization status checking of at-risk population, healthcare workers, and teachers.*

3. *Ensuring a strong laboratory network to support the case-based surveillance and genotyping: Laboratory network activities needs to be optimized to support the MR surveillance and monitoring the eradication process.*

3.1. *WHO continues to have an important role in monitoring the External Quality Assurance (EQA) of Regional Reference (RRL) and National Laboratories (NLs).*

3.2. *Responsibility for coordination and maintenance of the quality of subnational Laboratories (SNLs) should be with the National (reference) Laboratory in that country, with support and guidance of SEARO.*

3.3. *Regular MR genetic sequence information from the region should be analysed and reported.*

3.4. *WHO HQ should conduct an updated IgM assay assessment to provide evidence for countries to make decisions on procurement of appropriate kits.*

3.5. *WHO should continue to provide kits for low-income countries.*

3.6. *The capacity of the SEAR LabNet is appropriate for the current/expected workload, however the full impact of Rash-Fever only surveillance is still unknown. Any Subnational LabNet expansion needs to be balanced with a careful analysis of all the factors and a cost-benefit analysis exercise.*

3.7. *Members states to ensure data harmonization between laboratory and surveillance and WHO should supervise and support.*

3.8. *Regular MR genetic sequence information from the region should be analysed and reported in the vaccine preventable disease (VPD) surveillance bulletin along with evidence of transmission patterns, both within the region and globally.*

4. *Strengthening the advocacy and communication strategies: Adoption of appropriate advocacy and communication strategy and tools needed for furthering the MR efforts and prevent the vaccine resistance and hesitance issues.*

4.1. *WHO includes review of measles eradication and rubella control program in the annual agenda of the Regional Committee Meetings to bring focus and accountability.*

4.2. *WHO advocates with Member States for greater ownership and investment in the MR immunization.*

4.3. *WHO incorporates rubella elimination along with measles in the regional goal.*

4.4. *National Verification Committees continue to play advocacy roles with their respective governments for achieving the MR goal.*

4.5. *WHO and Member States urgently develop a well-thought out media strategy for achieving quantum impact on the ongoing elimination efforts.*

4.6. *WHO and Member States develop country specific (tailoring for subnational needs) budgeted social mobilization and communication plan for both MR activities under routine immunization (RI) and supplementary immunization activity (SIA) campaigns.*

4.7. *WHO to support and facilitate systematic mapping of vaccine hesitancy and resistance and the Member States are encouraged to develop context specific debunking strategies."*

Other recommendations made by the MTR team related to concerns around the polio transition and its potential impact on measles and rubella goals, addressing programming to offer measles rubella vaccine (MR) in emergency and conflict settings, and calling for increasing investment to implement the Regional measles and rubella strategic plan and to conduct operations and implementation research.

ITAG conclusions

The SEAR-ITAG commends the progress made towards measles elimination and rubella/CRS control in the Region despite challenges in big countries such as India and Indonesia.

The SEAR ITAG endorses the recommendations made by the MTR of the implementation of the SEAR strategic plan for measles elimination and rubella/CRS control.

The SEAR ITAG expects NITAGs of countries to work with national programmes and national verification committees (NVCs) to advocate, support and monitor implementation of the recommendations of the MTR and the SEAR ITAG.

The ITAG recommends that NITAGs follow-up and monitor activities taken to address recommendations from the 2017 ITAG meeting that are still ongoing and ensure that these activities are completed and reported on at the next ITAG.

ITAG recommendations

ITAG recommendations for all countries

- Recommendations made during 2017 meeting are followed-up and implemented fully.

Immunization

The ITAG reiterates the need to strengthen RI as the backbone of measles elimination and rubella/CRS control and recommends that:

- MCV2 be included in the definition of a fully-immunized child (FIC), MCV1 vs MCV2 drop-out be monitored;
- any policy and programmatic framework barriers to vaccination of children presenting to immunization centres beyond the regular age of scheduled vaccination be removed, and vaccination services be extended until the age of at least 5 years;
- considering that seven countries will be conducting MR supplementary immunization activities (SIAs) in the Region in 2018-2019, recommends:
    - pre-campaign readiness assessments should be conducted, as per the WHO guidelines, and an evaluation of campaign coverage should be an integral part of SIA planning and implementation;
    - MR SIAs should be used as a platform to strengthen RI and this should be documented, with a report to SEAR ITAG during its next meeting;
- the WHO *Measles Subnational Programmatic Risk Assessment Tool* be used to develop subnational plans to mitigate the risk of measles transmission;
- any outbreak response plan should include a root cause analysis to identify and address gaps in immunization system to prevent future VPD outbreaks.

Surveillance

With regard to measles, rubella and CRS surveillance, the ITAG recommends that:

- countries that have yet to update surveillance guidelines to conform to elimination-standard surveillance should do so urgently;

- reporting of suspected measles cases be increased by ensuring expansion of the measles and rubella surveillance reporting system and ensuring fever-maculopapular rash surveillance in all countries;
- periodic data quality assurance for measles and rubella surveillance data and data triangulation be regularly conducted to ensure high-quality data, and that data be used for action; there be an update on the commercialization and evaluation of the programmatic feasibility of point-of-care testing (POCT) at the next ITAG meeting.

With regard to laboratory support:

The ITAG commends the Region for putting together a laboratory quality management system to ensure sustained proficiency of the measles rubella laboratory network and recommends that recommendations made during the 2017 meeting be followed up and implemented fully.

ITAG recommendations for specific countries

- India:
    - The country should move from aggregate reporting to nation-wide, case-based surveillance at the earliest.
    - The ITAG notes the risk to the 2020 measles elimination goal due to challenges in implementation of measles elimination strategies in India and recommends a close monitoring of the implementation of strategies by the NITAG and the India Expert Advisory Group (IEAG) for measles elimination.
- Indonesia:
    - The ITAG recommends that Indonesia ensure a nationwide expansion of case-based surveillance for fever-maculopapular rash, involving the private sector as well, preferably before the end of 2018 to accelerate progress towards the 2020 goal.
    - The ITAG recommends that the country consider facilitating fast-track customs clearance for proficiency-test sample transport, shipment related to quality assurance (QA) samples, test kits and laboratory supplies related to VPD surveillance.
- Myanmar:
    - The ITAG notes the low MCV1 and MCV2 coverage and the low sensitivity of surveillance for measles and rubella. The ITAG recommends that the NITAG work with NIP to develop strategies to accelerate progress in increasing MCV1 and MCV2 coverage and enhancing the sensitivity of surveillance.
- Nepal:
    - The ITAG recommends that the NITAG work with the NIP to review the reasons for low MCV2 coverage and implement strategies to accelerate the coverage of MCV2.

- Sri Lanka:
    - The ITAG encourages the country to do a further analysis of why the surveillance indicators of a non-measles non-rubella discard rate of 2 per 100 000 population and AFP rates of 2 per 100 000 children aged less than 15 years are not being met.
- Thailand:
    - The ITAG recommends aligning the measles rubella surveillance guide to elimination standards through an adaptation of Regional guidelines and building country capacity to implement the revised guidelines.
    - The ITAG recommends that Thailand take immediate measures to close the immunity gap for measles and rubella that has resulted in a number of measles outbreaks in the country and conduct a root cause analysis of the cause of the measles outbreaks in the country.

1.3.3.3 Goal 3. Polio-free status is maintained

The SEA Region has achieved the goal of polio eradication and maintained its polio-free status for the past seven years. However, the Region continues to be at risk of importation of wild poliovirus (WPV) from countries with current poliovirus transmission and any outbreak due to circulating vaccine-derived poliovirus (cVDPV).

To maintain its polio-free status, the Region continues to follow the Global Polio Eradication and Endgame Strategic Plan 2013-2018, which has the following four objectives:

1. detecting and interrupting poliovirus circulation,
2. withdrawal of oral poliovirus vaccine (OPV), beginning with the type 2 component, introduction of inactivated polio vaccine (IPV) and strengthening RI,
3. containment of polioviruses and certification,
4. transition planning.

Acute flaccid paralysis (AFP) and environmental surveillance (ES)

The overall non-polio AFP rate in the SEAR in 2017 was 7.10 (data as per week 24, 2018) per 100 000 population under 15 years of age, which exceeds the globally-recommended operational target of 2 per 100 000. The non-polio rate was above 2 in 2017 in seven SEA Region countries, namely Bangladesh, Bhutan, India, Indonesia, Maldives, Myanmar and Nepal, while it was between 1 and 2 (which meets certification standards) in three countries, namely DPR Korea, Sri Lanka and Thailand. The non-polio AFP rate of Timor-Leste was less than 1 per 100 000 population under 15 years of age. In 2017, two stool samples were collected at least 24 hours apart and within 14 days of onset from 86% of the reported AFP cases in the Region, as compared to the globally-recommended target of at least 80%. Nationally, the target was achieved in 2017 by eight countries, namely Bangladesh, Bhutan, DPR Korea, India, Indonesia, Myanmar, Nepal and Sri Lanka. However, for both performance indicators there is considerable subnational variance in several countries.

In 2017, ES activities in the Region were expanded to include additional sites in Indonesia and India and were initiated in Myanmar and Nepal. A total of 63 sites in 23 provinces of six countries, namely Bangladesh, India, Indonesia, Myanmar, Nepal and Thailand, are currently conducting ES. Bangladesh operates four temporary sites in Cox's Bazaar. ES data provided important evidence for the disappearance of Sabin-like poliovirus type 2, following the switch from trivalent OPV (tOPV) to bivalent OPV (bOPV) during 2016.

No vaccine-derived polioviruses (VDPVs) were detected in AFP cases in 2017 or during the period January to May 2018. A type 2 VDPV was detected in sewage samples in India in 2017. A detailed risk analysis was conducted which concluded that the event was low risk, no evidence of circulation was found, and that the event had been adequately responded to in terms of surveillance and RI strengthening. Investigations to assess population immunity and surveillance quality are currently ongoing in the area in India where, in May 2018, a type 3 VDPV was isolated in a sewage sample. Response measures taken include strengthening AFP surveillance and improving routine coverage with bOPV and intradermal (ID) IPV in the sewage catchment area.

Population immunity through RI and SIAs

Six countries (Bangladesh, Bhutan, DPR Korea, Maldives, Sri Lanka, and Thailand) have reported coverage with the third dose of oral polio vaccine (OPV3) above 90%; India, Indonesia, Myanmar, and Nepal have coverage between 80% and 90% while Timor-Leste had coverage of 75% in 2017, based on the WHO and UNICEF July 2018 revision of estimates of national immunization coverage for 2017. To close immunity gaps against polio, SIAs with OPV were conducted in 2017 in Bangladesh, India, Myanmar and Nepal.

IPV introduction, challenges and actions to mitigate the risks

All countries in the Region introduced IPV between 2014 and 2016. In view of the global supply constraints and in the context of studies that demonstrate that two doses of intradermal IPV (one fifth of the full dose) are superior to one intramuscular dose of IPV, India and Sri Lanka have provided two ID doses of IPV to all infants since mid-2017. Stock-outs of IPV occurred in four countries (Bangladesh, Bhutan, DPR Korea, Nepal). Supplies have been restored to all four countries. Bangladesh has shifted to a two-ID-dose schedule, while preparations for the same are currently underway in Nepal and it is likely that the country will also introduce a two-dose-ID IPV schedule by August 2018. Bhutan and DPR Korea reintroduced IPV in 2018. Catch-up of missed cohorts with IPV is being planned in Bhutan in 2018, using ID IPV, and in DPR Korea in 2019, using intramuscular IPV.

Poliovirus laboratory containment

Activities to contain type 2 polioviruses in facilities are progressing in the Region. Poliovirus essential facilities (PEF) have been identified to store/handle type 2 polioviruses in two countries of the Region, namely India and Indonesia. National authorities for containment (NACs) have been established in both countries and processes to undertake certification of these facilities as per the global containment certification scheme (CCS) have commenced. All countries are implementing new surveys of biomedical laboratories to meet requirements outlined in the *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 (GAPIII). Special trainings on GAPIII requirements for national containment taskforces (NCTF), PEFs, NACs and vaccine manufacturers were successively conducted by WHO in January, February and October 2016, followed by training for CCS auditors in January 2017 and a Regional review and planning meeting in April 2017. More capacity-building activities are planned in late 2018/early 2019. The Regional Poliovirus Laboratory Network (RPLN) has conducted several bio-risk management capacity building activities. Laboratories are expected to fully implement the assessment, mitigation and performance (AMP) model on top of the quality cycle (plan do check act) to ensure that their performances meet GAP III requirements. Countries are being supported with direct technical assistance to prepare their activity plans for containment of Sabin2/type 2 OPV (OPV2) materials. One of the challenges in GAPIII implementation is involvement of facilities that collect, handle and store clinical and environmental samples for purposes other than polio research. WHO has developed *Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses (PIM)*'; this guidance was pilot tested in Bangladesh in December 2017 in a workshop with high-risk laboratories.

Certification of maintaining polio-free status

The Regional Certification Commission for Polio Eradication (RCCPE) and national certification committees for polio eradication (NCCPEs) in all 11 countries are functional and providing oversight and guidance to polio eradication activities. The tenth meeting of the SEA-RCCPE was successfully conducted in November 2017 in Nay Pyi Taw, Myanmar. The RCCPE reviewed progress in each country in the Region and concluded that the Region has remained polio-free.

Transition planning

Transition planning of polio assets that have been established in SEA Region is a critical part of preparing for the polio-free world. The Global Polio Eradication Initiative (GPEI) has begun to ramp down its funding and will eventually end in the post-eradication era. However, certain critical functions, as mentioned in the polio Post Certification Strategy (PCS) would still be required to be maintained after global certification. The five countries of the Region with substantial GPEI-funded polio infrastructure, namely Bangladesh, India, Indonesia, Myanmar and Nepal, have developed transition plans, which are at different stages of review by the respective governments. The transition plan of Bangladesh has been formally endorsed by the government. Fully mindful of the programmatic risks associated with the loss of polio networks, the transition plan development in countries of the SEA Region is focusing on mechanisms to transfer the capacity to government (to the extent possible), exploring alternative financial support to make up for the loss of the GPEI funding, and building capacity of polio teams to support 'new public health programmes'. Realizing that the involvement of governments is critical for the success of the transition process as well for longer-term financial sustainability, an active engagement of the government during the polio transition plan development is at the centre of transition planning.

ITAG conclusions

- The SEAR ITAG appreciates that the Region has remained polio-free for more than seven years but recognizes that the risk of poliovirus resurgence remains.

- The ITAG notes the challenge posed by the recent increase in the IPV price globally.
- The ITAG recognizes the risks associated with the ramp down of polio funding, especially regarding critical polio functions that need to be sustained for several years after global polio-free certification, as well as the adverse impact on immunization/other vaccine preventable disease surveillance programmes in countries with significant GPEI funded infrastructure.

ITAG recommendations

ITAG recommendations for all countries

- High-quality AFP surveillance must be maintained and high population immunity against polioviruses sustained during the post-eradication phase.
- A periodic risk assessment for polio should be conducted in close collaboration with the NCCPEs and plans to mitigate risks developed. Risk of containment breaches should be included in risk assessments and should be a part of national preparedness plans, as well as included in simulation exercises.
- Outbreak response capacity to respond to detection of any WPV or VDPV outbreaks should be updated in the countries, as per the most recent global guidelines.
- The ITAG recognizes the 2018 World Health Assembly (WHA) resolution on poliovirus facility containment and the challenges of GAPIII implementation, particularly in view of technical and managerial complexities and long-term commitment for the time of poliovirus use in vaccine production and research. While commending the progress made in the Region, the ITAG reiterates the importance of GAPIII compliance in view of the polio reintroduction risk from facilities/laboratories.
- Recognizing the risks to polio and other immunization/surveillance programmes, the ITAG recommends that the draft polio transition plans in the four countries without finalized transition plans (India, Indonesia, Myanmar and Nepal) be urgently finalized and endorsed by the relevant ministries of health (MoHs). Continued commitment of MoHs with greater engagement of ministries of finance, as appropriate, will be critical for ensuring longer-term financial sustainability through allocation of domestic resources.

ITAG recommendations for specific countries

- Bangladesh: The ITAG urges the programme in Bangladesh to initiate reporting results of ES in the SEA Region's standardized reporting form, to harmonize reporting of results.

1.3.3.4 Goal 4. Elimination of maternal and neonatal tetanus is sustained

All countries in the Region follow the WHO recommendation on vaccinating pregnant women with tetanus-toxoid-containing vaccine (TTCV). Over 80% coverage with two or more doses of TTCV in pregnant women (TT2+) has been reported by seven countries for several years, as reported through the WHO/UNICEF Joint Reporting Form (JRF). Regional TT2+ coverage improved from 64% in 2014 to 78% in

2015 and has been maintained at this level. However, lower coverage does not necessarily indicate weak programme performance. After accumulating repeated vaccine doses during multiple pregnancies and SIAs, women of childbearing age (WCBA) eventually become non-eligible for further vaccination during pregnancy while still contributing to the target denominator for calculation of TT2+ coverage. Field surveys conducted during validation exercises have indicated much higher protection at birth than reported TT2+ coverage suggested.

Infant immunization against tetanus (DTP and Penta) rose from 56% in 2000 to 88% in 2017 according to JRF country official estimates. Several countries give booster doses in early childhood or have integrated TTCV vaccination into their school health programmes. NIPs also provide a combination of tetanus and diphtheria toxoid as booster doses in late childhood and/or for pregnant women.

In 1988, countries in the Region reported almost 15 000 neonatal tetanus (NT) cases. However, this number was estimated to only represent 10% of the true number of cases, as the majority of NT cases were not reported. As a result of immunization efforts and improved NT surveillance, often integrated with other VPD surveillance, 443 NT cases from six countries were reported in 2017.[2] . None of the countries exceeded the "elimination" definition of <1 NT case per 1 000 live births (LB) in each district, considered as the third administrative level of a country.

ITAG conclusions

- The SEAR ITAG acknowledges that the Region has maintained its status as having eliminated maternal and neonatal tetanus, however, there is no room for complacency and the Region needs to continue to work to achieve the targets for the various key strategies outlined for sustaining maternal and neonatal tetanus elimination (MNTE).

ITAG recommendations

ITAG recommendations for all countries

- National programmes should engage with NITAGs to review and optimize the TTCV schedule.
- NITAGs should engage with national programmes to regularly conduct national reviews of the status of indicators related to MNTE and recommend corrective actions as required.
- Appreciating the positive impact of the "post-elimination validation assessment" in Timor-Leste, the ITAG recommends that programmes in all countries should plan such exercises every three to four years, as per the global guidelines.

1.3.3.5 Goal 5. Control of JE is accelerated

Currently, 10 of 11 countries in the SEA Region are endemic for JE, with the exception being Maldives. Vaccination is the most cost-effective strategy to prevent and control JE and WHO recommends that JE vaccination be integrated into national immunization schedules in all areas where JE is recognized as a

[2] *Source: JRF; no data included for Bhutan and Indonesia and India figures provisional*

public health priority. Three countries, Nepal, Sri Lanka and Thailand, have introduced immunization against JE nationwide, while India has introduced it in high-risk areas. All countries (excluding Maldives) in the Region are conducting JE and acute encephalitis syndrome (AES) surveillance with varying levels of intensity: nationally in seven countries (Bangladesh, DPR Korea, Myanmar, Nepal, Sri Lanka, Thailand and Timor-Leste), in all high-risk areas in India and sentinel sites in Bhutan, and Indonesia). JE/AES surveillance is supported by 14 laboratories in the Region (with 10 of them accredited by WHO as of 2017) for confirmation of suspected cases. Four laboratories are provisionally accredited.

In 2016 and 2017, about 2000 cases of AES were reported each year in Myanmar. Around 20% of these were confirmed as JE. The case fatality rate in different states and regions of the country varied from 10-35%. Following comprehensive analysis of data, Myanmar conducted a JE immunization campaign for children aged 9 months-15 years in November and December 2017. Of 13 605 174 children targeted. 92.5% were vaccinated. This campaign was followed by a nationwide introduction of JE vaccine in January 2018. The vaccine is now administered under routine immunization programme to infants at 9 months of age. Due to the successful campaign, only 37 laboratory-confirmed JE cases have been reported up to June 2018. The high coverage achieved during the campaign was due to meticulous preparations, careful monitoring and effective communication strategies.

Based on its disease burden, the Indonesian island of Bali conducted a JE vaccination campaign in March and April 2018 during which 964 011 children aged 9 months-15-years were vaccinated. Following the vaccination campaign, Bali has introduced JE vaccine into its routine immunization schedule.

With the administration of the JE vaccine (either nationwide or in selected high-risk areas) through SIAs followed by introduction of the vaccine into the routine infant immunization schedule, JE is under control in Nepal, Sri Lanka and Thailand. Discussions during the ITAG meeting revealed that, in Sri Lanka and Thailand, there have been a few laboratory-confirmed cases among children who had received a single dose of live attenuated JE vaccine. Nonetheless, most reported cases were among unvaccinated adults.

ITAG conclusions

- The ITAG appreciates the progress made towards the introduction of JE vaccine in the Region and the progress made towards control of JE.
- The ITAG compliments the programme in Myanmar for the successful implementation of one of the largest high-quality JE vaccination campaigns.

ITAG recommendations

ITAG recommendations for all countries

- NITAGs of potentially—JE-endemic countries, such as Bangladesh, Bhutan, DPR Korea, Indonesia, and Timor-Leste, should engage with national programmes to review disease burden and the potential benefit of JE vaccine introduction in RI, and report back to the ITAG at the next meeting.
- NITAGs should work with national programmes of countries where JE vaccine has been introduced in RI to ensure high coverage of JE vaccine nationally and sub-nationally.

- National programmes in all countries should ensure high-quality laboratory-supported JE surveillance in line with the recently-released Regional JE Surveillance Guide.
- The Regional Office for South-East Asia should coordinate studies and analysis of surveillance data to gather information on the protection provided by vaccines in immunization campaigns or when used in the RI system.

ITAG recommendations for specific countries

- Bhutan: The ITAG recommends that Bhutan consider the introduction of JE vaccine in the country.

1.3.3.6 Goal 6. Control of Hepatitis B is accelerated

In 2017, all 11 countries in SEAR had hepatitis B vaccine (HepB) in their RI schedules as part of combination vaccines, and eight countries (Bhutan, DPR Korea, India, Indonesia, Maldives, Myanmar, Thailand and Timor-Leste) had introduced a universal HepB birth dose (HepB-BD) (WHO Monitoring System 2017).

The overall coverage with the third dose of HepB (HepB3) in the Region increased from 53% in 2010 to 88% in 2017.[3] Although HepB3 coverage is reported to be 90% or more in seven countries, it does not yet reach these levels in India (88%) and Indonesia (85%), which account for the largest births cohorts in the Region, or in Myanmar (89%) or Timor-Leste (81%). Among the eight countries that included HepB-BD in their vaccination schedule in 2017, coverage was above 90% in four (Bhutan, DPR Korea, Maldives and Thailand). India, which contributes 70% of the births annually in the Region, reported a timely HepB-BD coverage of 53%. Indonesia reported a total HepB-BD coverage of 86%. No relevant coverage figures were yet available for Myanmar due to the recent introduction of HepB-BD.

Nationally-representative serosurveys among children at least 5 years of age to estimate post-vaccination seroprevalence of hepatitis B surface antigen (HbsAg) are available in Bangladesh, Bhutan, Nepal and Thailand. In India, there are a number of studies, but they have all focused on one area or state. In Nepal, subnational studies have shown geographic variability in HbsAg prevalence. The DPR Korea is planning to conduct a national household-based survey among children aged more than 5 years and Maldives is planning a national school-based survey among children in Grade 1. Timor-Leste has no serosurvey data and the Immunization and Vaccine Development Unit of WHO's Regional Office for South-East Asia (IVD SEARO) is assessing the feasibility of a combined lymphatic filariasis and hepatitis B serosurvey in the coming years.

Several countries have sustained high HepB-BD and HepB3 coverage for at least 5 years and have likely achieved the target of reducing chronic hepatitis B prevalence to less than 1% among children. IVD SEARO is currently developing the mechanism for verifying countries' attainment of this target. The main evidence for verification would include both a nationally-representative serosurvey to measure, with adequate precision, the prevalence of chronic hepatitis B among children at least 5 years of age born after vaccine introduction, and high sustained HepB coverage. It is proposed that, upon countries' request for

[3] *Source: calculated on country official estimates in JRF 2017*

verification, a committee composed of three independent experts, including one committee chair, would be appointed by the Regional Office for South-East Asia. The committee will review the evidence submitted by the country, request additional information or clarifications from the country as needed, and make a recommendation to the Regional Office as to whether the target has been achieved. IVD SEARO would support countries conducting serosurveys, assemble the documents and information needed for verification, and facilitate the verification process. Countries' achievements of the target will be publicly recognized.

ITAG conclusions

- The SEAR-ITAG appreciates the progress made in the Region towards control of hepatitis B through vaccination.

ITAG recommendations

ITAG recommendations for all countries

While recommendations made at the 2017 meeting remain valid, the ITAG added the following:

- The proposed verification process should be finalized, and its implementation initiated prior to the next ITAG meeting.
- National programmes should prioritize achieving high coverage of HepB3 and ensure that children under five years of age are covered with catch-up or patch-up vaccination with HepB3.
- Countries should introduce HepB-BD and ensure timely delivery of the HepB-BD, where indicated by disease epidemiology.
- Encouraged by the methodology and results of the hepatitis B sero-survey in Bhutan, the ITAG recommends that WHO ensure adequate support for other countries planning to conduct nationally-representative hepatitis B serosurveys among children under 5 years of age;
- The ITAG encourages countries with a high percentage of home deliveries to explore the feasibility of introducing HepB using Uniject.

ITAG recommendations for specific countries

- Bangladesh: The ITAG recognizes the results of the 2011/2012 national seroprevalence survey indicating very low levels of HbsAg in children but recommends further study of the epidemiology of hepatitis B infection in the country in view of the fact that no birth dose is provided in the country.
- Myanmar: The ITAG recommends measures to improve coverage of HepB-BD urgently; the NITAG should monitor coverage and timeliness of HepB-BD.
- Timor-Leste: The ITAG recommends that HepB-BD coverage be increased, as well as coverage achieved with vaccinations offered during the 2nd year of life platform, with a focus on MCV2.

1.3.3.7 Goal 7. Introduction of new vaccines and related technologies is accelerated

New and increasingly sophisticated vaccines have become available in the last decade for diseases that have not traditionally been targeted by NIPs. As a result, all countries in the Region have added two or more new vaccines to the national immunization schedule during the last decade and have strengthened their NIPs in the process. In the process of a new vaccine introduction specific activities that are considered include integrating surveillance of the disease targeted by the new vaccine into the national disease surveillance system or establishing sentinel surveillance, analysing disease burden, decision-making by the NITAG, conducting studies of the cost-effectiveness of introducing the vaccine, reviewing the sustainability of integrating the vaccine into the RI system, developing comprehensive plans for introduction based on the experiences with previous new vaccine introductions, monitoring for adverse events following immunization (AEFI) following vaccine introduction and conducting post-introduction evaluations.

The target under this goal of the SEAR-VAP is for each country to introduce at least two additional new or underutilized vaccines between 2016 and 2020. Table1 highlights the progress in new and underutilized vaccine introduction in the Region.

Table 1: Introduction of new and underutilized vaccines in the SEA Region, 2016-2018

Country	National	Subnational	Planned introductions
Bangladesh		HPV vaccine (1 district)	Rotavirus vaccine (2018)
Bhutan	MMR		
India	MR	Rotavirus vaccine (11 states), PCV (5 states) HPV (2 districts),	
Indonesia	IPV, MR	HPV (1 province and 4 districts), PCV (2 districts), JE (1 province)	
Myanmar	PCV, JE		
Nepal		HPV (1 district)	Rotavirus vaccine (2018)
Sri Lanka	HPV		
Thailand	HPV		Rotavirus vaccine (2019)
Timor-Leste	IPV		

Priority vaccines for consideration based on the disease burden of countries are pneumococcal conjugate vaccine (PCV), human papilloma virus (HPV) vaccine, JE vaccine and rotavirus vaccine (RV). In addition, cholera, mumps, seasonal influenza and typhoid vaccines could be considered for specific geographical areas and age groups.

A Regional meeting on prevention of cervical cancer through HPV vaccination was conducted in New Delhi, India from 5 to 7 June 2018 with the overall objective of strengthening the capacity of Member States for prevention of cervical cancer through HPV vaccination and other prevention strategies. Following were the key observations and follow-up actions of the meeting.

- All countries of the Region except DPR Korea and Timor-Leste have analysed the disease burden due to cervical cancer and have evidence that cervical cancer is a public health problem.
- Bhutan, Sri Lanka and Thailand are conducting school-based HPV vaccination. The percentage of girls who are attending school is high in these countries. A demonstration project in Bangladesh, showed that school-based HPV vaccination is acceptable to families, school management and communities. More than 90% coverage with HPV vaccine has been achieved among girls in these countries through school-based vaccination. The remaining girls could be covered through the RI centres. Hence, a joint approach of school-based immunization and vaccination through RI centres seems appropriate for most countries in the Region.
- To date there have been no reports of severe AEFI with HPV vaccine in the SEA Region. Mild adverse events have been reported from all countries; reporting of these events is an indicator of the sensitivity of AEFI surveillance. Globally, more than 250 million doses of HPV vaccine have been administered from 2006 to 2017. The WHO Global Advisory Committee on Vaccine Safety has stated that, since licensure of HPV vaccines, no new adverse events of concern based on many very large high-quality studies have been found.
- Even though the vaccine is relatively expensive, the overall costs to the health system diminish over time due to a reduction in the costs for treatment of cervical cancer. Research shows that the HPV vaccine is highly cost-efficient, particularly for low-income countries. Despite the existing disease burden and recommendations from the relevant NITAGs that the HPV vaccine be introduced, India and Indonesia have had challenges in allowing policy makers to understand cost-benefit and cost-effectiveness of HPV vaccination. Bangladesh and Nepal are planning to conduct cost effectiveness studies.
- Conducting a cost effectiveness analysis of HPV vaccination will help with advocacy – making the case for securing internal and external financial resources, selecting the right mix of interventions to optimize the healthcare budget, and facilitating tender negotiations between purchasers and vaccine manufacturers.
- Gavi has supported HPV vaccination since 2013. Following the recommendation by SAGE to target multiple age cohorts instead of targeting a single age cohort, Gavi revised guidelines in 2016 to allow countries to target multiple age cohorts. Despite Gavi having approved proposals which will

result in the vaccination of 25 million girls by 2020, realizing this vision will be difficult due to constraints in vaccine supply. To facilitate supply planning for this costly vaccine, countries are encouraged to submit applications for funding to Gavi immediately. Doing so will ensure that vaccine will be available 18-24 months after the application is approved.

- There are mature school health programmes and adolescent health programmes in the countries of the SEA Region. HPV vaccine can be integrated into these programmes. HPV vaccine introduction can be linked to augmenting cervical cancer screening programmes for women. However, a coordinated approach among different government departments as well as partner agencies is needed to introduce HPV vaccine and control cervical cancer.

A Regional consultation on rotavirus and RVs was conducted in 2017. Following were the key observations and follow-up actions.

- Countries that wish to obtain genotyping data may refer up to 60 rotavirus-positive specimens for genotyping to the regional reference laboratory (RRL) each year.
- If considered useful, countries may decide to investigate other causes of paediatric diarrhoea, especially after RV is introduced. Sentinel surveillance should be sustained for a minimum of two to three years after vaccine introduction to assess vaccine impact.
- Bhutan and Maldives need to be supported to initiate sentinel surveillance.
- All SEA Region countries should consider joining the Global Rotavirus Surveillance Network.
- Intussusception is a rare event but monitoring for this event and communicating with providers and caregivers regarding its possibility is important. Hence awareness and capacity building is necessary for healthcare providers and immunization staff.
- The risk of intussusception associated with RVs is best evaluated in countries with available background data or those with large birth cohorts. Where background data on intussusception is not available, initiation of intussusception surveillance should be planned with relevant partners before RV introduction.
- Cost-effectiveness and cost-benefit analyses are valuable and should be used to enable informed decision-making regarding vaccine introduction by national authorities. These studies need to be conducted in collaboration with ministries of health to create ownership of data.
- Regional networking to provide analytic support to smaller countries could be facilitated by the WHO Regional office.
- When a decision to introduce RVs is made, the choice of vaccines should be made early for procurement planning, appropriate training, and logistic arrangements. Given the different composition and presentations of available RVs, both technical specifications and programme implementation need to be considered in order to make adequate preparations.
- Interchangeability of RVs within the programme should be avoided as the various vaccines differ with regard to dose volume, required buffer, presentation of doses, reconstitution requirements,

temperature for transport and storage, shelf-life and vaccine vial monitors. Once introduced, a change in the vaccine preparation should be permitted only if there is a compelling reason. Such reasons may include significant differences in vaccine safety, performance or cost.

- Countries may conduct a readiness assessment before introduction of the vaccine.
- Post-introduction monitoring with systematic evaluation of data and post-introduction evaluation six to twelve months after vaccine introduction will help to identify programmatic gaps and address these.

ITAG Conclusions

- The SEAR ITAG notes that the Region had conducted a Regional consultation on rotavirus disease and RV as well as a Regional meeting on the control of cervical cancer through HPV vaccination and other public health interventions. These activities provided an opportunity to national programmes to understand the evaluation of disease burden, available vaccines and their impact, the operational needs associated with their introductions, cost effectiveness analysis and the available support for introduction of these vaccines from Gavi.

ITAG recommendations

ITAG recommendations for all countries

- NIPs should conduct disease burden analysis and, based on these data, make decisions around the introduction of new vaccines such as HPV vaccine, RV and PCV, as appropriate.
- National programmes should follow up on the recommendations of the Regional consultation on RV and the Regional meeting on the control of cervical cancer with HPV vaccination.
- Noting the outcomes of the post-introduction evaluations (PIEs), the ITAG reiterates the necessity of following up on the recommendations of these evaluations.
- National programmes and partner agencies should seek opportunities to link PIEs to EPI reviews or joint appraisals, as appropriate.
- NITAGs should discuss with national programmes the SAGE recommendations related to:
    - new vaccines (typhoid, cholera, rabies, seasonal influenza)
    - the impact of vaccines on broader issues such as antimicrobial resistance (AMR).

ITAG recommendations for specific countries

- DPR Korea: The ITAG recommends that VPD surveillance be strengthened to cover diseases prevented by existing vaccines as well as those by potential new vaccines.
- Maldives: The ITAG recommends that the country consider the introduction of new vaccines of public health importance into the RI programme.

- Sri Lanka: The ITAG recommends a review by the NITAG of the burden of pneumonia and diarrhea for consideration of relevant vaccine introductions in the context of broader public health value of vaccines, as advocated recently by SAGE.

1.3.3.8 Goal 8. Access to high-quality vaccines is ensured

Recognizing that access to affordable vaccines of assured quality is central to the performance of immunization programmes, the SEAR-VAP 2016-2020 has identified ensuring access to high-quality vaccines as one of its eight goals.

Vaccine development and production capacity in the Region is growing and playing an increasingly positive role, both at Regional and global levels. Three of the 11 countries of the SEA Region are WHO-prequalified (PQ) vaccine-producing nations, contributing significantly to lower-middle-income countries (LMICs) access to high-quality vaccines at affordable prices. Bangladesh has established vaccine manufacturing capacity and is currently positioned to manufacture cholera vaccine for the United Nations (UN), which could help address a global shortage. However, the national regulatory authority (NRA) in Bangladesh needs to be assessed for its functionality before the cholera vaccine produced in the country can be prequalified for use by the UN. At present, only Indonesia, India and Thailand have NRAs assessed as functional by WHO.

The key strategy to ensure access to high-quality vaccines is to enhance Regional cooperation through the expansion of centres of excellence (e.g., WHO Global Learning Opportunities (GLO)) to provide training and technical supports to countries in the Region in the areas of vaccine regulatory and immunization supply chain management. In April 2017, the Regional Office for SEA supported the first South-East Asia Regulatory Network (SEARN) meeting in New Delhi to promote Regional collaboration in the areas of vaccine regulation. Similar collaboration to address access to high-quality vaccines is promoted in the Asia Pacific region with the Association of Southeast Asia Nations (ASEAN) Vaccine Security and Self-Reliance (AVSSR) working group established and endorsed by the ASEAN Health Cluster work plan for 2016-2020 as part of the ASEAN Post 2015 Health Development Agenda.

There is a strong need in the Region to invest in research, development and manufacturing techniques to identify the best ways to access appropriate technology and expertise, to manage intellectual property rights and to develop thermostable and suitable products as well as new bioprocessing and manufacturing technologies. Governments can promote enabling environments for NRAs and manufacturers by communicating regularly and working in partnership with researchers, biotech companies and universities to develop new vaccines and technologies.

ITAG conclusions

- The SEAR-ITAG appreciates the AVSSR, a Regional cooperation mechanism to ensure access to assured quality vaccine and expects WHO to explore possibilities of extension of such initiatives to all countries in SEA Region.
- The ITAG appreciates the extensive use of web-based modern technology by Maldives to enhance the use of modern technologies (web-based applications and social media applications) to

strengthen immunization systems and build confidence about vaccination and encourages countries to do the same.

- The ITAG notes the different challenges but also opportunities to supply vaccine for RI, for SIAs and to respond to outbreaks and/or the emergence or re-emergence of VPDs and new pathogens. However, the ITAG acknowledges that pharmaceutical industry prioritizes RI and encourages partners to invest in R&D for outbreak preparedness.
- The ITAG appreciates the increased investments in cold chain equipment in the SEA Region countries using both Gavi and domestic funding.
- The ITAG acknowledges the responsibility of the NRA for safety, quality and efficacy of vaccine down to the point of use.

ITAG recommendations

ITAG recommendations for all countries

- WHO should explore the possibilities of building on the AVSSR initiative in order to extend this to all SEA Region countries. The ITAG would like a report on the progress in implementing the AVSSR and other Regional mechanisms of co-operation for access to vaccines.
- The ITAG acknowledges the need to better understand vaccine market trends and notes that WHO's Vaccine Product, Price and Procurement (V3P) Web Platform is a reliable source of information on vaccine price and procurement. This platform offers easy access to multiple types of analysis, which is very useful for making informed decisions regarding the selection of vaccine products, prices and procurement strategies. The ITAG would recommend to all SEA countries to upload data to V3P.
- Progress has been reported by NRAs with regard to vaccine regulation. Regional collaboration and networking among institutions have helped to strengthen NRAs. Similar strategies to foster Regional collaboration are required to strengthen in-country immunization supply chain management (ISCM) and ensure all stakeholders are involved. This should include regulatory inspectors to enforce Good Distribution Practices (GDPs) of medicines (including vaccines).
- Countries should use standardized WHO monitoring tools such as the Vaccine Adverse Events Information Management System (VAEIMS) to report AEFI through the existing district health information software (DHIS), as well as using algorithms to conduct causality assessments. These practices will enable countries to exchange vaccine safety information.
- To sustain investment in cold chain equipment and make the best use of newly acquired equipment, the ITAG recommends that country investments in HR and infrastructure be increased to establish sustainable ISCM.
- The EPI and NRA are encouraged to enhance collaboration to implement GDP and the development of indicators to monitor implementation of GDPs.
- Several countries, i.e., Bangladesh, Nepal, and Myanmar, received Gavi cold chain equipment optimization platform (CCEOP) support to upgrade cold chain infrastructure. These funds were used

to procure cold chain equipment, but less investment in infrastructure was reported. The ITAG encourages countries to write a multi-year plan aimed at ensuring the development of the vaccine cold chain infrastructure, as well as human resources (HR) capacity and in-service training to permit installation, maintenance and operation of newly acquired equipment.

- The ITAG recognizes country capacity strengthening activities to establish regulatory functions in compliance with International/WHO standards to regulate vaccine safety, quality and efficacy. The ITAG encourages countries to continue implementing their Institutional Development Plans and establish a SEA NRA technical collaboration agreement whereby NRAs assessed as functional would provide technical support to NRAs with more limited capacity.

ITAG recommendations for specific countries

- Bangladesh: The ITAG recognizes the role of Bangladesh as a vaccine-producing country and recommends that WHO facilitates the process of making the NRA functional.
- Bhutan: The ITAG recommends strengthening of AEFI surveillance in Bhutan.
- India: The ITAG acknowledges the very comprehensive national cold chain development plan that included a revamp of the existing cold chain system and the establishment of resource centre for technical and training support in India. The ITAG recommends exploring the possibility of expanding the activities of this resource centre to serve other countries in the SEA Region.

2. Informational sessions

The presentations on four informational sessions conducted during the ITAG are summarized below:

Rabies:

WHO published an updated position paper on Rabies vaccine in February 2018 that focuses on programmatic feasibility, simplification of vaccination schedules and improved cost-effectiveness of the vaccine. The two main strategies for rabies immunization include post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) for which WHO recommends cell culture and embryonated egg-based rabies vaccines (CCEEVs). These vaccines are shown to be safe, highly immunogenic and well tolerated. These vaccines can be given through both intramuscular and intradermal route. The intradermal route requires smaller amount per dose. Randomized trials for rabies vaccine are not possible so assessment of vaccine efficacy depends on observational data and animal models. It has been seen that most individuals who receive PEP achieve adequate antibody titer of 0.5 IU/ml by 7-14 days, irrespective of age or nutritional status. The SAGE working group on Rabies was set up in June 2016. The SAGE reviewed scientific evidence and country practices in the use of Rabies vaccine and Rabies Immunoglobulins (RIG). The SAGE emphasized on implementation of the recommendations on intradermal use of vaccines, prudent use of RIG and monoclonal antibodies to improve access to care and enhance public health impact.

Cholera:

Cholera affects at least 47 countries across the globe, resulting in an estimated 2.9 million cases and 95,000 deaths per year worldwide. It continues to hit communities already made vulnerable by tragedies, natural calamities, conflicts and famines. The SAGE Working Group on oral cholera vaccines recommends that Oral Cholera Vaccines (OCVs) are safe for use among individuals ≥ 1 year of age, including in pregnant women. A single dose is efficacious and effective for at least 2 years for individuals above 5 years age. A two-dose schedule is efficacious and effective for at least 3-5 years among adults. Campaigns with OCV have demonstrated to be feasible and acceptable in endemic, epidemic and humanitarian emergency settings. Modelling studies suggest that cholera vaccination has the potential to be a cost-effective intervention for cholera control in countries at high risk of cholera.

Since 2013, inactivated whole cell oral cholera vaccines (OCV) have been made available for deployment from a global OCV stockpile, which is intended for cholera control in outbreaks, humanitarian crises and in settings with endemic cholera. Emergency deployment of OCVs from the stockpile is coordinated by an International Coordinating Group (ICG) with WHO serving as the secretariat. During 2014-2018, Gavi funded US$115 million for vaccine provision and is also funding operational costs for OCV campaigns.

Bangladesh has conducted various studies on cholera vaccines. In one such study it was shown that vaccine alone or integrated with WaSH had similar effectiveness in protecting against cholera. It has also been shown in Bangladesh that a single dose of the inactivated whole-cell OCV offered protection to older children and adults and this protection is sustained for at least 2 years. Another study has shown that the vaccine at higher temperature does not alter vibriocidal antibody responses.

Typhoid:

Globally there are 11-21 million cases of typhoid annually causing 128,000 to 161,000 deaths. The peak incidence is seen under 15 years of age and nearly 27% of all typhoid disease is seen in children under five years of age. Typhoid can be prevented and controlled by measures like access to safe water, adequate sanitation, hygiene (WaSH), following food safety practices and vaccination. Two typhoid fever vaccines have been recommended since 2000, namely parenteral unconjugated purified Vi polysaccharide vaccine and oral live attenuated Ty21a vaccine. In 2008, WHO recommended programmatic use of typhoid vaccines against endemic and epidemic typhoid with limited routine use in high risk populations in selected countries.

Typhoid conjugate vaccine (TCV) comprising of Vi polysaccharide available in the form of Vi polysachharide – Tetanus Toxoid conjugate was licensed in 2013 for use among individuals, 6 months to 45 years of age, and prequalified by WHO in December 2017. WHO, in its 2018 position paper, recommends TCV as the preferred vaccine in view of improved immunological properties, suitability for use in younger children and expected longer duration of protection. It also recommends, primary vaccination with a single IM dose for infants and children from 6 months of age and adults up to 45 years of age in typhoid endemic regions. TCV can be used in routine programme at 9 months of age, or in the 2nd year of life. Catch up vaccination is recommended up to 15 years of age when feasible and supported by epidemiology. The introduction of TCV should be prioritized in countries with the highest burden of typhoid disease or a high burden of antimicrobial resistant S. Typhi. Vaccination is recommended in response to confirmed

outbreaks of typhoid fever. Countries experiencing typhoid outbreaks should consider introduction or strengthening of routine immunization programmes.

Seasonal Influenza:

Seasonal influenza is responsible for an estimated 290 000 – 650 000 respiratory deaths annually. The goal of Global Action Plan (GAP) for Influenza Vaccines is to produce enough vaccine to immunize 70% of the global population with 2 doses. The status of the three objectives of GAP are:

1. Increase evidence based seasonal vaccine use: In 2014, 115 countries/territories reported to have influenza vaccination policies (81 for pregnant women) and there was an uptake of 486 million doses against uptake of 354 million doses in 74 countries/territories in 2006.
2. Expand vaccine production & regulatory capacity: Potential pandemic vaccine production has increased to 6.37 billion doses against 1.46 billion doses in 2006. Production capacity has been expanded to low middle-income countries (LMICs) and 10 GAP countries have reached regulatory maturity for vaccines against 4 in 2006.
3. Further research & development (R & D) for better vaccines: Some novel vaccines like recombinant, live attenuated influenza vaccine (LAIV), quadrivalent, adjuvanted seasonal for infants, high dose for elderly have been licensed but overall there has been little progress in R & D and a universal influenza vaccine is still distant.

Influenza surveillance is being carried out in SEAR with nine countries (Bangladesh, Bhutan, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand) routinely reporting to FluNet. Eight SEAR countries, namely Bangladesh, DPR Korea, India, Indonesia, Myanmar, Nepal, Sri Lanka and Thailand have at least one National Influenza Centre. Three SEAR countries (Maldives, Nepal and Thailand) have seasonal influenza included in their immunization schedule for at least one risk group.

3. Group work - immunization performance improvement using GRISP

The objectives of this session were for country groups to:

- conduct a self-assessment which would enable each group to identify the level of maturity in 2017 of the country's immunization system in terms of the nine transformative investment areas identified in GRISP;
- propose a target maturity level of each immunization system in terms of the nine transformative investments by 2020;
- identify broader strategies and activities based on the current and proposed status in 2020 to ensure that the 2020 maturity levels for all nine transformative investments are achieved.

Each country team reviewed the nine transformative investment areas and the four levels of maturity for each of the nine areas, as provided. Following a discussion, each country team established a baseline by self-assessing the maturity level of the country's immunization system in 2017 for each transformative change.

Using the immunization system strengthening grid provided, countries marked the level of maturity for each of the nine-transformative investments, plotted a graph for 2017 and set maturity targets to be achieved by 2020. The country teams also developed strategies to progress towards and achieve proposed targets for 2020, drawing upon GRISP as a resource.

Countries were expected to finalize the maturity indices that had been developed at the ninth ITAG meeting and share these indices with the WHO Regional Office for SEA. Large countries were also expected to conduct a similar exercise at subnational level.

4. Annexes

- **Annex: Opening address by Regional Director**

Ninth Meeting of the SEA Region Immunization Technical Advisory Group (SEAR-ITAG) 17-20 July 2018, New Delhi, India

Opening address delivered by DPM on behalf of Dr Poonam Khetrapal Singh, Regional Director, WHO South-East Asia Region

Members of the South-East Asia Region Immunization Technical Advisory Group, chairpersons of the National Immunization Technical Advisory Groups, SAGE members representing the Region, colleagues from WHO headquarters and countries of the South-East Asia Region, representatives of partner agencies, ladies and gentlemen,

A very warm welcome to New Delhi and to the ninth meeting of our Region's Immunization Technical Advisory Group, or ITAG.

Although our Regional Director, Dr Poonam Khetrapal Singh, would have very much liked to attend this important meeting, she is unable to do so due to a prior commitment. I therefore take great pleasure in delivering this message on her behalf.

When the Regional Director spoke at last year's meeting she emphasized the Region's remarkable progress, both in strengthening NIPs and in eliminating specific diseases. It is to each of your credit – as well as to the credit of health workers across the Region – that we have maintained and built on these achievements.

To this day we remain polio-free. We have maintained the elimination of maternal and neonatal tetanus as a public health problem. Key vaccines have been introduced in a number of countries, including for pneumonia, diarrhoea and Japanese encephalitis among other vaccine preventable diseases. The control of hepatitis B – which accounts for the largest proportion of associated mortality – has meanwhile been accelerated, with a host of countries now poised to follow Bhutan and Maldives in eliminating endemic measles.

Dr Khetrapal Singh notes that across the Region, immunization managers and health workers are better trained while cold-chain structures are more reliable. That injection safety has been enhanced and vaccine management systems are more effective. And that we have laboratory networks with greater capacity and surveillance systems that are better equipped to meet the challenges we face.

She says we are, in short, moving towards a brighter and healthier future for all – one that is free of vaccine preventable diseases and the unnecessary death and suffering they cause.

The Regional Director emphasizes that it is your technical input and resolve, combined with the energy and determination of health workers from the grassroots up, that made these achievements possible. Indeed, she says, let us be candid: Your efforts have saved millions of lives and supported the health and

wellbeing of whole communities and countries. That is an immensely powerful achievement, and one worth reflecting on as we begin this four-day meeting.

But let us also be candid about what is needed: immediate, accelerated and sustained progress. Of the 37 million children born in our Region every year, Dr Khetrapal Singh notes, more than 32 million receive three doses of the basic DTP-containing vaccine annually. That is a solid strike rate, but leaves just under 5 million children acutely vulnerable to these diseases. Identifying and reaching those children must, necessarily, be core to our mission.

Similarly, she says, a rise in diphtheria cases in areas once thought to be rid of the disease highlights that despite our gains, complacency and inaction can reverse them with rapid effect. Ensuring that momentum is maintained and high-level commitment secured is paramount. To that end, the Regional Director urges your continued advocacy and vigilance at all times and at all levels.

Distinguished participants,

During the Seventy-first World Health Assembly, WHO Member States from across the world – including the South-East Asia Region – adopted the Thirteenth General Programme Of Work, or GPW13. That plan outlines a mission that is aligned with the Sustainable Development Agenda and which has three components: First, to promote health; second, to keep the world safe; and third to serve the vulnerable.

To achieve the first component, the Regional Director says, one billion more people must gain access to quality health services. That reflects and will accelerate the global drive towards universal health coverage. To achieve the second component, one billion more people must be protected from health emergencies. That is aligned with and reinforces WHO's increased focus on emergency preparedness and response. And to achieve the third component, one billion more people must enjoy better health and wellbeing. That will be the outcome of promoting healthier populations and serving the vulnerable as a matter of priority.

As you appreciate, Dr Khetrapal Singh notes, our Region has the world's largest birth cohort and accounts for more than a quarter of the world's population. Achieving these commitments will therefore have life-changing impact here more than anywhere. Our success will be the world's success; our struggle the world's struggle. With regard to each of the GPW's targets, as well as those of the Sustainable Development Goals, stronger NIPs– achieved via the full implementation of the Regional Vaccine Action Plan – will have substantial impact.

This is so for a number of reasons.

First, providing access to quality health services means providing access to strong routine immunization programmes. That is the primary goal of the Regional Vaccine Action Plan which, among other strategic objectives, urges Member States to establish and maintain high-level commitment to immunization; to ensure individuals and communities understand the value of vaccines and demand them as both a right and responsibility; and to guarantee access to predictable funding, quality supply and innovative technologies.

Second, the Regional Director says, protecting people during public health crises requires high base-levels of immunization coverage, as well as a skilled workforce able to provide immunization with rapid effect.

As the Regional Plan emphasizes, the benefits of immunization must be extended equitably, including to marginalised or hard-to-reach populations – those who suffer acute events the most severely. The rapid, large-scale immunization campaigns carried out in recent months in Cox's Bazar, Bangladesh, demonstrate that a strong immunization system backed by a sizeable, well-trained health workforce can protect hundreds of thousands of people when they need it most.

And finally, the Regional Director emphasizes, promoting healthier populations by serving the vulnerable requires us reaching the unreached and underserved with the benefits vaccines provide. By ensuring each and every child, adolescent and pregnant woman in the South-East Asia Region receives the vaccines they need to stay healthy and strong, greater confidence and buy-in to health systems more generally will be achieved. That will increase and promote the health and wellbeing of all, helping each and every individual take full advantage of the opportunities before them.

As you can see, the Regional Plan is well aligned with GPW13 and the targets it sets, as well as the Global Vaccine Action Plan and the Decade of Vaccines. It also reflects the theme of this year's World Immunization Week, which we marked in the last week of April. Needless to say, the Regional Director emphasizes, being 'Protected Together' means creating 'a South-East Asia Region free of vaccine preventable diseases, where all countries provide equitable access to high-quality, safe, efficacious, affordable vaccines and immunization services throughout the life course' – the Regional Plan's vision statement. Our unity of purpose is indeed one of our greatest strengths.

Distinguished participants,

As you know, last year's ITAG meeting was documented in great detail, with key conclusions, recommendations and goals recorded and published. This meeting provides a critical opportunity to review progress and identify where impact can be enhanced. I trust you will be in a position to do so, thereby making full use of ITAG's function and potential.

Importantly, this meeting also provides an opportunity to hone our focus on the Flagship Priority of eliminating measles and controlling rubella by 2020. As outlined earlier, though substantial progress has been made, parts of the Region require immediate and accelerated gains. By sharing experiences and engaging with and learning from one another we can achieve that outcome.

Indeed, Dr Khetrapal Singh remarks, your input over the coming days will prove immensely valuable. You have demonstrated what can be achieved when sound strategy is matched with effective implementation, and when partners work together to harness the full power of vaccines to prevent diseases that need not – and must not – persist. As deliberations commence, the Regional Director urges you to take stock of these truths, and to recognize your capacity to drive real progress across our Region, and with it the world.

On that note, the Regional Director wishes you fruitful deliberations and a very pleasant stay in New Delhi.

I echo that sentiment and wish you all the best over the coming days.

Thank you.

- **Annex: Meeting Agenda of the Ninth Meeting of the WHO South-East Asia Regional Immunization Technical Advisory Group.**

Day 1, Tuesday, 17 July 2018		
08:00-9:00	Registration	
09:00-09:45	Opening Session	
09:45-10:15	Group photograph, followed by Tea/Coffee break	
10.15-11:45	– Remarks by chair SEAR ITAG	G Kang, Chair SEAR-ITAG
	– Remarks by chair SAGE	A Cravioto, Chair SAGE
	– Remarks by UNICEF, US CDC and Gavi	
	– South-East Asia Regional Vaccine Action Plan – progress and challenges (30 mins)	S Bahl, WHO SEARO
	– Global Vaccine Action Plan – an update (20 mins)	P Lydon, WHO HQ
	– Discussion (15 mins)	
11:45-13:00	– Immunization response to public health emergency in Cox's Bazar– key lessons on coverage and equity (20 mins)	MoH Bangladesh
	– Managing diphtheria outbreak in Indonesia (20 mins)	MoH Indonesia
	– Diphtheria – key immunization and surveillance issues (20 mins)	M Patel, WHO HQ
	– Discussion (15 mins)	
13:00-14:00	Lunch break	
14:00-15:20	Progress in immunization programme performance in SEAR countries	
	– Process of review of immunization performance in SEAR countries (10 mins)	G Kang, Chair ITAG
	– Timor-Leste – immunization progress report (20 mins)	NITAG, Timor-Leste
	– Thailand – immunization progress report (20 mins)	NITAG, Thailand
	– Discussion on Timor-Leste and Thailand (30 mins)	
15:20-15:50	Tea/Coffee break	
15:50-17:35	Routine immunization systems and services are strengthened (Goal 1 of RVAP)	

	– Progress and challenges in strengthening immunization systems and services: An overview (20 mins)	J Liyanage, WHO SEARO
	– Communication strategy to support immunization system strengthening: recent developments (20 mins)	A Hasman, UNICEF ROSA
	– Health system and immunization strengthening: Gavi perspective (20 mins)	C Szeto, GAVI
	– Discussion (20 mins)	
	– Life cycle approach to vaccination (15 mins)	MoH Sri Lanka
	– Discussion (10 mins)	
17:45-18:30	ITAG closed door	
19:00-21:00	Dinner/Reception	

Day 2, Wednesday, 18 July 2018		
08:30-10:00	Measles Elimination and Rubella/CRS Control (Goal 2 of RVAP)	
	– Progress and challenges in measles elimination and rubella/CRS control in SEAR: An overview (20 mins)	S Khanal, WHO SEARO
	– Mid-term Review (MTR) of SEAR strategic plan for measles elimination and rubella/CRS control – key findings and recommendations (20 mins)	NK Arora, MTR Lead
	– Discussion (20 mins)	
	– Point-of-care testing for measles diagnostics – findings from a recent study in India (15 mins)	L Sangal, WHO India
	– Strengthening surveillance for measles elimination (15 mins)	MoH DPR Korea
10.00-10:30	Tea/Coffee Break	
10:30-11:40	Progress in immunization programme performance in SEAR countries (contd.)	
	– Sri Lanka – immunization progress report (20 mins)	NITAG Sri Lanka
	– Nepal – immunization progress report (20 mins)	NITAG Nepal
	– Discussion on Sri Lanka and Nepal (30 mins)	
11:40-12:50	Polio-free status is maintained (Goal 3 of RVAP)	

	– Global polio update – key challenges and priorities (15 min)	J Ahmed, WHO HQ
	– Progress and challenges in maintaining polio-free status in SEAR: An overview (15 mins)	S Joshi, WHO SEARO
	– Poliovirus containment – progress and challenges in SEAR (15 mins)	S Roesel, WHO SEARO
	– Risk assessment oversight by certification bodies (10 mins)	S Chunsuttiwat, Chair RCCPE
	– Discussion (15 mins)	
12:50-13:50	Lunch break	
13:50-14:30	Managing polio transition - global strategic action plan and implications for SEAR countries (20 mins)	E Ekeman, WHO HQ
14:40-15:50	Discussion (20 mins) Progress in immunization programme performance in SEAR countries (contd.)	
	– Myanmar – immunization progress report (20 mins)	NITAG, Myanmar
	– Maldives – immunization progress report (20 mins)	NITAG, Maldives
	– Discussion on Myanmar and Maldives (30 mins)	
15:50-16:20	Tea/Coffee break	
16:20-17:10	Elimination of maternal and neonatal tetanus is sustained (Goal 4 of RVAP)	
	– Progress and challenges in sustaining maternal and neonatal tetanus in SEAR – An overview (20 mins)	S Roesel, WHO SEARO
	– Post-validation assessment of MNTE (15 mins)	MoH Timor-Leste
	– Discussion (15 mins)	
17:10-17:45	Informational session:	
	– Rabies vaccination (20 mins)	R Aggarwal, SAGE member
	– Discussion (15 mins)	
18:00-19:00	ITAG closed door	
Day 3, Thursday, 19 July 2018		
08:30-09:15	Control of Japanese Encephalitis is accelerated (Goal 5 of RVAP)	

	– Progress and challenges in acceleration of JE in SEAR: An overview (15 mins)	J Liyanage, WHO SEARO
	– JE campaign in Myanmar – lessons learnt (15 mins)	MoH Myanmar
	– Discussion (15 mins)	
09:15-10:15	Control of Hepatitis B is accelerated (Goal 6 of RVAP)	
	– Progress and challenges in acceleration of Hepatitis B in SEAR (20 mins)	S Roesel, WHO SEARO
	– Hepatitis B sero-survey in Bhutan – key findings (20 mins)	MoH Bhutan
	– Discussion (20 mins)	
10.15-10:45	Tea/Coffee Break	
10:45-11:55	Progress in immunization programme performance in SEAR countries (contd.)	
	– Indonesia – immunization progress report (20 mins)	NITAG Indonesia
	– India – immunization progress report (20 mins)	NITAG India
	– Discussion on Indonesia and India (30 mins)	
11:55-13:10	Introduction of new vaccines and technologies is accelerated (Goal 7 of RVAP)	
	– Progress and challenges in NUVI and related technologies in SEAR: An overview (15 mins)	J Liyanage, WHO SEARO
	– Planning for Rotavirus vaccine introduction in Nepal (15 mins)	MoH Nepal
	– Fractional IPV use in India – key findings from an evaluation study (15 mins)	MoH India
	– Vaccine investment strategy – some opportunities (15 mins)	D Patel, Gavi, The Vaccine Alliance
	– Discussion (15 mins)	
13:10-14:10	Lunch break	
14:10-15:20	Progress in immunization programme performance in SEAR countries (contd.)	
	– DPR Korea – immunization progress report (20 mins)	NITAG, DPR Korea
	– Bhutan – immunization progress report (20 mins)	NITAG, Bhutan

	– Discussion on DPR Korea and Bhutan (30 mins)	
15:20-15:45	Tea/Coffee break	
15:45-16:45	Informational sessions:	
	– Cholera vaccination (20 mins)	F Quadri, SAGE member
	– Typhoid vaccination (20 mins)	AD Bentsi-Enchill, WHO HQ
	– Discussion (20 mins)	
17:00-18:00	ITAG closed door	

Day 4, Friday, 20 July 2018		
08:30-09:30	Access to high-quality vaccines is ensured (Goal 8 of RVAP)	
	– Progress and challenges in ensuring access to quality vaccines in SEAR: An overview (15 mins)	S Guichard, WHO SEARO
	– ASEAN vaccine security and self-reliance – lessons learnt (15 mins)	MoH Thailand
	– EVM assessment using modern technology (15 mins)	MoH Maldives
	– Discussion (15 mins)	
09:30-10:05	Progress in immunization programme performance in SEAR countries (contd.)	
	– Bangladesh – immunization progress report (20 mins)	NITAG Bangladesh
	– Discussion on Bangladesh (15 mins)	
10:05-11:00	Informational session: Seasonal Influenza vaccination	S Goldin/ C Nannei, WHO HQ
11.00-11:30	Tea/Coffee Break	
11:30-14:00	Immunization performance improvement using GRISP pillars: Strengthening maturity index – Group work (ITAG closed door meeting in parallel)	Facilitated by WHO, UNICEF, Gavi, The Vaccine Alliance, US- CDC
13:00-14:00	Working lunch	
14:00-15:00	Country presentations on maturity index for immunization system strengthening	Selected countries
15:00-15:30	Tea/Coffee Break	

15:30-17:00	Closing Session	
	– ITAG conclusions & recommendations	G Kang, Chair ITAG
	– Remarks by partners	WHO/UNICEF/CDC/Gavi/others
	– Closing remarks	Chair ITAG and WHO-SEARO

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The Ninth Meeting of the World Health Organization's South-East Asia Regional Immunization Technical Advisory Group (SEAR-ITAG) was held from 17 to 20 July 2018 in New Delhi, India.

SEAR-ITAG is a technical group comprising experts from disciplines such as programme management, communicable diseases and vaccine preventable disease control, virology, epidemiology and immunization. SEAR- ITAG provides guidance on setting of regional priorities for immunization and technical support for strengthening routine immunization services to Member States. It meets annually with the participation of national Expanded Programme on Immunization (EPI) managers and surveillance focal points and partner agencies to review progress on increasing immunization coverage, improving surveillance performance, programme issues, and matters related to vaccine quality assurance. The SEAR-ITAG provides guidance on ways to improve and sustain overall high-quality performance in Member States.

This publication provides an overview of meeting proceedings, conclusions and recommendations from the 2018 annual meeting of the SEAR-ITAG expert group.

27TH MEETING OF THE TECHNICAL ADVISORY GROUP ON IMMUNIZATION AND VACCINE-PREVENTABLE DISEASES IN THE WESTERN PACIFIC REGION, 2018

The 27th Meeting of the Technical Advisory Group on Immunization and Vaccine-Preventable Diseases in the Western Pacific Region (TAG) was held in Manila, Philippines from 19 to 22 June 2018. Since 1991, the TAG has met annually to review the progress of the immunization programme in the Western Pacific Region and provide guidance on establishing and achieving immunization goals. The meeting was attended by six TAG members, three temporary advisers, 32 participants from 16 countries and areas, 43 representatives from partner organizations and World Health Organization (WHO) staff from headquarters, the Regional Office for the Western Pacific and county offices.

Objectives

The 27th Meeting of the Technical Advisory Group on Immunization and Vaccine-Preventable Diseases in the Western Pacific Region was held in Manila, Philippines from 19 to 22 June 2018. The objectives of the meeting were:

- to review progress, identify critical issues and determine key actions to achieve the regional immunization goals specified by the *Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific* (GVAP) and the strategic objectives of the GVAP;
- to identify opportunities to enhance coordination and collaboration among immunization-related initiatives, programmes and partners to support countries in achieving the regional immunization goals and the GVAP strategic objectives; and
- to prepare recommendations by the TAG for WHO and countries.

Conclusions

Immunization system strengthening (including progress towards GVAP strategic objectives)

- The TAG commends Member States' continuous efforts to strengthen immunization systems toward reaching immunization goals set by the GVAP and the *Regional Framework for Implementation of the GVAP in the Western Pacific*. The TAG congratulates the Western Pacific Region on its reported high regional coverage with three doses of diphtheria–tetanus–pertussis vaccine (DTP3) of 97.3% in 2017.
- The TAG acknowledges the efforts made by Member States to strengthen functions of the national immunization technical advisory groups (NITAGs)

or equivalent bodies and notes that, as of 2017, NITAGs of six countries and areas (Australia, Hong Kong SAR China), Mongolia, New Zealand, Republic of Korea and Singapore) have met all global indicators of NITAG functionality. However, there remains a need for comprehensive evaluation of the effectiveness of NITAGs. The TAG also notes that Cambodia (2017), the Lao People's Democratic Republic (2018) and Mongolia (2017) conducted international Expanded Programme of Immunization (EPI) reviews, leading to updated comprehensive multi-year plans (cMYP) and appropriate actions by the national immunization programmes (NIPs).

- The TAG acknowledges the efforts of WHO and partners in supporting the Philippines to strengthen immunization systems and improve access to vaccines. Further, the TAG notes the country fact sheet developed by the Vaccine Product, Price and Procurement Initiative (V3P) and disseminated to NIPs to support vaccine procurement decision-making. The TAG also notes that, since 2015, national regulatory authorities (NRAs) in seven countries have met WHO NRA assessment criteria. These NRAs have overseen the quality of vaccines for 91% of the total population of the Region. The TAG notes that, as of 2017, surveillance systems of adverse events following immunization (AEFI) are in place in 23 countries in the Region.

- Despite these achievements in regional immunization coverage and progress in strengthening immunization systems, the TAG notes with concern that the following immunization system issues and challenges have not yet been sufficiently addressed:

  (1) inadequate capacity for formulation of evidence-based immunization policy in lower middle-income countries (LMICs) and Pacific island countries;

  (2) insufficient budget and weak financing for subnational immunization programme activities in LMICs;

  (3) vaccine stock-outs due to insufficient capacity for forecasting, financing, procurement, stock management, and distribution, particularly in LMICs and Pacific island countries, and also due to global shortages and supply issues affecting some countries;

  (4) insufficient capacity for implementation of AEFI surveillance and response including risk communications in many countries;

  (5) inequities in vaccination coverage at the subnational level as a result of barriers to immunization access and insufficient engagement of communities in vaccination, especially for population groups such as migrants, minority ethnic groups and residents in both urban slums and remote areas; and

  (6) inadequate quality of immunization data; in countries with sufficient information technology infrastructure and capacity, electronic immunization information systems could support the improvement of data quality and better monitoring of immunization records for every child.

New vaccines introduction

- The TAG commends the progress in the introduction of new vaccines in low- and lower middle-income countries in the Region. Eighty-nine per cent of low- and lower middle-income countries in the Region have introduced at least one new vaccine since 2010. The TAG also commends progress in the Region for developing and using evidence for making decisions on introduction of new vaccines and the continued support that WHO gives to governments on vaccination policy. Achievement of the Decade of Vaccines goals for introduction of new and underutilized vaccines requires that countries evaluate evidence on disease burden including surveillance, cost, the role of other disease prevention and control measures, vaccine characteristics, vaccine supply, and immunization programme and health system strength.

- The TAG acknowledges challenges with new vaccine introduction, particularly the limited progress in new vaccine introduction in upper middle-income countries, and the need to promote and facilitate introduction in these countries. The TAG also notes the importance of laboratory-based surveillance for diseases prevented by new vaccines and the critical need to maintain surveillance and laboratory capacity in an era of declining resources.

Accelerated hepatitis B control

- The TAG congratulates the 21 currently verified countries and areas whose immunization programmes have met the 2017 prevalence target of less than 1% hepatitis B surface antigen (HBsAg) in 5-year-old children, including Cambodia and the Federated States of Micronesia, which were recently verified to have met this target.

- The TAG again notes the Hepatitis B Immunization Expert Resource Panel's (ERP's) [1] proposed 2018–2025 regional targets that have yet to be adopted by the Regional Committee, including: 1) to reduce HBsAg prevalence to less than 1% in 5-year-old children in all countries and areas by 2025; and 2) to further reduce HBsAg prevalence to less than 0.5% by 2025 in countries and areas that already have less than 1% prevalence in 5-year-old children. The TAG acknowledges that the ERP has written a request to the Japan and New Zealand ministries of health to demonstrate the effectiveness of their selective birth-dose administration programmes. The TAG also notes the ERP's request for Japan and New Zealand to consider universal administration of timely hepatitis B birth dose (HepB-BD), which is defined as a dose given within 24 hours of birth.

- The TAG further acknowledges the correlation between institutional deliveries and HepB-BD coverage, reflecting the challenges in reaching children born outside of facilities with a timely HepB-BD. Use of HepB-BD

[1] The coordinator for the Hepatitis B Immunization Expert Resource Panel can be reached through the Expanded Programme on Immunization, WHO Regional Office for the Western Pacific, at woodringj@who.int.

outside of the cold chain (OCC), an off-label use, or in a controlled temperature chain (CTC) with regulatory approval, can help address these challenges. The TAG is encouraged to know that package inserts for at least two monovalent hepatitis B vaccines already indicate that the vaccine is stable for one month at 37 °C, and for one week at 45 °C. Availability of HepB-BD for CTC use is expected in the future.

- The TAG acknowledges that the global goal to eliminate viral hepatitis as a public health threat by reaching 0.1% HBsAg prevalence in children by 2030 is ambitious but necessary for elimination of mother-to-child transmission (EMTCT) of hepatitis B virus (HBV). While reaffirming that HepB-BD and third-dose coverage remain the cornerstone of HBV control, the TAG acknowledges that EMTCT of HBV and HBV infection elimination will require interventions beyond those that are performed by immunization programmes such as antiviral treatment of pregnant women with high HBV loads and provision of hepatitis B immunoglobulin and post-vaccination serological testing to HBsAg-exposed newborns. Access to and delivery of hepatitis B interventions, including immunization, hepatitis B immunoglobulin, antiviral treatment and post-vaccination serological testing is necessary to ensure that HBsAg-positive pregnant women receive proper prevention, care and treatment services, along with their partners and their exposed newborns. Thus, the TAG appreciates the WHO Regional Committee's recent endorsement of the *Regional Framework for the Triple Elimination of Mother-to-Child Transmission of HIV, Hepatitis B and Syphilis in Asia and the Pacific 2018–2030*, which plans to use the shared maternal, newborn and child health platform to coordinate EMTCT of these three infections.

- The TAG notes that to build on the impressive progress towards accelerated HBV control and proposed coordinated triple EMTCT of HIV, HBV and syphilis (triple EMTCT), countries should develop clear strategies to incorporate EMTCT of HBV and to develop national triple EMTCT plans. The framework for triple EMTCT supports HBV control within immunization programmes and through coordination with other programmes such as maternal and child health, HIV, hepatitis and sexually transmitted infections programmes.

Sustaining polio-free status and implementation of polio endgame strategies

- The TAG acknowledges that overall population immunity against poliovirus in the Region remains quite high; performance of acute flaccid paralysis (AFP) surveillance exceeded established targets, and high quality of the polio laboratory network has been maintained since its establishment. The TAG commends efforts of the Philippines and Viet Nam in establishing environmental surveillance to monitor circulation of poliovirus that may not be captured by AFP surveillance, in addition to the environmental surveillance that had previously been established in Australia, China, Japan and Malaysia. The TAG congratulates the Region for having successfully completed Phase I of the Global Action Plan (GAPIII) for destruction or containment of wild poliovirus (WPV) and vaccine-derived poliovirus (VDPV) type 2 in all polio laboratories. The TAG

was informed that Mongolia and Viet Nam plan to introduce inactivated polio vaccine (IPV) in the second half of 2018.

- Despite the achievements and progress made in sustaining polio-free status and implementing the polio endgame strategy in the Region, the TAG notes that the following issues and challenges should be thoroughly addressed:
  - **(1)** risk of international spread of poliovirus remains a Public Health Emergency of International Concern;
  - **(2)** immunity and/or surveillance gaps remain at subnational levels in China, Cambodia, the Lao People's Democratic Republic, Malaysia, Mongolia, Pacific island countries, Papua New Guinea, the Philippines and Viet Nam;
  - **(3)** national inventories of all biomedical facilities that may contain poliovirus potentially infectious materials are not yet complete in all countries in the Region;
  - **(4)** designation of polio-essential facilities (PEFs) and establishment of fully functional national authorities for containment are not finalized in China, Japan, the Republic of Korea and Viet Nam; and
  - **(5)** international funding support for maintenance of polio-essential functions is scaling down in China, Cambodia, the Lao People's Democratic Republic, Mongolia, Pacific island countries, Papua New Guinea, the Philippines and Viet Nam.

Maternal and neonatal tetanus (MNT) elimination

- The TAG congratulates the Philippines on the 2017 achievement of validation of MNT elimination. This was possible after achieving more than 80% coverage in each of the three rounds of tetanus-diphtheria toxoid (Td) supplemental immunization activities (SIAs) in the Autonomous Region of Muslim Mindanao. The TAG acknowledges the draft *Implementation Guide for Sustaining Maternal & Neonatal Tetanus Elimination*. This guide will support Member States that were validated to have achieved MNT elimination in sustaining their elimination status. The TAG also notes the 2017 WHO position paper on tetanus vaccines that recommends that all countries include six doses (three primary plus three booster doses) of tetanus toxoid (TT)-containing vaccine in their schedules to sustain protection throughout adolescence and adulthood.[2] As many countries do not have six doses of TT-containing vaccine in their current schedules, the TAG acknowledges that it may take some time to update their schedules according to the new recommendations.

- Papua New Guinea is now the sole country in the Region not to be validated for MNT elimination. As of March 2018, there has been gradual progress in conducting TT SIAs in three high-risk provinces in Papua New Guinea. However, progress has been hindered by various issues including delay in cold chain equipment procurement and distribution, change in governance and leadership, and mobilizing funds and inadequate staffing.

[2] Tetanus vaccines: WHO position paper – February 2017. Weekly epidemiological record. 2017;6(92):53–76.

Measles and rubella elimination

- The TAG congratulates the Western Pacific Region on achieving the historically lowest reported incidence of measles and rubella in 2017. The TAG also congratulates New Zealand for achieving measles elimination, and congratulates New Zealand and Republic of Korea for being the first countries to be verified as having achieved rubella elimination. The TAG commends Cambodia and the Lao People's Democratic Republic for progress towards finalizing their draft national plans of action for achieving and sustaining elimination of measles and rubella. The TAG acknowledges the efforts that Member States are making to use the measles elimination platform to accelerate activities for rubella elimination, which many Member States are on track to quickly achieve.

- The TAG appreciates that the Regional Committee in October 2017 1) encouraged all Member States to eliminate rubella as soon as possible and establish a target year for each country or area, and 2) endorsed the *Regional Strategy and Plan of Action for Measles and Rubella Elimination in the Western Pacific* (WPR/RC68.R1). The TAG also acknowledges that a draft *Field Guide for the Surveillance of Congenital Rubella Syndrome (CRS) in the Western Pacific Region* was prepared by the WHO Secretariat in consultation with partners.

- Despite progress towards measles and rubella elimination in the Western Pacific Region, the TAG notes with concern that the following issues and challenges should be urgently addressed to achieve regional elimination of measles and rubella:

  (1) rapid accumulation of susceptible children, either nationwide or among specific communities, in Member States with inadequate or incomplete routine measles- and rubella-containing vaccine (MRCV) coverage;

  (2) risk of measles and/or rubella outbreaks due to residual measles and/or rubella immunity gaps among adolescents and adults who are not targeted by routine childhood immunization and traditional mass vaccination campaigns;

  (3) risk that cases of CRS will continue to occur, unless immunization strategies are implemented to fill adult immunity gaps and reduce rubella susceptibility among women of childbearing age who are not reached by immunization activities targeting children;

  (4) inadequate national or subnational capacity in some Member States for measles, rubella or CRS surveillance, including case detection, case investigation and/or case confirmation; and

  (5) insufficient capacity and preparedness in many Member States for responding to measles and rubella outbreaks, including lack of policies and procedures to ensure adequate surge capacity during large outbreaks; appropriate hospital infection control; appropriate data sharing and linkage between epidemiological and laboratory staff; and appropriate balance between epidemiological linkage and laboratory testing for case confirmation.

Accelerated Japanese encephalitis control

- The TAG commends Member States for progress in control of Japanese encephalitis (JE) in the Region, noting that, of the 12 Member States in the Region with JE virus transmission risk areas, eight have introduced the vaccine in most or all risk areas, two have very low levels of JE disease without immunization, one plans to introduce JE into its NIP in 2018, and one is assessing JE burden before making a decision about introduction of the vaccine.

- The TAG notes that the Second Consultation on Accelerated Control of Japanese Encephalitis in the Western Pacific Region was convened in May 2018 in Manila, Philippines. During this consultation, participants from the Region, JE experts and partners reviewed and discussed progress, current status and issues concerning accelerated control of JE in countries with JE virus transmission risk in the Region; discussed timelines for achieving accelerated control of JE in the Region; and reviewed and revised the draft *Guide for Accelerated Control of Japanese Encephalitis in the Western Pacific Region*.

- The TAG reaffirms the draft targets for accelerated control of JE in the Region that were recommended at the 25th TAG meeting in July 2016 but have yet to be endorsed by the Regional Committee, namely: 1) a primary target of less than 0.5 cases per 100 000 population in the targeted population (generally children under 15 years) in affected areas (national and subnational) annually; and 2) an interim target for Member States that do not have high-quality JE surveillance of coverage of at least 95% with a primary JE vaccination series among the targeted population (generally children under 15 years) in affected areas. The TAG affirms the proposal made at the Second Consultation on Accelerated Control of Japanese Encephalitis in the Western Pacific Region that the draft targets recommended for accelerated control of JE in the Region be achieved by 2030.

- The TAG notes: 1) that JE surveillance is not systematic in some areas and is fragmented into multiple systems, hindering data analysis and interpretation and limiting efforts to estimate disease burden, define target populations for vaccination, and measure the impact of vaccination in some countries; and 2) for the countries that have not yet achieved a high degree of JE control, strengthening surveillance with laboratory confirmation is critical for providing disease burden data and evidence of vaccine impact.

Preparedness for and Response to Diphtheria Outbreaks

- The TAG acknowledges the draft *Field Guide for Preparedness and Response to Diphtheria Outbreaks in the Western Pacific Region* and the report on gap analysis for diphtheria diagnostic capacity for laboratories in the Region. The TAG notes the challenges in ensuring availability and access to diphtheria antitoxin (DAT) and the efforts of a WHO headquarters ad hoc working group for DAT to ensure that any

population experiencing cases or an outbreak of diphtheria has rapid and easy access to equine DAT.

- The TAG notes that national schedules for diphtheria immunization, especially for booster doses, vary, and that the 2017 WHO position paper on diphtheria vaccines recommends a three-dose primary series and three booster doses for all persons.[3] As many countries do not have six doses of diphtheria toxin-containing vaccine in their current schedules, the TAG acknowledges that it may take some time for countries to update their schedules according to the new recommendations. The TAG also notes there is insufficient reporting of diphtheria cases from countries and areas. The TAG affirms the need for countries to enhance laboratory diagnostic capacity and ensure prompt management including proper DAT use.

Surveillance and data management for vaccine-preventable disease control and elimination

- The TAG acknowledges the Western Pacific Region for maintaining well-performing AFP, measles and rubella surveillance and establishing several sentinel sites to monitor the burden and changing epidemiology of diseases targeted by new or underutilized vaccines. The TAG also acknowledges the continued efforts made by Member States, WHO and partners to improve the quality of VPD surveillance data management by expanding the use of new tools (for example, web-based reporting tools for AFP and acute fever and rash surveillance), conducting VPD surveillance reviews in priority countries (Cambodia, the Lao People's Democratic Republic, Papua New Guinea and Viet Nam) and implementing new approaches (for example, Immunization and Surveillance Data Specialist project in the Lao People's Democratic Republic and Global Pediatric Diarrhea Surveillance in Fiji, the Lao People's Democratic Republic and Viet Nam). The TAG acknowledges WHO's effort in developing the new WHO VPD surveillance guidelines.

- Despite the achievements sustained and progress made in improving and strengthening VPD surveillance and data management in the Region, the TAG notes the following challenges to be addressed for further progress toward well-performing VPD surveillance, particularly for diseases targeted by elimination goals:

    1) inadequate surveillance system scope, in terms of geographical representativeness, use of recommended case definitions, reporting of cases on aggregate or case basis, as well as inclusion of all VPDs that should be under surveillance;
    2) insufficient training of human resources for detection and investigation of cases, surveillance data management and analysis;
    3) the need to maintain VPD surveillance key functions in integrated national surveillance systems (that is, reporting of suspected cases and case classification following adequate investigation and laboratory testing);
    4) lack of surveillance and outbreak response guidance for various diseases in some countries;
    5) inadequate financial support and/or no plan for financial sustainability for VPD surveillance in some countries; and

[3] Diptheria vaccines: WHO position paper – August 2017. Weekly epidemiological record. 2017; 31:417–36.

6) insufficient laboratory capacity for confirmation of some VPD cases (such as, diphtheria or pertussis) in several countries.

Laboratories and laboratory networks for vaccine-preventable disease control and elimination

- The TAG acknowledges the substantial efforts made by the WHO Secretariat and Member States to maintain regional VPD laboratory networks with high-level performance in the Western Pacific, in order to provide accurate and timely data for elimination and eradication of VPDs and for introduction of new vaccines. The TAG notes the need to maintain high-quality VPD laboratories by providing technical and financial support to network laboratories of priority countries, particularly for polio laboratories facing low workload and complacency due to the long absence of poliovirus detection.

- The TAG reaffirms the urgent need for many Member States to promote collaboration between epidemiological and laboratory surveillance for VPDs to ensure that case definition criteria are correctly applied, adequate specimens are collected, epidemiological and laboratory data are properly linked, and laboratory resources are adequately used, particularly during outbreaks.

- The TAG acknowledges the need to develop a regional strategy to maintain functional and sustainable laboratory surveillance for VPDs (polio, measles, rubella, JE, invasive bacterial VPD and rotavirus) with skilled staff and high-quality laboratory testing. Considering the reduction of financial support from donors for laboratory surveillance, the TAG reaffirms the urgent need to promote national ownership of laboratory surveillance.

Post-2020 immunization and vaccine-preventable diseases in the Western Pacific Region

- The TAG reaffirms that the Western Pacific Region has made significant progress and remarkable achievements in immunization and in control and elimination of VPDs since 1974, when the WHO EPI was founded and NIPs were established in Member States.

- Routine immunization coverage has continued to be improved at both national and regional levels since 1980 and has been more than 95% at the regional level since 2009. The regional polio eradication initiative was launched in 1988, and since 2000, the regional polio-free status has been sustained despite continuous challenges. The regional measles elimination initiative was launched in 2003, and as of 2017, six countries and two areas of the Region have achieved measles elimination. The regional rubella elimination initiative was launched in 2014, and by 2017, two countries of the Region had achieved rubella elimination. MNT elimination has been achieved in five out of six target countries. The 2017 target for accelerated hepatitis B control has been achieved in 21 countries and areas of the Region. An accelerated JE control goal has been established. Ten of 12 countries with JE risk use JE vaccine in some or all risk areas or have very low levels of disease without vaccination. At least one new vaccine has been introduced in 89% of low- and lower middle-income countries in the Region since 2010.

- The TAG acknowledges that these initiatives for control and elimination of VPDs and introduction of new vaccines have had synergies that led to strengthened immunization systems and programmes in the Western Pacific in the last four decades. Progress has accelerated during the current decade with implementation of GVAP, launched in 2012.

- Despite these achievements, the TAG notes with concern that the immunization gains in the Region may be at serious risk in the next decade. Causes of the risk may include: 1) demographic and socioeconomic changes such as growing population, urbanization, increased immigration and increased vaccine hesitancy; 2) epidemiologic changes such as repeated outbreaks (diphtheria, pertussis, measles, rubella, cVDPV, etc.) and increased VPD incidence among older children, adolescents and adults; 3) operational shifts as newer vaccines are targeted to selected populations; 4) significant reduction in external funding for immunization programmes as countries transition from the Global Polio Eradication Initiative (GPEI), Gavi, The Vaccine Alliance (Gavi) and other donor support; and 5) increasing fragility and instability of global vaccine supply as small numbers of manufacturers attempt to meet growing global demand.

- To address these issues and challenges in the coming decade, in order to sustain and expand the immunization gains of the last four decades, the TAG fully supports the WHO Secretariat to initiate development of a post-2020 regional framework of action for immunization and VPDs in the Western Pacific, in collaboration with Member States and partners.

Recommendations for Member States

Immunization system strengthening (including progress towards GVAP strategic objectives)

The TAG urges all Member States to:

(1) initiate implementation of the resolution of the Regional Committee on transitioning to integrated financing of priority public health services (WPR/RC68.R5) and use the *Regional Framework for Action on Transitioning to Integrated Financing of Priority Public Health Services in the Western Pacific* to guide actions to secure sustainable domestic financing for immunization; and

(2) explore and implement immunization system strengthening strategies articulated in the Global Routine Immunization Strategies and Practices (GRISP) document; consider in particular strategies needed to reduce inequities in immunization coverage by reaching children of ethnic minorities and migrant groups and those living in dense urban areas and remote areas.

The TAG recommends Member States to:

(1) strengthen the functionality and effectiveness of NITAGs or equivalent immunization decision-making bodies to support formulation of evidence-based immunization policy;

(2) strengthen vaccine procurement processes for timely vaccine supply and effective vaccine management practices;

(3) ensure NRA functioning to meet WHO global benchmarks, supporting the availability of quality-assured vaccines;

(4) improve AEFI reporting, investigation and timely response capacity including risk communications; and

(5) strengthen immunization information systems to improve vaccination data quality and accessibility.

The TAG recommends Brunei Darussalam, Macau and Papua New Guinea to:

(1) establish a NITAG or equivalent immunization decision-making body to support development and strengthening of evidence-based immunization policy.

The TAG recommends Papua New Guinea to:

(1) establish a national vaccine safety expert committee to conduct causality assessment of serious AEFIs.

The TAG recommends Cambodia, Papua New Guinea and Solomon Islands to:

(1) improve AEFI reporting to meet the GVAP minimal AEFI reporting target of at least 10 AEFI cases per 100 000 surviving infants per year.

New vaccines introduction

The TAG recommends Member States to:

(1) consider introduction of new vaccines and continue to seek guidance from NITAGs or other advisory bodies for evidence-based decision-making, taking into account public health priority, implementation issues, funding and sustainability.

Accelerated hepatitis B control

The TAG recommends Member States to:

(1) review the *Regional Framework for the Triple Elimination of Mother-to-Child Transmission of HIV, Hepatitis B and Syphilis in Asia and the Pacific 2018*–2030 and consider developing national plans for its implementation, acknowledging that coordination across programmes is required.

The TAG recommends Member States that have completed pilots of HepB-BD OCC to:

(1) consider scaling up OCC activities to facilitate timely HepB-BD for all newborns, if OCC use of HepB-BD has not already been fully considered. Countries that have completed HepB-BD OCC pilots are Cambodia, China, the Lao People's Democratic Republic, Papua New Guinea, Solomon Islands and Viet Nam. OCC off-label use

should follow WHO's OCC and CTC recommendations, as noted in the 2017 WHO position paper for hepatitis B.[4]

The TAG recommends Japan, the Marshall Islands, Samoa and Wallis and Futuna to:

(1) submit the results of their most recently completed nationally representative hepatitis B serosurvey to the ERP as part of their verification package to determine if they have met the 2017 regional target of less than 1% HBsAg prevalence in 5-year-old children.

The TAG recommends Japan and New Zealand to:

(1) respond to the ERP's request about their HepB-BD programme. The response may include a description of current hepatitis B vaccination practices for preventing mother-to-child transmission and results of serosurveys and related studies.

The TAG recommends Viet Nam to:

(1) revise the current national neonatal screening form to align contraindications with the 2017 WHO position paper for hepatitis B vaccines, and further improve HepB-BD uptake by continuing interventions in health facilities with low HepB-BD coverage and provinces with high home delivery rates.

Sustaining polio-free status and implementation of polio endgame strategies

The TAG urges all Member States to:

(1) achieve and maintain more than 90% coverage at the national level with all doses of polio-containing vaccines in the national schedule and address population immunity gaps, particularly in high-risk areas, by conducting SIAs, if needed;

(2) achieve and maintain the core AFP surveillance target of at least 1 AFP case per 100 000 population annually and conduct active surveillance in underperforming areas;

(3) ensure that national polio outbreak response plans are updated in accordance with the global guidance for timely and comprehensive response to any polio event or outbreak and tested by conducting polio outbreak simulation exercises;

(4) regularly analyse the risk of poliovirus transmission after importation of WPV or the emergence of VDPV, and ensure rapid and appropriate response;

(5) finalize GAPIII Phase 1, including identification followed by destruction, transfer or containment of type 2 poliovirus potentially infectious materials in all biomedical laboratories no later than April 2019, as described in the WHO guidance document;

(6) begin preparations to identify WPV type 1 and WPV type 3 materials and destroy, transfer or contain them in approved places, by the end of Phase II of GAPIII (at the time of global certification of poliomyelitis eradication); and

(7) submit annual polio containment reports to the Regional Certification Commission together with annual National Certification Committee (NCC) reports.

[4] Hepatitis B vaccines: WHO position paper – May 2017. Weekly epidemiological record. 2017;27:369–92.

The TAG urges Member States that are supported by international partners to maintain polio-essential functions to:

(1) establish capacity and resources for sustaining polio-essential functions, as outlined in the Polio Post-Certification Strategy.

The TAG urges Member States with polio-essential facilities (PEFs), namely, Australia, China, Japan, Republic of Korea and Viet Nam, to:

(1) establish and operationalize a national authority for containment responsible for certifying PEFs, if not already established (China, Japan, Republic of Korea and Viet Nam), by the end of 2018 in line with GCC recommendations; and

(2) start the containment certification process as soon as possible and submit associated reports to the GCC for validation.

The TAG urges Cambodia, the Lao People's Democratic Republic, Papua New Guinea and Viet Nam to:

(1) establish environmental surveillance for polioviruses to supplement surveillance for AFP, as part of the GPEI global plan for expansion of environmental surveillance.

The TAG recommends Mongolia and Viet Nam to:

(1) conduct an IPV catch-up campaign, once supply becomes available, to fill the poliovirus type 2 immunity gap that has developed since the switch from trivalent to bivalent oral polio vaccine in May 2016.

Maternal and neonatal tetanus (MNT) Elimination

The TAG recommends all Member States to:

(1) update their national immunization schedules in line with the 2017 WHO position paper on tetanus vaccines, to include for all children (male and female):

(a) a primary series of three doses of TT-containing vaccines, administered in the first year of life;

(b) three booster doses in childhood and completed by adolescence with doses specifically recommended to be given at: 12–23 months of age; 4–7 years of age; and 9–15 years of age; and

(c) for booster doses and when TT is indicated in older age groups, use of combination tetanus-diphtheria toxoid rather than TT alone.

The TAG encourages all Member States that were validated to have achieved MNT elimination to:

(1) develop and implement national plans for sustaining MNT elimination that are in line with the *Implementation Guide for Sustaining Maternal & Neonatal Tetanus Elimination*.

The TAG urges Papua New Guinea to:

(1) complete required actions as early as possible to achieve MNT elimination, including TT SIAs in high- and medium-risk provinces, and implement a validation assessment.

Measles and rubella elimination

The TAG urges all Member States to:

(1) implement the WHO Regional Committee resolution WPR/RC68.R1 by: (a) developing or updating national strategies and plans of action relating to measles and rubella elimination, including the establishment of a target year for rubella elimination; and (b) ensuring adequate technical and financial resources are available for the implementation of national strategies and plans of action for measles and rubella elimination.

The TAG recommends each Member State to:

(1) address residual measles and/or rubella immunity gaps among adolescents and adults by planning and conducting targeted immunization initiatives, which may include school-based, university-based or occupationally based immunization;

(2) develop and implement national policies and procedures for hospital infection control for any suspected measles or rubella case to prevent health-care-associated transmission and amplification of outbreaks;

(3) develop and implement national procedures to ensure that epidemiological and laboratory data can be linked and used by public health staff to guide action in preventing and responding to measles and rubella outbreaks; and to guide appropriate use of laboratory testing and epidemiological linkage for case confirmation in routine surveillance and during outbreaks; and

(4) continue to use investment in measles and rubella elimination activities as a means to strengthen immunization programmes and overall public health systems, including development of an immunization visit during the second year of life to achieve high coverage of the second dose of measles-containing vaccine.

Accelerated Japanese encephalitis control

The TAG recommends Member States that have not achieved effective control of the disease to:

(1) develop and implement national plans for accelerated control of JE.

The TAG recommends Member States that use or are planning to use live attenuated JE vaccine to:

(1) forecast the number of JE vaccine doses they will need to ensure that the vaccine doses are distributed in advance of when they are needed.

Preparedness for and response to diphtheria outbreaks

The TAG recommends all Member States to:

(1) update their national immunization schedules in line with the 2017 WHO position paper on diphtheria vaccines, to include:

(a) a primary series of three doses of diphtheria toxoid-containing vaccines, completed by 6 months of age, if possible; and

(b) three booster doses in childhood and completed by adolescence with doses specifically recommended to be given at: 12–23 months of age; 4–7 years of age; and 9–15 years of age.

The TAG encourages Member States that have been frequently affected by diphtheria outbreaks to:

(1) develop national guidelines for preparedness and response to diphtheria outbreaks, drawing on the draft *Field Guide for Preparedness and Response to Diphtheria Outbreaks in the Western Pacific Region*.

Surveillance and data management for vaccine-preventable disease control and elimination

The TAG recommends all Member States to:

(1) strengthen surveillance for diseases targeted by new vaccines (rotavirus and invasive bacterial VPDs) and build capacity for laboratory diagnosis through training workshops, introduction of new technologies and implementation of quality assurance programmes;

(2) review their VPD surveillance systems and ensure compliance with minimum requirements as detailed in the new WHO VPD surveillance guidelines, specifically with reference to the VPDs included in the surveillance system, case definitions, scope of the surveillance (that is, national or sentinel-based) and aggregate or case-based data collection; ensure that those minimum requirements are also met when VPD surveillance is integrated into broader communicable diseases surveillance; and

(3) sustain high-performing VPD surveillance systems, in the context of possible decreasing external funding from partners and donors.

Laboratories and laboratory networks for vaccine-preventable disease control and elimination

The TAG recommends Member States to:

(1) improve collaboration between epidemiological and laboratory surveillance for VPDs by:

(a) promoting collaboration of epidemiologists and laboratory experts in routine surveillance as well as in outbreak situations;

(b) engaging both immunization programme and laboratory experts in national expert committees (NCCs, national verification committees, etc.);

(c) ensuring that interpretation and use of data for reporting and final classification are jointly assessed from clinical and laboratory perspectives; and

(d) collecting adequate specimens from every case for virological testing in countries achieving or having achieved measles and rubella elimination to ensure all virus transmission is properly monitored; and

(2) develop plans to achieve sustainable laboratory surveillance for VPDs by:

(a) developing long-term plans for disease surveillance with clear objectives and realistic milestones;
(b) conducting self-assessments to map existing capacities and to identify strengths, gaps and challenges; and
(c) assessing financial sustainability of existing surveillance.

Post-2020 immunization and vaccine-preventable diseases in the Western Pacific Region

The TAG did not make any recommendations for Member States on post-2020 immunization and vaccine-preventable diseases in the Western Pacific Region.

Recommendations for WHO Secretariat

Immunization system strengthening (including progress towards GVAP strategic objectives)

The TAG reiterates the recommendations of the 26th TAG, including: (i) WHO and partners to support countries to overcome immunization coverage gaps, including through promotion of use of all available strategies; (ii) WHO to support Pacific island countries to improve their immunization programmes including immunization policy-making and addressing vaccine safety issues; (iii) WHO to support capacity-building in vaccine safety surveillance and response; and (iv) WHO and partners to support middle-income countries to achieve the Regional Framework goals through the *Middle Income Country Strategy* and other strategies.

The TAG recommends the WHO Secretariat to:

(1) continue to support Member States in strengthening NITAGs to improve the capacity for evidence-based immunization policy-making;

(2) continue to support Member States in conducting international EPI reviews and developing or updating cMYPs;

(3) support Member States in identifying and systematically addressing issues in procurement, supply and distribution of vaccines through: (a) conducting assessments and developing improvement plans for effective vaccine management; (b) continuing dissemination of the vaccine fact sheet developed by the V3P with NIPs for vaccine procurement decision-making; (c) mapping current and anticipated vaccine demand and supply for vaccines used for the NIP; and (d) considering options to address vaccine procurement including the potential feasibility of regional pooled procurement of vaccines to reduce vaccine costs;

(4) continue providing technical support to Member States in (a) conducting assessments of NRAs and developing and implementing institutional development plans; and (b) developing and conducting in-country AEFI training workshops;

(5) support Member States in developing guidance for use of information technology to support the NIPs and in building capacity to use information systems; and

(6) carry out high-level missions with partners to Cambodia and Papua New Guinea to support advocacy and key NIP activities.

New vaccines introduction

The TAG reiterates the recommendations of the 26th TAG meeting, including: (i) each Member State should develop a national plan for evidence-based introduction of new vaccines; (ii) each Member State in which surveillance includes laboratory confirmation for diseases targeted by new vaccines, should monitor and improve surveillance implementation; (iii) Member States should use recommended immunization schedules and should not add immunization visits solely for the purpose of preventing the administration of multiple injections during the same visit; (iv) the WHO Regional Office for the Western Pacific should continue to provide technical support and capacity-building for the development of national plans for evidence-based introduction of new vaccines; and (v) the WHO Regional Office for the Western Pacific should assess and improve the quality of surveillance implementation.

The TAG recommends the WHO Secretariat to:

(1) provide technical support and capacity-building to lower middle-income Member States (particularly Cambodia, the Lao People's Democratic Republic, Mongolia, Papua New Guinea, the Philippines, Solomon Islands and Viet Nam) to prepare for or implement introduction of new vaccines;

(2) support middle-income countries in the Region by leveraging all opportunities to promote the exchange of information, the sharing of lessons learned and peer-to-peer support to promote and facilitate introduction of new vaccines by addressing technical, logistical and financial barriers;

(3) provide technical support to ministries of health in Pacific island countries in introduction of new vaccines that the Asian Development Bank is funding;

(4) continue to provide technical support for special studies focusing on increasing the evidence base for NITAGs to consider for introduction of new vaccines and new vaccination technologies;

(5) support countries to use introduction of new vaccines as opportunities to further strengthen and enhance overall immunization systems and programmes; and

(6) encourage countries to make evidence-based decisions on introduction of new vaccines, including timing of introduction, vaccine safety and delivery system, while taking funding and country context into account.

Accelerated hepatitis B control

The TAG reiterates the recommendations of the 26th TAG meeting, including: (i) countries and areas with high and sustained high HepB-BD and third-dose coverage work to further EMTCT of HBV; (ii) incentivizing countries and areas to increase health facility delivery rates; and (iii) the ERP to develop and prioritize recommendations for additional HBV interventions to be incorporated into perinatal programmes to achieve the proposed post-2017 hepatitis B goals.

The TAG recommends the WHO Secretariat to:

(1) continue to provide support to Member States with low HepB-BD coverage in revising national HepB-BD improvement plans that were developed in 2012 by Cambodia, the Lao People's Democratic Republic, Papua New Guinea, the Philippines and Viet Nam, and in ensuring that necessary actions and planned activities are implemented;

(2) share lessons learned and best practices employed by Cambodia, which, after being one of five priority countries identified in 2012 to develop a national HepB-BD plan, was recently verified as achieving less than 1% HBsAg prevalence in 5-year-old children; and

(3) submit to the WHO Regional Committee for consideration the ERP's proposed post-2017 control goals, which include: (a) all Member States reduce HBsAg prevalence among children at least 5 years of age to less than 1% by 2025; and (b) reduce HBsAg prevalence among children at least 5 years of age in countries that have met the less than 1% goal to less than 0.5% by 2025.

Sustaining polio-free status and implementation of polio endgame strategies

The TAG encourages the WHO Secretariat to:

(1) continue to work with all Member States in maintaining polio-free status in the Region by addressing gaps in population immunity and AFP surveillance, particularly gaps in population immunity against type 2 poliovirus;

(2) support Cambodia, the Lao People's Democratic Republic, Papua New Guinea and Viet Nam in establishing environmental surveillance, in line with the GPEI global plan for expansion of environmental surveillance; and continue to support Member States in maintaining environmental surveillance where it has already established;

(3) continue to support Member States in implementing GAPIII, establishing functional national authorities for containment and implementing the containment certification process for PEFs; and

(4) work with priority Member States to identify necessary resources for maintaining polio-essential functions as defined by the *Polio Post-Certification Strategy*.

Maternal and neonatal tetanus elimination

The TAG recommends the WHO Secretariat to:

(1) assist Papua New Guinea to address the identified impediments that serve to preclude MNT elimination; and

(2) provide technical support to the Member States in developing and implementing national plans for sustaining MNT elimination in accordance with the *Implementation Guide for Sustaining Maternal & Neonatal Tetanus Elimination*, once finalized.

Measles and rubella elimination

The TAG reiterates the recommendations of the 26th TAG meeting, including that Member States should (i) prevent outbreaks of rubella and CRS by protecting women of reproductive age and their babies from infection with rubella virus by identifying and filling rubella immunity gaps; (ii) use SIAs and school-based vaccination screening and/or delivery to achieve high vaccination coverage among susceptible populations as quickly as possible; (iii) develop, or update, and accelerate implementation of national plans for measles and rubella elimination as soon as possible; (iv) establish CRS surveillance systems based on the forthcoming *Field Guide for the Surveillance of Congenital Rubella Syndrome (CRS) in the Western Pacific Region*; and (v) use MRCV rather than single-antigen vaccine at every opportunity.

The TAG requests the WHO Secretariat to:

(1) finalize the draft *Field Guide for the Surveillance of Congenital Rubella Syndrome (CRS) in the Western Pacific Region* through further consultation with the TAG, NIPs and partners, and submit it to the 28th TAG meeting in 2019 for review and possible endorsement;

(2) develop draft regional guidelines for preparedness and response to measles and rubella outbreaks through consultation with the TAG, NIPs and partners; and

(3) develop other regional technical guides as recommended during the 26th TAG meeting, including: (a) field guidance for planning and implementing MRCV SIAs; and (b) field guidance for measles and rubella surveillance.

The TAG recommends WHO Secretariat to:

(1) continue to support priority Member States to: (a) develop, update and implement their national plans for measles and rubella elimination and set a national target date for rubella elimination; (b) plan, prepare and conduct high-quality SIAs to fill immunity gaps due to inadequate routine immunization; (c) develop and implement quality CRS surveillance based on the forthcoming *Field Guide for the Surveillance of Congenital Rubella Syndrome (CRS) in the Western Pacific Region*; and (d) strengthen measles and rubella case-based laboratory-supported surveillance;

(2) work with Member States that have residual measles and/or rubella immunity gaps among adolescents and adults, to plan and conduct targeted immunization initiatives, which may include school-based, university-based or occupationally based immunization;

(3) support Member States to develop and implement national policies and procedures for hospital infection control for any suspected measles or rubella case to prevent health-care-associated transmission and amplification of outbreaks;

(4) support Member States to identify opportunities, and when agreed, develop and implement plans for subregional and multi-country collaboration, coordination and synchronization of strategies and activities for measles and rubella elimination; and

(5) continue to work with the Regional Verification Commission on Measles and Rubella Elimination in the Western Pacific in documenting, evaluating progress towards and verifying measles and rubella elimination.

Accelerated Japanese encephalitis control

The TAG reiterates the recommendations of the 26th TAG meeting, including: (i) Member States to develop national plans for JE control; (ii) Member States to consider improving collection of cerebrospinal fluid specimens and sharing these specimens to allow genotyping and sequencing at reference laboratories; (iii) Member States to encourage laboratories to continue to achieve performance criteria set forth by the WHO JE laboratory accreditation programme; (iv) JE surveillance with laboratory confirmation to be further strengthened in endemic areas of the Western Pacific Region, and sentinel surveillance be systematized to facilitate reporting at the regional level; (v) WHO Regional Office for the Western Pacific to expand the use of the JE surveillance structured tool for the assessment of detection and reporting of JE and vaccine impact; (vi) WHO Regional Office for the Western Pacific to develop a regional guidance document to help Member States to develop national JE control plans; and (vii) WHO to revise the 2007 WHO *Manual for the Laboratory Diagnosis of Japanese Encephalitis Virus Infection* to reflect current responsibilities of the network and to provide recommendations, resources and guidelines for laboratory diagnosis of JE, data management and reporting of laboratory results, and implementation of quality assurance.

The TAG requests the WHO Secretariat to:

(1) finalize the draft *Guide for Accelerated Control of Japanese Encephalitis in the Western Pacific Region* and submit the final draft to the 28th TAG meeting in 2019 for its review and endorsement; and

(2) support Member States that have not achieved effective control of the disease in developing national plans for accelerated control of JE in countries.

The TAG recommends the WHO Secretariat to:

(1) submit to the Regional Committee for consideration the draft incidence and coverage targets for achieving accelerated control of JE in the Western Pacific;

(2) submit to the Regional Committee for consideration that the draft incidence and coverage targets for achieving accelerated control of JE in the Western Pacific be achieved by 2030;

(3) support countries to ensure that JE surveillance is implemented in accordance with the revised JE surveillance standards;[5] and

(4) continue working with Gavi and other partners and stakeholders to forecast JE vaccine needs in the Region in the next three years and to ensure that sufficient JE vaccine doses can be procured by countries that have introduced JE vaccine, by countries that are planning to introduce JE vaccine, and by countries that are planning JE vaccine campaigns.

[5] WHO Revised Surveillance Standards are being finalized and will be disseminated in mid-2018. The revised JE surveillance standards recommend two types of surveillance: 1) minimal surveillance, consisting of year-round, case-based surveillance with laboratory confirmation at sentinel hospitals in national and subnational areas where JE is suspected to be a problem; and 2) enhanced surveillance, consisting of nationwide, case-based surveillance for JE and acute encephalitis syndrome, where possible.

Preparedness for and response to diphtheria outbreaks

The TAG reiterates the recommendations of the 26th TAG meeting, including: (i) Member States to improve accuracy and completeness of diphtheria case data submitted to the WHO/UNICEF Joint Reporting Form on Immunization and consider implementation of case-based diphtheria surveillance; and (ii) Member States to analyse diphtheria surveillance data to better define the disease burden and potential need for DAT.

The TAG requests the WHO Secretariat to:

(1) finalize the draft *Field Guide for Preparedness and Response to Diphtheria Outbreak in the Western Pacific Region* through further consultation with the TAG, NIPs and partners and submit the final draft to the 28th TAG meeting in 2019 for its review and endorsement; and

(2) consider hands-on laboratory training for priority countries to strengthen laboratory diagnostic capacity for diphtheria.

The TAG recommends the WHO Secretariat to:

(1) support Member States to:

(a) achieve the regional vaccination coverage targets defined by the *Regional Framework for Implementation of the GVAP in the Western Pacific*;

(b) develop national plans or field guides based on the finalized version of the *Field Guide for Preparedness and Response to Diphtheria Outbreaks in the Western Pacific*;

(c) prepare for and respond to diphtheria outbreaks with appropriate public health interventions including DAT, and assess the need and feasibility of establishing a regional DAT stockpile; and

(d) strengthen laboratory diagnostic capacity for diphtheria and support countries with the shipment of samples to regional reference laboratories for laboratory diagnosis.

(2) establish a regional case-based reporting system for diphtheria outbreaks.

Surveillance and data management for vaccine-preventable disease control and elimination

The TAG reiterates the recommendations of the 26th TAG meeting, including: (i) Member States that have not yet established a CRS monitoring system to do so as soon as possible; (ii) countries with VPD surveillance of suboptimal representativeness and/or sensitivity to strengthen their surveillance systems; (iii) countries to prioritize strengthening the systems that support surveillance of diseases targeted by elimination goals; and (iv) countries to continue strengthening rotavirus and invasive bacterial VPD surveillance with laboratory confirmation.

The TAG encourages the WHO Secretariat to:

(1) continue to provide support to priority Member States in strengthening VPD surveillance and improving data quality through: (a) development of national training materials on surveillance based on case studies and problem solving; (b) expansion of the Immunization and Surveillance Data Specialist project or similar activities to other

countries; and (c) strengthening of linkages between epidemiological and laboratory data, including further expansion of WHO Regional Office of the Western Pacific web-based data management tools;

(2) provide technical support to Member States in ensuring that national VPD surveillance systems, whether stand-alone or integrated with surveillance for other communicable diseases, are compliant with minimum requirements (that is, number of VPDs under surveillance, national or sentinel surveillance, aggregate or case-based reporting, and case definitions) in accordance with the new WHO VPD surveillance guidelines; and

(3) support priority Member States (that is, those relying on external funding to support surveillance functions) in conducting cost–benefit analyses of VPD surveillance, particularly AFP and acute fever and rash surveillance, to advocate for adequate domestic funding to sustain high-quality surveillance systems.

Laboratories and laboratory networks for vaccine-preventable disease control and elimination

The TAG requests the WHO Secretariat to:

(1) continue providing technical support to Member States in maintaining high-quality VPD laboratories; and

(2) start planning for developing a regional strategy to maintain functional and sustainable laboratory surveillance for VPDs, including: (a) providing technical support to laboratories where needed to maintain technical skills and address gaps; (b) ensuring that all network laboratories receive timely updates and recommendations on new developments in laboratory testing; (c) addressing country-specific gaps and challenges; and (d) supporting countries in the polio transition period.

The TAG recommends the WHO Secretariat to:

(1) work with Member States to promote collaboration between epidemiological and laboratory surveillance for VPDs by: (a) organizing country-specific joint epidemiologic and laboratory workshops or meetings for advocacy purposes and exchange of experiences; (b) ensuring that interpretation and use of data for reporting and final classification are jointly assessed from clinical and laboratory perspectives; and (c) ensuring participation of both epidemiological and laboratory experts during country VPD surveillance reviews; and

(2) support Member States with insufficient capacity to manage increased laboratory workload during VPD outbreaks to consider establishing subnational laboratories.

Post-2020 immunization and vaccine-preventable diseases in the Western Pacific Region

The TAG recommends the WHO Secretariat to:

(1) initiate a consultation process with Member States and partners for development of a post-2020 regional framework of action for immunization and VPDs in the Western Pacific; and

(2) prepare a draft regional framework and submit it to the 28th TAG meeting in 2019 for review by the TAG, Member States and partners.

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Global Advisory Committee on Vaccine Safety, 6–7 June 2018

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 38th meeting in Geneva, Switzerland, on 6–7 June 2018.[2] The Committee discussed 2 vaccine safety issues: pharmacovigilance in the RTS,S malaria vaccine pilot study and data on dengue vaccine from the Philippines. It also reviewed three generic issues: progress in the Global Vaccine Safety Initiative (GVSI), communication about vaccine safety and new developments in the Vaccine Safety Net (VSN).

Pharmacovigilance in pilot use of malaria vaccine

Following a joint review convened by the African Vaccine Regulatory Forum (AVAREF), the national regulatory authorities of Ghana, Kenya and Malawi granted special authorization in May 2018 for use of the RTS,S malaria vaccine in the planned pilot implementation programme. It is anticipated that introduction will commence later this year. GACVS has assessed the safety profile of RTS,S throughout its development and clinical trials and will continue to assess safety data arising from the pilot implementation.[3] Safety data will be derived from: (i) post-marketing monitoring of cohort

[1] See No. 41, 1999, pp. 337–338.

[2] GACVS invited additional experts to present and discuss evidence related to particular topics. The experts included people affiliated with: Department of Health, Manila, the Philippines; Food and Drugs Authority and Expanded Programme on Immunization, Ghana Health Service, Accra, Ghana; Pharmacy and Poisons Board and National Vaccine and Immunization Programme, Nairobi, Kenya; Pharmacy, Medicines and Poisons Board and Expanded Programme on Immunization, Ministry of Health, Lilongwe, Malawi; Centers for Disease Control and Prevention, Atlanta (GA), USA; Ospedale Pediatrico Bambino Gesu, Rome, Italy; Monash Children's Hospital, Melbourne, Australia; and Sanofi Pasteur, Lyon, France.

[3] See No. 28, 2017, pp. 393–396.

Comité consultatif mondial pour la sécurité des vaccins, 6-7 juin 2018

Le comité consultatif mondial pour la sécurité des vaccins (GACVS), un organe consultatif indépendant composé d'experts cliniques et scientifiques, qui fournit 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 38e réunion à Genève (Suisse) les 6 et 7 juin 2018.[2] À cette occasion, il a examiné les 2 questions relatives à la sécurité vaccinale suivantes: pharmacovigilance dans le cadre de l'étude pilote du vaccin antipaludique RTS,S et données relatives au vaccin contre la dengue provenant des Philippines. Il a aussi traité 3 questions génériques: progrès de l'Initiative mondiale pour la sécurité des vaccins (GVSI), communication à propos de l'innocuité des vaccins et faits nouveaux concernant le Réseau pour la sécurité des vaccins (VSN).

Pharmacovigilance pour l'utilisation pilote du vaccin antipaludique

Suite à un examen conjoint organisé par le Forum africain pour la réglementation des vaccins (AVAREF), les autorités de réglementation nationales du Ghana, du Kenya et du Malawi ont accordé en mai 2018 une autorisation spéciale pour l'utilisation du vaccin antipaludique RTS,S dans le cadre du programme de mise en œuvre pilote prévu. L'introduction de ce vaccin devrait débuter ultérieurement dans l'année. Le GACVS a évalué le profil d'innocuité du RTS,S tout au long de sa mise au point et des essais cliniques et continuera d'apprécier les données d'innocuité apportées par la mise en œuvre pilote.[3] Ces données proviendront: (i) de la surveillance post-commercialisation des événements survenant parmi des

[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: Department of Health, Manila (Philippines), Food and Drug Authority and Expanded Programme on Immunization, Ghana Health Service, Accra (Ghana), Pharmacy and Poisons Board and National Vaccine and Immunization Programme, Nairobi (Kenya); Pharmacy, Medicines and Poisons Board and Expanded Programme on Immunization, Ministry of Health, Lilongwe (Malawi); Centers for Disease Control and Prevention, Atlanta (GA, Etats-Unis d'Amérique); Ospedale Pediatrico Bambino Gesu, Rome (Italie); Monash Children's Hospital, Melbourne (Australie) et Sanofi Pasteur, Lyon (France).

[3] Voir N° 28, 2017, pp. 393-396.

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events by the manufacturer GlaxoSmithKline (GSK), with detailed active follow-up; (ii) surveillance of mortality throughout the pilot area and surveillance of meningitis and cerebral malaria in sentinel hospitals in both control and RTS,S areas; (iii) active surveillance of adverse events of special interest (AESI); and (iv) pharmacovigilance through passive reports of adverse events following immunization (AEFI) with all vaccines from each country. A communications strategy and mechanisms for sharing these data during implementation are being developed to ensure that data flow between and within each country (as part of the pilot study and as part of national pharmacovigilance) and from GSK to the African Regional Safety Committee and the coordinators of the pilot implementation study, AVAREF and GACVS.

In June 2017, GACVS endorsed criteria to ensure that each country had a functioning system for reporting and assessing AEFI in time for introduction of the pilot project.[4] The criteria are: (i) a minimum of 10 AEFI reports per 100 000 surviving infants; (ii) a functioning AEFI committee that meets regularly; (iii) trained, resourced AEFI investigation teams; (iv) safety communications plans evaluated and tested; (v) an identified focal person in each country's expanded programme on immunization to oversee and ensure optimal reporting and training; and (vi) methods for active surveillance of AESI developed and data collection initiated.

Each country reported progress at the GACVS meeting in December 2017 and have now provided further updates. Ghana is meeting all the criteria. Regular training is provided to health care workers in reporting AEFI, and further training is planned for both the AEFI committee and the investigation teams. Reporting targets are shared with regions, and job aids have been developed. A communications plan is ready to be tested. In Malawi, although the reporting rates for 2017 are on target, more training is required in the pilot areas to sensitize health care workers and for investigation teams to assess AEFI and to use the reporting tools. Communications plans have been developed and have been pilot-tested, and training is planned. In Kenya, although the reporting rate is below 10 per 100 000, sensitization projects were begun in May 2018, and a second round of sensitization is planned just before introduction of RTS,S. Electronic reporting is being pilot-tested in one county. A communications plan is being drafted and members of the national AEFI committee appointed. Training for AEFI investigation teams is planned.

GACVS encouraged each country to ensure training of investigation teams and sensitization for reporting as soon as possible, so that AEFI surveillance would be functioning when pilot implementation began. It also stressed the importance of ensuring the timely availability of individual data on AEFI in order that the levels and quality of reporting can be monitored regularly throughout the pilot project and any improvements made when necessary. GACVS also noted that barriers

cohortes de personnes vaccinées par le fabricant GlaxoSmithKline (GSK), accompagnée d'un suivi actif détaillé de ces événements; (ii) de la surveillance de la mortalité dans l'ensemble de la zone pilote et de celle de la méningite et du paludisme cérébral dans les hôpitaux sentinels des zones où l'on administre le RTS,S et des zones témoins; (iii) de la surveillance active des événements indésirables présentant un intérêt particulier (AESI); et (iv) de la pharmacovigilance par le biais des rapports passifs de manifestations post-vaccinales indésirables (MAPI) émis par chacun des pays pour l'ensemble des vaccins. Une stratégie de communication et des mécanismes permettant d'échanger ces données pendant la mise en œuvre sont en cours de développement pour s'assurer d'une bonne circulation des données entre les pays et au sein de chacun d'eux (dans le cadre de l'étude pilote et de la pharmacovigilance nationale) et en provenance du GSK vers le Comité de sécurité régionale africain et les coordonnateurs de l'étude de mise en œuvre pilote, l'AVAREF et le GACVS.

En juin 2017, le GACVS a approuvé des critères visant à garantir que chaque pays dispose d'un système fonctionnel de notification et d'évaluation des MAPI à temps pour l'introduction du projet pilote.[4] Ces critères sont: (i) un minimum de 10 notifications de MAPI pour 100 000 naissances vivantes; (ii) un comité des MAPI fonctionnel, se réunissant régulièrement; (iii) des équipes d'investigation des MAPI formées et dotées de ressources suffisantes; (iv) des plans de communication à propos de la sécurité vaccinale évalués et testés; (v) un point focal pour le Programme élargi de vaccination désigné dans chaque pays pour superviser et garantir une notification et une formation optimales; et (vi) des méthodes de surveillance active des AESI bien au point et une collecte des données déjà entamée.

Chaque pays a rendu compte des progrès réalisés à la réunion de décembre 2017 du GACVS et a fourni à ce jour des points réguliers. Le Ghana remplit tous les critères. Les agents de santé reçoivent une formation régulière à la notification des MAPI et des formations supplémentaires sont prévues à la fois pour le comité des MAPI et les équipes d'investigation. Les cibles en matière de notification sont communiquées aux régions et des aide-mémoires ont été mis au point. Un plan de communication est prêt à être testé. Au Malawi, si les taux de notification pour l'année 2017 atteignent la cible, des formations supplémentaires sont nécessaires dans les zones pilotes pour sensibiliser le personnel soignant et les équipes d'investigation à l'évaluation des MAPI et à l'utilisation des outils de notification. Des plans de communication ont été élaborés et testés à l'échelle pilote et des formations sont prévues. Au Kenya, malgré un taux de notification inférieur à 10 pour 100 000, des projets de sensibilisation ont débuté en mai 2018 et il est prévu une seconde tournée de sensibilisation immédiatement avant l'introduction du vaccin RTS,S. La notification électronique fait l'objet d'un essai pilote dans un pays. Un plan de communication est en cours d'élaboration et les membres du comité des MAPI national ont été nommés. La formation des équipes d'investigation des MAPI est planifiée.

Le GACVS a encouragé chaque pays à former les équipes d'investigations et à les sensibiliser à la notification dès que possible, de manière à ce que la surveillance des MAPI soit opérationnelle lors du début de la mise en œuvre pilote. Il a aussi souligné l'importance de garantir la disponibilité en temps utile de données individuelles concernant les MAPI afin de pouvoir suivre régulièrement le niveau et la qualité de la notification sur l'ensemble du projet pilote et toutes les améliorations effectuées en cas de besoin. Le GACVS a aussi noté qu'il

[4] See No. 3, 2018, pp. 17–19.

[4] Voir N° 3, 2018, pp. 17-19.

to reporting, such as the belief of health care workers that a report indicates an error on their part, should be addressed in training.

For criterion (vi), on active surveillance, a working group with representatives from each country, WHO and the Centers for Disease Control and Prevention (Atlanta, GA, USA) has produced a manual that can be adapted in each country to its protocols for AESI surveillance. The manual, which covers 11 adverse events with both Brighton case definitions and simplified working case definitions, was presented for comment to GACVS. Surveillance would be limited to the duration of the pilot implementation project and to the target age group in both the control areas and those receiving RTS,S. Each country will identify which health care workers and health care facilities are to be responsible for active surveillance. Cases will be identified by regular review and extraction of case details at the facilities on reporting forms. The data will then be entered into a dedicated AESI database. GACVS agreed that development of country protocols, training and testing should proceed as soon as possible, and these activities are planned for the third quarter of 2018. GACVS noted that, if pilot implementation of RTS,S starts later in 2018, AESI surveillance may not be fully in place. Surveillance is an important component of the safety evaluation that allows comparison of control areas with those in which RTS,S is implemented and should be initiated as soon as possible.

Safety of dengue vaccine in the Philippines

GACVS last reviewed the CYD-TDV dengue vaccine at its meeting on 6–7 December 2017.[5] The Committee noted that long-term follow-up in clinical efficacy trials indicated that, overall, vaccinated trial participants had a reduced risk of virologically confirmed severe dengue and hospitalization; however, a subset of trial participants who had not been infected with dengue virus before vaccination (i.e. dengue-naïve, seronegative according to the NS1 assay) had a higher risk of severe dengue and hospitalization. The new evidence presented at that meeting was based on a reanalysis of the clinical trial data by the manufacturer, with a new test that distinguishes individuals with and without previous exposure to wild dengue virus retrospectively.[6] The WHO Strategic Advisory Group of Experts (SAGE) on immunization previously identified research on vaccine safety in this seronegative population as a priority.[7] Following the December 6–7 meeting in 2017, GACVS recommended that CYD-TDV not be administered to individuals who have not been previously infected with wild dengue virus. GACVS also noted that no data are currently available to allow an analysis of risk according to the number of vaccine doses received by people who are seronegative at baseline.

At its meeting on 17–18 April 2018, SAGE advised countries considering CYD-TDV vaccination as part of their dengue control programme to include pre-vaccination

[5] See No. 3, 2018, pp. 21–25.

[6] Sridhar S et al. Effect of dengue serostatus on dengue vaccine efficacy. N Engl J Med 2018. doi: 10.1056/NEJMoa1800820.

[7] See No. 21, 2016, pp. 282–284.

fallait réduire par la formation les obstacles à la notification tels que la croyance des membres du personnel soignant selon laquelle une notification indiquerait une erreur de leur part.

Concernant le critère (vi), relatif à la surveillance active, un groupe de travail comprenant des représentants de chaque pays, de l'OMS et des Centers for Disease Control and Prevention (Atlanta, GA, États-Unis d'Amérique) a produit un manuel pouvant être adapté aux protocoles de surveillance des AESI de chaque pays. Ce manuel, qui couvre 11 manifestations indésirables avec des définitions de cas de Brighton et des définitions de cas de travail simplifiées a été présenté pour observations au GACVS. La surveillance devrait se limiter à la durée du projet de mise en œuvre pilote et à la tranche d'âge ciblée, à la fois dans la zone témoin et dans celle recevant le RTS,S. Chaque pays identifiera quels membres du personnel soignant et quels établissements de soins seront responsables de la surveillance active. Les cas seront repérés par des examens réguliers et une extraction des informations relatives aux cas au niveau des établissements pour les consigner dans les formulaires de notification. Ces données seront ensuite saisies dans une base de données spécialement affectée au MAPI. Le GACVS est convenu qu'il fallait procéder à l'élaboration des protocoles, aux formations et aux tests dans les pays dès que possible et que ces activités étaient planifiées pour le troisième trimestre 2018. Le GACVS a aussi noté que si la mise en œuvre pilote du vaccin RTS,S devait débuter plus tardivement en 2018, la surveillance des AESI pourrait ne pas être totalement en place. Cette surveillance est une composante importante de l'évaluation de l'innocuité, permettant une comparaison entre les zones témoins et celles où l'on administre le RTS,S et devrait être lancée dès que possible.

Innocuité du vaccin contre la dengue aux Philippines

Le GACVS a examiné pour la dernière fois le vaccin CYD-TDV contre la dengue lors de sa réunion des 6 et 7 décembre 2017.[5] Le comité a pris note qu'un suivi à long terme dans le cadre d'essais cliniques d'efficacité indiquait que, globalement, les participants aux essais vaccinés présentaient un risque réduit de dengue sévère virologiquement confirmée et d'hospitalisation; néanmoins, un sous-ensemble de participants n'ayant pas été infectés par le virus de cette maladie avant leur vaccination (c'est-à-dire naïfs pour cette maladie, séronégatifs selon l'essai NS1) manifestaient un risque accru de dengue sévère et d'hospitalisation. Ces nouveaux éléments, présentés lors de la réunion, reposaient sur une réanalyse des données de l'essai clinique par le fabricant à l'aide d'un nouveau test distinguant rétrospectivement les individus avec ou sans exposition antérieure au virus sauvage de la dengue.[6] Le Groupe stratégique consultatif d'experts de l'OMS (SAGE) sur la vaccination a désigné la recherche sur l'innocuité du vaccin dans cette population séronégative comme une priorité.[7] Suite à la réunion des 6 et 7 décembre 2017, le GACVS a recommandé de ne pas administrer le CYD-TDV à des individus n'ayant pas subi d'infection antérieure par le virus sauvage de la dengue. Le GACVS a aussi noté qu'on ne disposait actuellement d'aucune donnée permettant d'analyser les risques en fonction du nombre de doses vaccinale reçues par les personnes séronégatives au départ.

Lors de sa réunion du 17 et 18 avril 2018, le SAGE a conseillé aux pays envisageant la vaccination par le CYD-TDV dans le cadre de leur programme de lutte contre la dengue d'inclure

[5] Voir N° 3, 2018, pp. 21-25.

[6] Sridhar S et al. Effect of dengue serostatus on dengue vaccine efficacy. N Engl J Med 2018. doi: 10.1056/NEJMoa1800820.

[7] Voir N° 21, 2016, pp. 282-284.

screening, so that only dengue-seropositive persons are vaccinated; the limitations of such screening should be clearly communicated to those offered vaccination.[8]

WHO will release a revised position paper on dengue vaccine in September 2018. The purposes of an update of the GACVS statement on dengue vaccine are: (i) to review the reports on vaccine safety received by the Philippines Ministry of Health after announcement of the risk for severe dengue of vaccine recipients who were dengue-naïve at the time of vaccination; (ii) to review difficulties in determining whether, apart from vaccine failure, the cases of severe dengue in vaccine recipients who were dengue-naive at the time of CYD-TDV vaccination were due to vaccine-related immune enhancement; and (iii) to review the updated safety profile of CYD-TDV.

The Philippines Food and Drug Administration approved use of CYD-TDV in December 2015, and the Disease Prevention and Control Bureau proposed its introduction as part of the National Dengue Prevention and Control Program. Vaccine administration began in 2016, first as part of a school programme in highly endemic regions and then extended to community programmes in October 2016. Surveillance of the safety of all vaccines is well established in the country, as a part of integrated disease surveillance and response. Should a serious AEFI or cluster be detected, the epidemiology bureau of the Department of Health is notified within 24–48 h. Serious cases are investigated, and the results of the investigations are compiled and sent to the regional and national AEFI committees. Before the programme was suspended, over 875 000 children had received at least 1 dose, almost 350 000 had received all 3 doses, and about 400 000 had received 2 doses.

Post-marketing data were presented to GACVS by the manufacturer. CYD-TDV is registered in 20 countries, and most doses are distributed in Brazil (where it is used in a public programme in Parana State) and the Philippines. In Brazil, dengue cases are reported through a national reportable disease information system, and data on AEFI are collected through passive surveillance in a national immunization programme. Guidelines for enhanced reporting and training of vaccine centre workers were provided by local authorities in Parana State.

The 14 fatal case reports in the Philippines were first reviewed by the national AEFI committees and the Dengue Investigative Task Force (DITF). The reports included 3 cases of dengue shock syndrome and 6 cases with other clinical diagnoses and no clear causal link other than a temporal association. The other cases were coincidental (3) or unclassifiable (2). A further review of 12 cases (8 fatal and 4 non-fatal) was undertaken by the DITF after training in AEFI methodology by international specialists. Although the DITF found that most cases were indeterminate, coincidental or unclassifiable, it recognized several cases of dengue disease. GACVS maintained its earlier recommendation that CTD-TDV should not be administered to people who have not previously been infected with wild dengue virus. It

un dépistage prévaccinal de manière à ce que seules les personnes séropositives pour cette maladie soient vaccinées, les limites d'un tel dépistage devant être clairement indiquées à toutes les personnes auxquelles la vaccination est proposée.[8]

L'OMS publiera une note de synthèse révisée indiquant sa position à propos du vaccin contre la dengue en septembre 2018. Cette actualisation de la déclaration du GACVS concernant ce vaccin a pour buts: (i) d'examiner les rapports sur l'innocuité du vaccin reçus du ministère de la santé des Philippines après l'annonce du risque de dengue sévère pour les personnes vaccinées qui étaient naïves pour cette maladie au moment de leur vaccination; (ii) d'étudier les difficultés pour déterminer si, en dehors des échecs vaccinaux, les cas de dengue sévère parmi les personnes vaccinées naïves pour cette maladie au moment de l'administration du CYD-TDV étaient dus à un renforcement de la maladie résultant d'une première immunisation par le vaccin; et (iii) d'examiner le profil d'innocuité actualisé de ce vaccin.

La Food and Drug Administration des Philippines a approuvé en décembre 2015 l'utilisation du CYD-TDV et le Disease Prevention and Control Bureau a proposé son introduction dans le cadre du programme national de prévention et de lutte contre la dengue. L'administration du vaccin a commencé en 2016, d'abord dans le cadre d'un programme scolaire appliqué dans les régions de forte endémie, puis a été étendue aux programmes communautaires en octobre 2016. La surveillance de l'innocuité de l'ensemble des vaccins est bien établie dans le pays, dans le cadre de la surveillance et de la riposte intégrées pour les maladies. Si une MAPI grave ou une grappe de MAPI venait à être détectée, le bureau d'épidémiologie du département de la santé serait avisé dans les 24 à 48 heures suivantes. Les cas sévères font l'objet d'investigations et les résultats de celles-ci sont compilés et expédiés aux comités des MAPI régionaux et nationaux. Avant la suspension du programme, >875 000 enfants ont reçu au moins 1 dose, près de 350 000 ont reçu la totalité des 3 doses et environ 400 000 ont reçu 2 doses.

Des données post-commercialisation ont été présentées au GACVS par le fabricant. Le CYD-TDV a été homologué dans 20 pays et la plupart des doses sont distribuées au Brésil (où il est utilisé dans le cadre d'un programme public mené par l'Etat de Parana) et aux Philippines. Au Brésil, des cas de dengue sont rapportés par le biais d'un système national d'information sur les maladies sujettes à notification et les données relatives aux MAPI sont collectées par la surveillance passive dans le cadre d'un programme national de vaccination. Des directives visant à améliorer la notification et la formation des agents des centres de vaccination ont été fournies par les autorités locales de l'Etat de Parana.

Les 14 notifications de cas mortels survenus aux Philippines ont été d'abord reçues par les comités des MAPI nationaux et la Dengue Investigative Task Force (DITF). Ces notifications incluaient 3 cas de syndrome de choc lié à la dengue et 6 cas pour lesquels d'autres diagnostics cliniques avaient été portés et sans lien causal clair autre qu'une association temporelle. Les autres cas résultaient d'une coïncidence (3) ou étaient impossibles à classer (2). Un examen plus poussé de 12 cas (8 mortels et 4 non mortels) a été réalisé par la DITF après formation à la méthodologie des MAPI par des spécialistes de niveau international. Même si cet examen a constaté que la plupart des cas étaient indéterminés, dus à une coïncidence ou impossibles à classer, il a reconnu plusieurs cas de dengue maladie. Le GACVS a maintenu sa recommandation antérieure de ne pas administrer le CTD-TDV à des personnes n'ayant pas été infectées auparavant par le virus sauvage de cette maladie.

[8] See No. 23, 2018, pp. 337–340

[8] Voir N° 23, 2018, pp. 337-340

concluded that, in the absence of criteria for distinguishing vaccine failure from vaccine-related immune enhancement, individual cases cannot be attributed to one or the other. As a result, such cases should be classified as indeterminate, irrespective of the time since vaccination.

Between December 2015 and March 2018, 1876 adverse events were reported to the manufacturer, mainly from Brazil and the Philippines; reporting was consistent with the pattern of dose distribution in both countries. The most frequently reported adverse events were fever, headache, dizziness, vomiting and rash. Of the 211 serious AEFI reported, most were consistent with an underlying infectious disease, including dengue fever. By 20 March 2018, 87 cases of dengue infection had been reported after vaccination with CYD-TDV; 23 were serologically confirmed, 61 suspected with no virological confirmation and 3 with negative virological tests. Of the 87 dengue cases, 14 were fatal. Of the 14 cases, 6 had completed the vaccination schedule, 3 had received 2 doses and 5 had received only 1 dose. All 9 cases for which the interval between vaccination and disease onset was known occurred within 6 months of the last vaccination.

Progress was reported in cohort event monitoring, sponsored by the manufacturer to obtain information on selected AEFI and serious adverse events in people vaccinated with CYD-TDV over 5 years in Brazil, Mexico and the Philippines. The target for enrolment in the study of post-authorization safety is 30 000 vaccinated participants. As of 5 April 2018, 12 573 participants had been enrolled and had received at least 1 dose of CYD-TDV.

One of the challenges in conducting post-market surveillance after vaccination with CYD-TDV is determining whether the vaccine gives rise to vaccine-related immune enhancement. An increasing number of AEFI were reported after suspension of the vaccination programme in the Philippines and media coverage. A task force was established by the Department of Health to review all fatal cases, and guidelines on AEFI reporting and response to vaccine recipients were issued by the Department of Health. In addition, the National AEFI Committee, established in 2012, was charged with reviewing all non-fatal AEFI.

GACVS also examined the possible risk of viscerotropic or neurotropic disease associated with the yellow fever backbone of the CYD-TDV vaccine. Although this remains a theoretical possibility, non-clinical and clinical evaluations do not provide evidence of an association. Viscerotropic and neurotropic diseases are rare serious reactions to yellow fever vaccination and occur only in close temporal association with vaccination. As severe dengue may also be accompanied by haemorrhagic systemic phenomena, a differential diagnosis can be made only if the vaccine strain is isolated from affected organs and if such syndromes occur within the accepted interval between vaccination and symptom onset (8 days).

Progress in the Global Vaccine Safety Initiative

The Global Vaccine Safety Blueprint, a framework of 8 objectives for enhancing global vaccine safety activi-

Il a conclu qu'en l'absence de critère pour distinguer les échecs de la vaccination des renforcements de la maladie liés à une première immunisation par le vaccin, les cas individuels ne pouvaient être attribués à l'une ou l'autre de ces situations. En conséquence, ces cas devront être classés comme indéterminés, quel que soit le moment où ils interviennent après la vaccination.

Entre décembre 2015 et mars 2018, 1876 événements indésirables ont été signalés au fabricant, principalement par le Brésil et les Philippines; ces notifications étaient cohérentes avec le schéma de distribution des doses dans les deux pays. Les événements indésirables les plus fréquemment rapportés comprenaient de la fièvre, des céphalées, des vertiges, des vomissements et des éruptions cutanées. Parmi les 211 MAPI graves notifiées, la plupart étaient compatibles avec une maladie infectieuse sous-jacente, et notamment avec une fièvre dengue. Jusqu'au 20 mars 2018, 87 cas d'infection par le virus de la dengue suite à une vaccination avec le CYD-TDV ont été rapportés; 23 étaient sérologiquement confirmés, 61 étaient des cas suspects sans confirmation virologique et 3 avaient donné des tests virologiques négatifs. Sur les 87 cas de dengue, 14 ont été mortels. Parmi ces 14 derniers cas, 6 avaient reçu la série complète de vaccinations, 3 avaient reçu 2 doses et 5 n'avaient reçu qu'une dose. La totalité des 9 cas pour lesquels l'intervalle entre la vaccination et l'apparition de la maladie était connu, étaient apparus dans les 6 mois suivant la dernière vaccination.

Il a été rendu compte des progrès dans le suivi des événements indésirables parmi des cohortes de personnes vaccinées, réalisé avec l'appui financier du fabricant, pour obtenir des informations sur certaines MAPI et manifestations indésirables graves chez les sujets vaccinés par le CYD-TDV, sur une période de 5 ans, au Brésil, au Mexique et aux Philippines. L'objectif est de recruter dans cette étude d'innocuité post-homologation 30 000 participants vaccinés. Le 5 avril 2018, 12 573 participants avaient été recrutés et avaient reçu au moins 1 dose de CYD-TDV.

L'un des défis à relever grâce à la surveillance post-commercialisation après une vaccination avec le CYD-DTV est de déterminer si celle-ci donne lieu à un renforcement de la maladie lié à l'immunisation vaccinale. Un nombre accru de MAPI a été signalé après la suspension du programme de vaccination aux Philippines et la couverture de l'événement par les médias. Le département de la santé a mis en place un groupe de travail spécial pour examiner tous les cas mortels et a émis des directives concernant la notification des MAPI et leur prise en charge chez les personnes vaccinées. En outre, le comité national des MAPI, établi en 2012, a été chargé d'examiner les MAPI non mortelles.

Le GACVS a aussi étudié le risque potentiel de maladie viscérotrope ou neurotrope associé à la souche amarile servant à l'élaboration du vaccin CYD-TDV. Bien que ce risque reste une possibilité théorique, les évaluations cliniques et non cliniques ne fournissent aucune preuve d'une telle association. Les maladies viscérotropes et neurotropes sont des réactions graves rares à la vaccination contre la fièvre jaune et n'apparaissent qu'en association temporelle étroite avec cette vaccination. Une dengue sévère peut aussi s'accompagner de phénomènes systémiques hémorragiques et le diagnostic différentiel ne peut être établi que si la souche vaccinale est isolée dans les organes touchés et si un tel syndrome se produit dans l'intervalle considéré comme acceptable entre la vaccination et l'apparition des symptômes (8 jours).

Progrès de l'Initiative mondiale pour la sécurité des vaccins

Le Plan mondial pour la sécurité des vaccins, un cadre comprenant 8 objectifs pour renforcer les activités en faveur de la sécurité

ties, was last discussed by the Committee in 2012. The Blueprint was later used as the basis for the vaccine safety strategy in the Global Vaccine Action Plan. GACVS provided input to the Blueprint and implemented it in the GVSI. At its meeting in December 2012, the Committee reviewed the GVSI work plan and examined areas of interaction between its own mandate for vaccine safety issues of global importance and that of the GVSI to support global vaccine pharmacovigilance capacity.[9] GACVS was notified of progress made through the GVSI in achieving its objectives 6 years after launch of the Initiative and was informed about a programme to strengthen global monitoring of vaccine safety, the Global Vaccine Safety Observatory. It also discussed the global vaccine safety strategy in the context of development of the Global Vaccine Action plan after 2020.

The Blueprint vision of effective vaccine pharmacovigilance systems established in all countries has progressed steadily. Countries are reporting AEFI and are meeting indicators of improvement in safety surveillance capacity. Six annual GVSI meetings have brought partners and countries together to build collaborations and plan future activities. Resources, training packages on basic vaccine safety, guidelines, AEFI surveillance and management, signal detection and communications are integral to robust building and maintenance of capacity for vaccine pharmacovigilance and trust in immunization programmes.

GACVS has advocated for the GVSI and supported its objectives on several fronts, from assisting in development of tools and helping to identify priorities to responding to safety concerns raised by countries either during the regular 6-monthly meetings or ad hoc. Five of the 8 strategic objectives of the GVSI benefit directly from input by GACVS: AEFI monitoring, investigation, harmonized tools and methods, technical support platforms and expert advice.

The concept of the Global Vaccine Safety Observatory was discussed. It was conceived as a clearinghouse for data on vaccine safety systems to assist member countries in achieving the Blueprint objectives. The Observatory will start with 4 regional nodes that provide academic, programmatic, regulatory and technical expertise. The expected outputs of the Observatory include presentation and analysis of relevant data, a website to provide indicators of vaccine safety capacity and links to relevant activities for vaccine vigilance, and an annual report. The products of the Observatory will be disseminated through several activities, some of which have had to evolve and recruit more than minimal capacity to deal with emerging safety issues. Each node will present relevant specialized data to allow members to track and compare progress over time, aggregate more sensitive data regionally, share regulatory recall and safety alerts, map globally reported safety concerns and make links to relevant experience.

[9] See No. 6, 2013, pp. 69–70.

vaccinale dans le monde, a été discuté pour la dernière fois par le Comité en 2012. Ce plan a servi ultérieurement de fondement à l'élaboration de la stratégie pour la sécurité des vaccins du Plan d'action mondial pour les vaccins. Le GACVS a fourni des apports à ce plan et l'a mis en œuvre dans le cadre de la GVSI. Lors de sa réunion de décembre 2012, le Comité a examiné le plan de travail de la GVSI et les domaines d'interaction entre son propre mandat pour les problèmes de sécurité des vaccins susceptibles d'avoir une portée mondiale et celui de la GVSI qui est d'appuyer les capacités de pharmacovigilance à l'égard des vaccins dans le monde.[9] Le GACVS a été avisé par le biais de la GVSI des progrès obtenus dans la réalisation des objectifs de celle-ci 6 ans après le lancement de l'Initiative et a reçu des informations sur un programme destiné à renforcer le suivi à l'échelle mondiale de la sécurité des vaccins, l'Observatoire mondial pour la sécurité des vaccins. Il a également discuté de la stratégie mondiale pour la sécurité des vaccins dans le contexte de l'élaboration du plan d'action mondial pour les vaccins au-delà de 2020.

Le projet du Plan mondial consistant à mettre en place des systèmes de pharmacovigilance pour les vaccins efficaces dans tous les pays a progressé régulièrement. Les pays signalent des MAPI et obtiennent des valeurs satisfaisantes pour les indicateurs mesurant l'amélioration des capacités de surveillance de l'innocuité. Six réunions annuelles de la GVSI ont rassemblé les partenaires et les pays pour renforcer les collaborations et planifier les activités à venir. Les ressources, les modules de formation aux aspects fondamentaux de la sécurité des vaccins, des lignes directrices, une surveillance et une prise en charge des MAPI, la détection des signaux et la communication font partie des moyens indispensables pour renforcer et maintenir des capacités solides de pharmacovigilance à l'égard des vaccins et la confiance dans les programmes de vaccination.

Le GACVS a plaidé en faveur de la GVSI et soutenu ses objectifs sur plusieurs fronts, allant de l'assistance à la mise au point d'outils et de l'aide à l'identification des priorités à la réponse aux préoccupations en matière de sécurité émises par les pays à l'occasion de ses réunions semestrielles régulières ou en fonction des besoins. Cinq des 8 objectifs stratégiques de la GVSI bénéficient directement des apports du GACVS: suivi et investigation des MAPI, harmonisation des outils et des méthodes, plates-formes de soutien technique et conseils d'experts

Le concept d'observatoire mondial de la sécurité des vaccins a également été examiné. Cet observatoire avait été conçu comme une chambre d'approbation pour les données sur les systèmes de sécurité des vaccins, destinée à aider les pays membres dans la réalisation des objectifs du plan mondial. Il commencera à fonctionner avec les 4 nœuds régionaux fournissant une expertise pédagogique, programmatique, réglementaire et technique. On attend de l'Observatoire qu'il délivre les prestations suivantes: présentation et analyse des données pertinentes, maintien d'un site Web fournissant des indicateurs qui mesurent les moyens pour assurer la sécurité des vaccins et des liens vers les activités en rapport avec la vigilance à l'égard des vaccins, et production d'un rapport annuel. Les prestations de l'Observatoire seront diffusées par le biais de plusieurs activités, dont certaines devront évoluer et recruter du personnel au-delà de la dotation minimale, pour faire face aux problèmes de sécurité émergents. Chaque nœud présentera des données spécialisées appropriées pour permettre aux membres de suivre et de comparer les progrès au cours du temps, de regrouper les données plus sensibles au niveau régional, de communiquer les rappels réglementaires et les alertes de sécurité, de cartographier à l'échelle mondiale les problèmes de sécurité et d'établir des liens avec l'expérience en rapport avec ces problèmes.

[9] Voir N° 6, 2013, pp. 69-70.

Finally, as the Decade of Vaccines will be completed by 2020, a new vaccine strategy is being developed, which will be aligned with the recently approved WHO General Programme of Work 2019–2023 in support of the sustainable development goal for health. GACVS therefore recommends close collaboration to ensure that the global vaccine safety strategy is well positioned in the new global approach to immunization.

Vaccine safety communication

A new GACVS subcommittee on vaccine safety communication has been established in order to integrate safety assessments with better capacity to communicate them. It is proposed that a framework and templates for communication on vaccine safety be prepared by mapping vaccine safety communication activities throughout the life cycle of products, examining current vaccine safety communication tools and identifying gaps, and proposing approaches to fill the gaps. The first task of the subcommittee was to prepare a more detailed action plan, with case studies to illustrate how safety is communicated under various circumstances.

The Committee noted the extensive strategies and education resources already available for avoiding and mitigating crises in communicating vaccine safety and highlighted two.

- The new Council for International Organizations of Medical Sciences (CIOMS)[10] Guide to Vaccine Safety Communication covers strategic communication issues, particularly for regulators but also for immunization programmes and other stakeholders. It stresses the importance of personnel with appropriate skills in safety communication and provides guidance and templates for a communications plan.
- The WHO Vaccination and Trust Library includes overviews of how concerns arise, describes the role of communication in mitigating crises, provides resources to help immunization stakeholders to avoid and manage crises and outlines a training programme.

Strategies, guidelines and resources are available for mitigating and managing vaccine safety crises. A case study was presented that highlighted the value of trust, clear communication at all levels and credible sources. GACVS considers that vaccine safety communication requires coordination among many stakeholders in 5 areas: (i) a framework that includes scenarios and proposes common principles for addressing specific situations; (ii) common messaging of vaccine safety issues for global partners; (iii) sharing of existing communications resource materials through an e-library; (iv) quality standards for planning and implementing vaccine safety communications; and (v) collaboration and coordination of partners so that each stakeholder has opportunities to make actionable contributions.

[10] See https://cioms.ch/

Enfin, la Décennie des vaccins devant s'achever en 2020, une nouvelle stratégie pour les vaccins est en cours de développement en accord avec le Programme général de travail de l'OMS 2019-2023, destiné à soutenir l'objectif de développement durable relatif à la santé. Le GACVS préconise donc une collaboration étroite pour s'assurer que la stratégie mondiale pour les vaccins se positionne correctement dans le cadre de la nouvelle approche mondiale de la vaccination

Communication à propos de la sécurité des vaccins

Un nouveau sous-comité du GACVS chargé de la communication à propos de l'innocuité des vaccins a été mis en place en vue d'intégrer les évaluations de l'innocuité et des moyens plus efficaces pour les communiquer. Il est proposé qu'un cadre et des modèles de communication concernant la sécurité vaccinale soient élaborés en repérant les activités de communication sur l'ensemble du cycle de vie des produits, en examinant les outils de communication à propos de cette innocuité disponibles actuellement, en identifiant les lacunes et en proposant des démarches pour les combler. La première tâche de ce sous-comité a été de préparer un plan d'action plus détaillé, avec des études de cas, pour illustrer la façon dont on communique sur la sécurité dans diverses circonstances.

Le Comité a pris note des stratégies bien élaborées et des ressources pédagogiques déjà disponibles pour éviter et atténuer les crises dans la communication sur la sécurité des vaccins et a mis l'accent sur 2 d'entre elles.

- Le nouveau guide du CIOMS,[10] *Guide to Vaccine Safety Communication,* couvre les questions relatives aux stratégies de communication, en particulier pour les responsables de la réglementation, mais aussi pour les programmes de vaccination et les autres parties prenantes. Il souligne l'importance de disposer de personnel doté de compétences appropriées en communication à propos de la sécurité vaccinale et fournit des recommandations et des modèles pour un plan de communication.
- La Bibliothèque de la vaccination et de la confiance de l'OMS contient des descriptions générales de la façon dont les inquiétudes apparaissent, présente le rôle de la communication dans l'atténuation des crises, fournit des ressources pour aider les parties prenantes à la vaccination à éviter et gérer les crises et expose, dans ses grandes lignes, un programme de formation.

Des stratégies, des lignes directrices et des ressources sont à disposition pour atténuer et gérer les crises en rapport avec la sécurité des vaccins. Une étude de cas faisant ressortir l'intérêt de la confiance d'une communication claire à tous les niveaux et de sources crédibles a été présentée. Le GACVS considère que la communication à propos de la sécurité des vaccins nécessite une coordination entre de nombreuses parties prenantes dans 5 domaines: (i) un cadre incluant des scenarios et proposant des principes communs pour faire face à des situations spécifiques; (ii) des messages communs pour les problèmes de sécurité vaccinale à l'intention des différents partenaires dans le monde; (iii) la mise en commun des ressources existantes en matière de communication par le biais d'une bibliothèque électronique; et (iv) des critères de qualité pour la planification et la mise en œuvre des communications à propos de cette sécurité; et (v) la collaboration et la coordination des partenaires de manière à ce que chacun d'eux ait la possibilité d'apporter des contributions susceptibles de déboucher ensuite sur des actions.

[10] Voir https://cioms.ch/

Vaccine safety net

The Vaccine Safety Net (VSN) is a WHO initiative initially launched to identify trustworthy information on vaccine safety and immunization on the Internet.[11] GACVS supports the VSN by providing advice and criteria for website quality and content, thereby facilitating access by public health authorities, health professionals and the public to reliable information on vaccine safety. There are currently 58 member websites in 16 languages, covering the 6 WHO regions.

VSN members met on 4–5 June 2018 in Veyrier-du-Lac (France), for the second time in less than 2 years, to review the status of their activities, reflect on recent advances in social media and the Web and further discuss approaches, strategies and challenges in managing digital information and communication on vaccine safety. A preliminary report of the meeting was presented to GACVS. Despite increasing recognition worldwide, VSN members identified a number of challenges, including additional investment. The Net requires more partnerships and collaborations, qualitative research based on the experience of the VSN websites, communication research involving VSN members, engagement of young professionals and students in vaccination communication to stimulate more engagement by advocates and champions, and engagement of global and regional foundations in building vaccine acceptance and addressing vaccine hesitancy.

The good alignment of VSN members provides new opportunities for research. A recently explored area is web analytics to document patterns of web-searching on specific vaccine safety issues around the globe and at each VSN site. Web analytics could also be used to monitor the effects of digital communication strategies in real time. Research on measuring, understanding, tracking and addressing vaccine confidence was identified as another important area. A digital toolkit or newsletter would provide updates, tips, lessons learnt and risk communication guidance and resources for responding to vaccine safety events that occur locally in member countries.

During the 2-day meeting, participants were presented with preliminary results from the VSN web analytics project and plans for digital communication models for vaccine safety. GACVS continues to seek improved communication of vaccine safety information to the public and to its partners and therefore welcomes the contribution of the VSN and supports the work presented. In the overloaded web communications environment, where information competes for attention, easy access to reliable, trustworthy content on vaccination and immunization remains of paramount importance. ■

[11] See WHO, Vaccine safety net (http://www.who.int/vaccine_safety/initiative/communication/network/vaccine_safety_websites/en/, accessed June 2018).

Réseau pour la sécurité des vaccins

Le VSN est une initiative de l'OMS lancée au départ pour identifier les informations disponibles sur Internet à propos de la sécurité des vaccins et de la vaccination dignes de foi.[11] Le GACVS appuie le VSN en fournissant des conseils et des critères portant sur la qualité et le contenu des sites Web, les rendant ainsi plus facilement accessibles aux autorités de santé publique, aux professionnels de la santé et au public désireux d'obtenir des informations fiables sur la sécurité des vaccins. Il existe actuellement 58 sites Web membres, présentés dans 16 langues et couvrant les 6 régions de l'OMS.

Les membres du VSN se sont réunis les 4 et 5 juin 2018 à Veyrier-du-Lac (France), pour la deuxième fois en moins de 2 ans, afin d'examiner l'état d'avancement de leurs activités, de réfléchir aux évolutions récentes des médias sociaux et du Web et de poursuivre la discussion des démarches, des stratégies et des difficultés dans la gestion des informations numériques et de la communication concernant la sécurité des vaccins. Un rapport préliminaire de cette réunion a été présenté au GACVS. Malgré une reconnaissance grandissante à l'échelle mondiale, les membres du VSN ont identifié un certain nombre de défis restant à surmonter, y compris des investissements supplémentaires. L'exercice sur le Net requiert davantage de partenariats et de collaborations, une recherche qualitative s'appuyant sur les expériences acquises par les sites Web du VSN, des recherches en communication impliquant des membres de ce réseau, la participation de jeunes professionnels et d'étudiants en communication dans ce domaine pour stimuler l'engagement des avocats et des défenseurs de cette cause et une implication des fondations mondiales et régionales en faveur d'une meilleure acceptation du vaccin et de l'élimination des réticences devant la vaccination.

Le bon accord des membres du VSN ouvre de nouvelles possibilités de recherche. L'un des domaines récemment explorés est l'analyse du Web dans le but de recenser les schémas de recherche sur ce réseau pour répondre à des questions relatives à la sécurité des vaccins dans l'ensemble du monde et sur chaque site du VSN. L'analyse du Web pourrait aussi être utilisée pour suivre les effets des stratégies de communication numérique au cours du temps. Les recherches sur la mesure, la connaissance, le suivi et l'amélioration de la confiance dans les vaccins ont été identifiées comme un autre domaine majeur. Une boîte à outils ou un bulletin numériques pourraient fournir des mises à jour, des conseils, des enseignements à retenir ainsi que des recommandations et des ressources en matière de communication à propos des risques pour répondre aux événements en rapport avec la sécurité des vaccins qui se produisent localement dans les pays membres.

Dans le cadre de la réunion sur 2 jours, on a présenté aux participants les résultats préliminaires du projet d'analyse du Web du VSN et des plans pour l'élaboration de modèles numériques de la sécurité des vaccins. Le GACVS poursuit ses efforts pour améliorer la communication des informations relatives à la sécurité vaccinale en direction du public et de ses partenaires. Il accueille donc très positivement la contribution du VSN et exprime son soutien au travail présenté. Dans un environnement surchargé en communications transitant par Internet, où les informations sont en compétition pour retenir notre attention, un accès facile à un contenu fiable et digne de confiance sur la vaccination et l'immunisation reste d'une importance capitale. ■

[11] Voir OMS, Réseau pour la sécurité des vaccins. (http://www.who.int/vaccine_safety/initiative/communication/network/vaccine_safety_websites/fr/, consulté en juin 2018).

Annotated IVIR-AC Agenda 2018 (draft 14 September 2018)

Monday, 24 September 2018

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
12.30-12.45	Welcome	Charge of the Committee		R. Breiman
		THEME 1: Research to minimize barriers and improve coverage of vaccines currently in use		
12.45-14.15	***Session 1:*** Global vaccine demand and acceptance	- Introduction and context by L. Menning (10 min) - Update IVIR-AC WG on Vaccine Demand and Acceptance including generic framework on vaccine acceptance and demand by M. Weiss (15 min) - HPV vaccine demand and acceptance study protocol South-Africa by F. Scorgie (15 min) - IVIR-AC reviewers' comments (each 3 min) Discussion (45 min)	- Does IVIR-AC have any comments/suggestions to the proposed ToR of IVIR-AC working group? - Does IVIR-AC have any feedback on the generic vaccine acceptance and demand framework proposed? - Does IVIR-AC have any feedback on the study protocol on vaccine demand and acceptance from South-Africa?	IVIR-AC members: V. Nankabirwa J-D. Lelièvre WHO focal point: L. Menning

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
		THEME 2: Research to conduct impact evaluation of vaccines in use		
14.15-15.30	***Session 2:*** Cervical cancer elimination model comparison	- Introduction by R. Hutubessy (5 min) - WHO's cervical cancer elimination roadmap by N. Broutet (10 min) - Introduction of Policy-1 model by K. Canfell (10 min (*by Webex*)) - Introduction of Harvard model by J. Kim (10 minutes) - Introduction of HPV-ADVISE model by M. Brisson (10 minutes) - Cervical cancer elimination model comparison exercise to inform the elimination targets and scenarios by J. Kim and M. Brisson (30 min) - IVIR-AC reviewers' comments (each 5 min)	- Does IVIR-AC have any feedback on the modeling methods of the individual modeling groups? - Is there agreement on the collaborative model comparison work for defining the cervical elimination thresholds and the strategies towards global cervical cancer elimination?	IVIR-AC members: P. Beutels D. Burke WHO focal point: R. Hutubessy
15.30-16.00	***Coffee/tea break***			
15.30- 17.00	***Session 2 continued:***	Discussion continued (90 min)		
17.00-17.30 ***17.30***	Summary Day 1 **Cocktail**	Summary of key conclusions and next steps ***TBC***		**R. Breiman**

Tuesday, 25 September 2018

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
08.30-10.00	***Session 3:*** Total System Effectiveness (TSE)	- Introduction and context by A-L Khan (10 min) *(by WebEx)* - An update on TSE following the recommendations from IVIR-AC March 2018 by S. Botwright (15 min) - Country level dashboard to inform policy and monitoring progress by W. Panhuis (15 min) - IVIR-AC reviewers' comments (each 3 min) - Discussion (30 min)	- Are all TSE recommendations from the IVIR-AC March 2018 meeting addressed? - Does IVIR-AC have any feedback the methods and tools used to support country level up take of vaccines and/or R&D decisions? - Does the IVIR-AC have any feedback on the TSE implementation activities of TSE in Indonesia, Thailand, Mali and Rwanda? - Does IVIR-AC have any feedback on the usefulness of country level dashboard and/or has suggestions for improvement?	IVIR-AC members : M. Jit A. Lopez WHO focal point: A-L. Khan
10.00-10.30	***Coffee/tea break***			

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
10.30 – 11.45	***Session 4*:** Measles Rubella vaccines investment case and timing of SIAs	- Introduction and context by A. Dabbagh (10 min) - Measles Rubella Investment Case by M. Jit (10') - An update of the timing of SIAs project following the recommendations from March 2018 by Mark Jit (10') - IVIR-AC reviewers' comments (each 3 min) Discussion (35 min)	- Does IVIR-AC have any comments/suggestions on the update on the investment case and proposed ways forward? - Are all SIA recommendations from the IVIR-AC March 2018 meeting addressed??	IVIR-AC members: Q. Bassat W. Orenstein WHO focal points: A. Dabbagh
11.45-12.45	***Lunch***			

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
12.45-14.00	***Session 5:*** WHO Guide on typhoid vaccine cost-effectiveness	- Introduction and context by A. Bentsi-Enchill (10 min) - Presentation of WHO Guide by N. Chaiyakunapruk and G. Pitzer (20 min) - IVIR-AC reviewers' comments (each 3 min) - Discussion (30 min)	- Does IVIR-AC has any feedback on the CEA guide for Typhoid vaccines, specifically on the modelling chapter?	IVIR-AC members: S. Verguet W. Ndifon WHO focal point: A. Bentsi-Enchill
14.00-15.15	***Session 6:*** Guidelines for multi-model comparisons	- Introduction and context by R. Hutubessy (5 min) - Model comparison guide by S. den Boon (15 min) IVIR-AC reviewers' comments (each 3 min) Discussion (30 min)	- Does IVIR-AC have any feedback on the model comparison guide as a follow up from the IVIR-AC recommendations from May 2016?	IVIR-AC members: D. Burke S. Verguet WHO focal point: R. Hutubessy
15.15-15.45	***Coffee/tea break***			
	THEME 3: Research to improve methods for monitoring of immunization programs			
15.45-17.00	***Session 7:*** Using available data to identify areas of risk	- Introduction and context by A. Henao-Restrepo (5 minutes) - Pragmatic tool to identify immunization gaps by A. Acosta (15 minutes) - Options for risk analysis: Vaccine Decision Information Systems by W. Panhuis (15 minutes)	Does IVIR-AC have any feedback on usefulness and methods used underlying the tools presented to identify areas of risk?	IVIR-AC members: S. Sow M. Weiss WHO focal point: A. Henao-Restrepo

		IVIR-AC reviewers' comments (each 3 min) Discussion (30 min)	
17.00-17.15	Summary Day 2	Summary of key conclusions and next steps	**R. Breiman**
17.15	***Adjourn***		

Wednesday, 26 September 2018

CLOSED SESSION FOR IVIR-AC MEMBERS ONLY

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
9.00-10.30	Formulation of IVIR-AC recommendations			
10.30-11.00	***Coffee/tea break***			
11.00 -12.30	Formulation of IVIR-AC recommendations			
12.30	***Adjourn***			

WORLD HEALTH ORGANIZATION
IMMUNIZATIONS, VACCINES AND BIOLOGICALS

IMMUNIZATION PRACTICES ADVISORY COMMITTEE
(IPAC) 12th Meeting
10 – 11 July 2018

Final meeting report and recommendations

Opening and Introduction

IPAC Members present:
Chris Morgan (Chair)
David Brown
Craig Burgess
Nora Dellepiane
Michael Free
Ian Gemmill
Masahiko Hachiya
Kelly Moore
Adelaide Shearley
Carla Vizzotti

The Immunization Practices Advisory Committee (IPAC) convened for the 12th time on 10-11 July 2018 in Geneva, Switzerland to support and advise the Director and staff of the WHO Department for Immunization, Vaccines and Biologicals (IVB) with the review and/or formulation of immunization practices, operational standards, tools and technologies. Advice aimed to strengthen and improve the delivery of immunization programmes at the country level to realize the goals of the Global Vaccine Action Plan (GVAP).

Special thanks were given to Dr Chris Morgan, the IPAC Chair, who had extended his term by one year to provide continuity to IPAC during the management transition currently ongoing in the IVB Department. IPAC members were thanked for the valuable and generous contribution of their time.

This year's agenda emphasized innovation, a theme which, in light of the WHO Director General's commitment to reach one billion more people with access to universal health coverage (UHC), is now more essential than ever. The topics deliberated over the two days related to:

- Improving coverage and equity by better facilitating access to vaccine innovations;
- Receiving an update on the activities of the different working groups and committees;
- Optimizing vaccine delivery through better financing, access, and supply chains.

A closed session for IPAC members only was held on the third day to discuss how to ensure IPAC's work remains relevant and impactful, one of the key issues being the linkages between IPAC and the Strategic Advisory Group of Experts (SAGE) on Immunization.

The Chair opened the meeting by highlighting that immunization is going through a time of change – administrative changes in WHO, and changes in the complexity of process of immunization – and that as such, the immunization community needs to focus on navigating these transitions. He noted that vaccination is key to disease control, and that the Expanded Programme on Immunization (EPI) is one of the world's most successful public health platforms. EPI has always been characterized by simplicity and predictability, but this is no longer the case. There are new vaccines and new ways of delivering them that are to be embraced if ambitious global goals are to be met. He remarked on a possible tension in the meeting agenda of how to accommodate new opportunities and innovations while remaining oriented to the needs of field programmes at all levels, that is: how to combine current complexity and historical simplicity.

Session I. Innovation for improved coverage and equity

IPAC reviewed reports on the slowing of improvements in global immunization coverage. Although the Expanded Programme on Immunization (EPI) is successfully vaccinating increasing numbers of children every year, the effect of population growth in settings such as sub-Saharan Africa means that it is unlikely that the current coverage with the third dose of diphtheria-tetanus-pertussis containing vaccine (DTP3) of 85% will rise to the global goal of 90% by 2020. IPAC noted that **better subnational data** to identify under-vaccinated groups is increasingly available at the global level. This enables new thinking on tailored solutions, but also calls for new tools and methods to translate this data into innovative immunization strategies and practices to reach under-served populations. Adaptation of existing approaches such as Reaching Every District (RED), the transformative actions within the Global Routine Immunization Strategies and Practices (GRISP) guidance, and examples such as an 'urban toolkit', can also support setting-specific responses.

Three recent initiatives were discussed, all seeking broader alignment between programme needs and product innovation. The **Total System Effectiveness (TSE)** approach aims to support countries in reaching coverage and equity targets by strengthening informed, transparent and holistic decision-making for national immunization programmes, and by ensuring that global policy, market shaping and research and development (R&D) priorities reflect the needs and priorities of low and middle-income countries. The current testing of this approach in Asian and African settings was discussed, noting that formal reporting to the Immunization and Vaccines Implementation Research Advisory Committee (IVIRAC) took place in March 2018 and an update is scheduled for September 2018. IPAC supported the use of TSE in generating a flexible toolkit to be used by countries to analyse barriers to progress and decide which vaccines and related technologies to introduce. The potential value of TSE in providing assessments that can be used in other prioritization efforts was also noted. IPAC noted the conceptual links with the **Doses Per Container Partnership (DCP)** that aims to help country decision-makers include consideration of how differing numbers of doses per multi-dose vaccine vial could optimize equitable and cost-effective coverage; and to strengthen the feedback to developers and manufacturers.

The **Vaccine Innovation Prioritization Strategy (VIPS)** is a new programme of work sponsored by global immunization partners to incorporate the needs of countries into the projected impact of vaccine product innovations to help prioritize those that will more clearly address the barriers countries face in achieving optimal immunization coverage. This accompaniment to Gavi's Vaccine Investment Strategy will support prioritization of innovations in vaccine product attributes, such as primary containers, delivery technologies (for example micro-array patches), labelling, and packaging. VIPS is a multi-partner initiative that includes formal involvement of IPAC and WHO's Product Development Advisory Committee (PDVAC), and envisages production of a prioritized short-list of vaccine product innovations by the end of 2019. IPAC affirmed the VIPS

approach and provided input to strategic concepts, suggested applying a service delivery framework to analyses and early engagement with manufacturers, as well as providing input to the tools for the first round of country consultations.

IPAC noted that VIPS, TSE and DPCP all reflect an attempt to introduce a properly nuanced country view into global policy, into communications with developers and manufacturers, and into the upstream development of new products and tools. IPAC noted the value in categorizing new products or innovative approaches according to their usefulness in different service delivery platforms, to enable application to various settings and across a range of vaccines. To ensure that Middle Income Countries (MICs) are also able to contribute to, and benefit from, these initiatives the Committee agreed that expanding the scope of VIPS and TSE to include MICs and Gavi transition countries would make the work more relevant and could contribute to a better understanding of potential market for manufacturers.

i. Improving how we collectively address Coverage & Equity and evaluate barriers to immunization. *(Jan Grevendonk, WHO/EPI - presented for Partner Alignment)*

The goal of the global immunization community is to achieve the highest possible levels of equitable vaccination coverage at an affordable cost. While coverage with the third dose of diphtheria-tetanus-pertussis containing vaccine (DTP3) has improved steadily in the past, it is now stagnating at 85-86% - not fast enough to reach the global goal of 90% by 2020, leaving 20 million children vulnerable to death and disability from vaccine-preventable diseases. Of the 20 million under immunized, half of these are in the African Region where population growth means although more children are vaccinated each year, this only suffices to maintain current coverage levels. In order to focus efforts to address these inequities, greater insight is needed into who and where these unvaccinated children are.

WHO and UNICEF now have sub-national immunization coverage data from 141 countries, a key step in understanding inequities between geographical areas, districts and wealth quintiles. In countries with large numbers of unvaccinated children, identification of under-vaccinated groups and establishing tailored strategies to serve them is the next step. The Reaching Every District (RED) Strategy[1] and its operational components remain relevant, however additional planning tools are needed to tailor strategies to reach the urban poor, rural remote and conflict-afflicted populations in particular. The Global Routine Immunization Strategies and Practices (GRISP) Framework[2] encompasses nine transformative investments than can be coupled with innovation in systems and products. New assessment tools, including Total System Effectiveness (TSE) and the Vaccine Innovation Prioritization Strategy (VIPS) will need to demonstrate how product innovations can meet the needs of specific settings and communities, if further advances in equitable coverage are to be achieved.

Discussion:
IPAC members welcomed the overview provided on global coverage and the reminder that there are continuing pockets of unreached populations whose vaccination is key to achieving coverage and equity goals. It was noted that implementation of the tailored approaches needed to access these hard to reach populations is challenging, and that adopting a health systems approach, integrating with other health programmes, to deliver a package of interventions for these populations would be more cost-effective. The Committee supported increased dissemination and uptake of tools to support

[1] http://www.who.int/immunization/programmes_systems/service_delivery/red/en/
[2] http://www.who.int/immunization/programmes_systems/policies_strategies/GRISP/en/

countries in devising tailored approaches. The "urban toolkit" being rolled out in African countries is one example of a first step for reaching chronically under-immunized populations in urban areas and its adoption was encouraged.

ii. (a) Country use case for Total System Effectiveness (TSE). *(Siobhan Botwright, WHO/IVR – presented for Strategic Guidance)*

IPAC received a further update of TSE, focusing on the development of the country use cases, which applies TSE to national immunization programme prioritization decisions. The overall intent of TSE is to support countries in reaching coverage and equity targets. TSE is an approach to identify the value of products from a country immunization programme perspective, both to support national decision-making on uptake and to direct market shaping at the global level so that country demand informs product development and create a 'pull' for new products that meet the needs of low and middle income countries (LMICs). TSE started out as a partnership between the Bill and Melinda Gates Foundation (BMGF), Gavi, UNICEF, PATH and WHO. Other partners have subsequently joined the initiative to enlist expertise in modelling and multi-dimensional criteria analysis, and partners for country implementation.

TSE is currently being piloted through analysis of rotavirus vaccine introduction, to establish whether low- and middle-income countries (LMICs) see benefit in a TSE approach to decision-making and, if so, what tools would be needed and what might be the constraints on data or capacity. In 2018, TSE workshops are being held in Indonesia, Thailand, Mali, Rwanda, with the objective of developing a long-term proposal and recommendation by the Immunization and Vaccines Related Implementation Research Advisory Committee (IVIRAC) in September 2018.

Initial results from Indonesia and Thailand varied in accordance with the maturity and nature of their national decision-making processes. Country stakeholders identified value in using TSE to support the review of different presentations of the same vaccine, to inform the local research and development agenda, and to assess vaccination within broader disease control programmes and/or for considering interventions across the EPI programme. While there is potentially broad applicability for TSE, better flexibility is needed to link TSE to existing country guidelines, studies and methods. Immediate next steps are to complete the country pilots, especially in an African context, and to understand how TSE can influence research and development. In the longer term, the group will develop a "TSE toolkit" for country use, devise a mechanism for the analysis of barriers, develop tools and processes for global use of TSE to direct market shaping, and implement the TSE approach, including an evaluation framework.

IPAC was asked to consider several issues during the meeting, and offline through suggestions to the Secretariat. For the analysis of barriers to TSE, these included which ongoing initiatives and forums should be leveraged, and which important partners should be engaged. In relation to country use of TSE, questions included whether it is feasible to consider "archetype countries" as TSE is developed, and how representative countries should be selected.

ii. (b) Dose per Container Partnership (DPCP) *(Craig Burgess, JSI and IPAC Member – presented for information)*

IPAC received an update on the DPCP, noting completion of Phase 1 and near completion of Phase 2 of this initiative. The DPCP acknowledges that while countries need access to affordable and appropriate vaccine products there is a risk that products are supply driven and there is an over-reliance on multi-dose presentations to maintain low costs. At the service delivery level, fear of wastage and stock-outs leads to missed opportunities to immunize, for example if health care workers only open a 10-dose measles vial if more than five children are present and otherwise instruct a caregiver to

return later for a dedicated measles vaccination session. Historically, there has been little focus on the impact of dose per container (DPC) on coverage, and DPC trade-offs between system savings and performance. The goal of the Dose per Container Partnership (DPCP) is to support vaccine product and programme decision-making in considering the impact of DPC on equitable, timely, safe, and cost-effective coverage. The Technical Advisory Group of the DPCP includes representatives from WHO, UNICEF SD, Gavi, industry, academia, and countries.

In Phase I, from April to October 2015, country consultations and literature reviews indicated that most EPI Managers prefer a 5-dose measles vial and are interested in allowing different DPC presentations of the same vaccine to be in the system at the same time. There was also strong interest from countries in strengthening the feedback loop to manufacturers to inform product development to meet their needs.

IPAC heard that in Phase II, findings suggest that national decision-making processes are based on global availability of products and are reliant on options proposed by procurement agents. As cold chain requirements and vaccine price are more easily quantifiable than the impact of failing to reach coverage and equity goals, national decisions on vaccine products are influenced more by budget than by national goals. However, in countries where vaccine is locally produced, manufacturers can play a key role in the decision-making and can be responsive to DPC requests.

The next steps for the DPCP are to translate the evidence gathered into tools that support national decision-making by helping countries consider the impact of different vaccine DPC sizes on the various system components and to understand the trade-offs involved. Incorporating DPC into a tool that is already owned and used by countries, e.g. the UNICEF Supply Division (SD) ordering form, the Effective Vaccine Management (EVM) tool, the Comprehensive Multi-Year Plan (cMYP) or the new TSE tools, would contribute to easier uptake.

IPAC was asked to consider how DPCP results (processes, interventions and guide) could make a difference to the front line, how DPCP evidence could strengthen links to industry and increase choice of product development, and how to ensure synthesis and communications influence policy making.

Discussion on TSE and DPCP:
IPAC Members expressed interest in seeing how adaptable the final TSE tool is to countries' situations, and how flexible it is to countries uploading existing country data. While it may be difficult for countries to adapt the tool, the intent should be to make a generic flexible tool in which countries can select their own criteria for decision making, insert their own data, and be able to run the analyses. The 'tool-kit' approach was encouraged, such as that adopted by the Global Routine Immunization Strategies and Practices (GRISP) guidance, in order that countries have access to a menu of instruments from which they can choose. The Committee also urged the TSE Partnership to articulate clearly the gap in tools for country decision-making at country level, and how TSE will address this.

Although there was some caution expressed about the expansion of TSE beyond its original mandate of focusing on assisting countries to choose between different products for a specific vaccine, the responsiveness of the initiative to the interest expressed by countries in a framework to choose between vaccines and other interventions was welcomed.

IPAC Members applauded the linkages between downstream implementers and upstream manufacturers evident in these two presentations, and also recognized that the TSE and DPCP are important tools to use to advocate for political commitment for immunization. As TSE has broader inputs than other existing decision-making models, it would useful if

it could also be used to assess the trade-offs between different service delivery platforms, to consolidate information for a country on their barriers to increasing immunization coverage, and link this with the work of the DPCP. IPAC also noted and welcomed the adoption of TSE within the IVIRAC agenda of work.

iii. Vaccine Innovation Prioritization Strategy (VIPS).

(a) Overview of initiative, rationale and objectives. *(Marion Menozzi-Arnaud, Gavi – presented for strategic feedback)*

Innovation is one of the Alliance priorities for shaping markets to the benefit of Gavi-supported countries. Vaccine product innovation, using new technologies, has been identified as one of the levers to achieving coverage and equity goals by driving product innovations to better meet country needs. As vaccine development occurs on a long time horizon, that exceeds Gavi's strategic and funding cycle, and as Alliance partners sometimes lack alignment and clarity around longer-term priorities, manufacturers have indicated that even a non-binding indication of the interests of the Alliance in this area could inform their decision-making.

The objective of the Vaccine Innovation Prioritization Strategy (VIPS) is to develop a common language for valuing innovation and to identify common priorities by convening the market-shaping community. The scope of the VIPS covers innovations in vaccine products' attributes, i.e. delivery technologies (for example micro-array patches), formulations, for example heat stability, primary containers, labelling, and packaging.

VIPS will first prioritize antigen-agnostic innovations then vaccine-specific innovations. The first phase includes landscaping of all innovations, assessment of country needs, development of methodology and criteria for assessing innovations, and an initial prioritization of antigen-agnostic innovations. A second phase applies product innovations to specific antigens, conducts further consultations, in-depth analyses (including usage of relevant TSE assessments), and finalizes the priority listing.

Governance of the VIPS is through an Alliance Working Group, comprising representatives from WHO, UNICEF, Gavi, BMGF, and PATH. This is supported by a Steering Committee with designated seats for members of IPAC and PDVAC (Product Development Vaccine Advisory Committee), whose mandate will be to review the VIPS analyses and make recommendations to the VIPS Alliance Working Group.

The work of the VIPS will take place in 2018 and 2019 with a final set of prioritizations expected at the end of 2019 that articulate the Alliance perspective on what innovations to be prioritized and the rationale to make investment decisions.

(b) Country consultation approach. *(Anna Osborne, Gavi – presented for strategic feedback)*

One of the key pillars of the VIPS mandate is to understand countries' needs by leveraging countries' and technical partners' field experience to consider financial and non-financial impact of innovations. Currently there is no formal process to articulate country needs and communicate these to developers and manufacturers to inform product development. There will be three main touchpoints with countries: firstly to provide input into the development of the evaluation criteria; secondly to review the draft conclusions on country needs for product innovation; and thirdly to validate the analysis conclusions and identify additional considerations.

Initial country consultations are expected to generate a broad range in level of detail and differing opinions across a large number of reported barriers to equitable coverage. The challenge will be to condense these into usable inputs for the VIPS evaluation framework

and definition of quantitative weighting criteria. It will also be important to document country insights into the likelihood of product uptake, including characterization of the trade-offs inherent in an innovation and its relative importance in addressing specific barriers. Two further country-level inputs are planned. Once the preliminary analysis of all innovations in scope is finalised, a short-list of the most promising will be presented to countries to discuss their potential to address implementation challenges, and their known trade-offs. Country inputs will also be incorporated into the final scoring of each innovation to guide final prioritization of antigen-agnostic innovations.

The next step in the VIPS work is the launch of the online survey in August 2018, targeting a large audience including EPI Managers, National Immunization Technical Advisory Groups (NITAGS), national logisticians, and similar stakeholders. As healthcare workers (HCWs) are a key respondent group who may not have access to an online survey, face to face interviews with 10-15 HCWs will be conducted in October 2018 in 4-5 countries. The analysis of results will be presented in November 2018 to the first Steering Committee meeting.

IPAC was requested to consider the focus of country consultations, their format, target countries and audience, and other possible support.

Discussion:
IPAC recommended allowing collection of information on innovations that will solve barriers in different sub-populations, including areas where government service delivery is weak, to evaluate innovations needed in fragile settings. The Committee also recommended including consultations with Civil Society Organizations (CSOs) or Non-Governmental Organizations (NGOs) who are delivering immunization in such settings to obtain their perspective on the innovations that could be most effective.

IPAC Members suggested that the VIPS develop a common taxonomy of service delivery platforms, for use in categorizing data collection and analysis. Platform types may include facility-based, outreach, and campaign service delivery; possibly also considering outbreak response, community-based service delivery, vaccination in later ages of life, and school health platforms. Considering how product innovations could apply to various typologies of service delivery could also enable the findings to be tailored in application and possibly be applied beyond Gavi vaccines and countries, for example to overcome barriers in middle-income countries (MICs).

The Committee highlighted the importance of including the perspective of manufacturers early in consideration of innovations, both to specify target populations and potential market, and to identify likely trade-offs inherent in manufacturing processes of product innovations, such as the time to market. In order to avoid any conflict of interest, VIPS will present the findings to the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and the Developing Countries Vaccine Manufacturers Network (DCVMN), including a specific session on VIPS at the DCVMN conference in October 2018. In addition, both IPAC and PDVAC deliberations provide forums where these groups, and other manufacturers can access information on VIPs.

IPAC members were also requested to email to VIPS any suggested changes to the tools and to the country consultations approach, and on possible support that could be provided from IPAC Members.

Session II. IPAC working groups and other advisory committee updates

IPAC's **Controlled Temperature Chain Working Group (CTC-WG**) presented progress against the GVAP strategic objective for increasing the number of vaccines licensed under CTC for deployment beyond the standard cold chain. This included review of the four priority vaccines highlighted in the CTC Strategic Roadmap, which IPAC had endorsed in 2017. IPAC noted the recent prequalification of Shanchol® oral cholera vaccine, that one human papilloma vaccine (HPV, Gardasil®) is already licensed and prequalified for use in CTC, two different manufacturers have committed to relabelling hepatitis B birth-dose vaccines and, for tetanus toxoid-containing vaccines, one manufacturer has committed to CTC, but has yet to generate all data required. More advocacy and financial resources are required to achieve further progress with this and other vaccines, noting the potential for CTC deployment to advance coverage and equity in a variety of service delivery scenarios.

Pilots of CTC deployment of HPV vaccine in Uganda were discussed, noting the overall high level of acceptability and increased ease of use, supporting CTC as a strategy likely to improve coverage and efficiency in HPV vaccination programmes. The main drawback noted was difficulties in target population estimation, which requires improved micro-planning to optimize CTC deployment. IPAC provided input into ideal format and scope of guidance documents for country use. Among recommendations on usage, IPAC supported flexibility in decisions on whether local pilots are needed prior to CTC implementation, but reinforced the CTC principle that only one excursion outside the cold chain be allowed. IPAC noted the HPV vaccine deployment in CTC as a valuable demonstration of how aligning interests across regulators, manufacturers and national planners can enable the expansion of vaccine service delivery beyond traditional parameters.

IPAC reviewed the potential for **CTC strategies for oral cholera vaccine**, to improve coverage, accelerate response times, and reduce operational costs. Discussions focused on the limitations of the current CTC timing of 14 days, and the types of data that will be most informative in proposed pilot studies in planned (non-crisis) campaigns in endemic settings.

Defining demand and usage scenarios for **hepatitis B vaccine birth-dose in a CTC** is the most challenging of the four priority vaccines and this remains under discussion. IPAC noted that known thermostability data of potential candidates does not yet match ideal usages and reviewed several options for re-defining CTC for this vaccine. IPAC recognized the unique difficulties of reaching new-borns with timely vaccination and noted that the CTC-WG will need to continue work to better characterize the likely demand and feasibility of HepB-BD in a CTC, recognizing that this may require tighter focus on very specific usage scenarios such as community outreach.

IPAC appreciated the achievements of the **Delivery Technologies Working Group (DTWG)** over 2017-2018, including: development of and reporting against a delivery innovation indicator for the Global Vaccine Action Plan (GVAP indicator G4.2); country assessments on the potential of micro-array patches (MAP); review of a broad range of pipeline technologies; and contributions to the TSE and VIPS initiatives. IPAC heard updates on acceptability studies of the measles-rubella vaccine MAP (MR-MAP), contributed to a revision of its Target Product Profile (TPP), welcomed the establishment of a PATH MAP centre of excellence, and recommended additional work on public health need and implementation potential to sustain momentum on MR-MAP.

Other reports included the Standing Committee of PSPQ and updates on the work of PDVAC and IVIRAC. IPAC considered how evidence and discussion for implementation issues can be coordinated across PDVAC, IVIRAC and IPAC. Discussions recognized clear

demarcations between the roles of the three Advisory Committees, and also identified potential for increased synergy through work on linked topics. Examples include the cross-cutting work of the TSE initiative across all three committees, and the mixture of 'upstream' and 'downstream' inputs to the VIPS process provided by PDVAC and IPAC respectively. In consideration of the reporting on progress in GVAP, IPAC noted the need for future global strategies to balance aspirational with achievable goals, and the potential for richer, possibly less frequent, analyses to help contextualize and inform country-level reflections on their programmes.

i. Delivery Technologies Working Group

(a) Update on working group activities. *(Darin Zehrung, PATH - presented for information)*

The Delivery Technologies Working Group (DTWG), established in 2015, provides feedback to developers of technologies on product development considerations and programmatic suitability of their products for use in LMICs. This contact happens through meetings and through a dedicated discussion group on the TechNet 21 Forum. IPAC noted with appreciation that the DTWG's accomplishments over 2017-2018, included: development of an indicator for the Global Vaccine Action Plan (GVAP) Platform Delivery Technology (Indicator G4.2) along with a contribution for the 2018 report on progress and recommendations; country assessments by PATH and Agence de Médecine Préventive (AMP) on the potential usage of micro-array patches (MAP); review of a broad range of pipeline technologies (including glass cartridges, MAPs, prefill/blow-fill-seal vaccine presentations, and electroporation); and contributions to the TSE and VIPS initiatives.

(b) Report from the WHO workshop on measles-rubella vaccine micro-array patch (MR-MAP) product development. *Birgitte Giersing, WHO/IVR – presented for strategic guidance*

Microarray patches (MAPs) are needle free patches that deliver a dry formulation of vaccine into the upper layers of the skin. MAPs require no reconstitution, remove needle waste, potentially reduce cold chain storage, and are perceived to be easier to administer, possibly by community health workers, or even through self-administration. These attributes could aid the global immunization community to accelerate progress towards measles-rubella elimination goals. Previous work reported to IPAC includes the 2015 consultation held to assess the potential for MAP vaccine delivery in LMICs, which concluded that the value proposition for low cost, well established EPI vaccines such as measles and rubella (MR) was weak, with poor incentives for development of innovative products. One of the recommendations from that meeting was to develop the Target Product Profile (TPP) for MR-MAP, and this was presented to IPAC in 2016. Following this, in 2016, the Strategic Advisory Group of Experts (SAGE) for Immunization issued a recommendation that licensure of measles containing vaccines in MAPs be expedited.

IPAC heard that, while the planning for the first MR-MAPS is expected to enter Phase I clinical studies in 2019 and that PATH is forming a MAP Centre of Excellence, other initiatives to define public health need and create momentum for MAPs are required to establish pathways to licensure and prequalification, identify manufacturing and implementation barriers, and forecast uptake of MR-MAPs in LMICs. IPAC was updated on the main conclusions from MAP acceptability studies conducted by PATH and AMP: there is much interest and enthusiasm for MAPs, but assumptions about how these products will be adopted in countries cannot be made. There are important trade-offs between the potential benefits in ease of delivery and increased access, and the additional cost of the MAP. Modelling is underway for five different potential demand scenarios for a measles-containing vaccine (MCV)-MAP, however the realistic timeline for product availability is

10 years, and much will be required, especially in estimating demand, to incentivize manufacturers and developers to invest in this.

Discussion:
IPAC Members were pleased to learn of the progress made in this area and recognized the possibilities of using microarray patches to reach the fifth child, especially in settings where it is possible to expand cadres of lesser-qualified vaccinators capable of delivering immunization through MAPs. IPAC noted that while articulating a TPP is one clear and effective way to communicate with manufacturers, additional tools to help describe usage cases in more detail may be helpful to developers in understanding programmatic issues involved in rolling out MAPs. IPAC members also provided, through a separate survey and document review, detailed suggestions on a revision to the MR-MAP TPP, with a focus on issues such as optimal wear time and acceptable temperature ranges.

ii. Product Development for Vaccines Advisory Committee (PDVAC) update. *(Birgitte Giersing, WHO/IVR – presented for information)*

The mission of PDVAC is to accelerate product development of urgently needed vaccines and technologies and ensure they are appropriately targeted for use in low- and middle-income contexts. This recognises that on average it takes several years from vaccine licensure to first introduction in LMICs, and over a decade for implementation of the vaccine to reach 50% coverage. PDVAC reviews vaccines in early clinical development, evaluates the probability of technical and regulatory success, and ensures the pipeline will meet the unmet public health need for a vaccine from an LMIC perspective. PDVAC communicates priorities by articulating the public health value and preferred product characteristics (PPCs); developing roadmaps early in product development to help define a value proposition; encouraging investment; and reducing the implementation gap.

IPAC was updated on candidate vaccines and initiatives under PDVAC consideration, including: HIV, Tuberculosis, Malaria, Influenza, Enterotoxigenic *E.coli* (ETEC), Shigella, Respiratory Syncytial Virus (RSV), Group B and Group A streptococcus, Herpes Simplex Virus (HSV), Microarray patch product development for MR vaccines, TSE and VIPS. IPAC acknowledged the importance of ensuring new vaccines meet the needs of the end-users such as national immunization programmes, and noted the benefit of mechanisms (such as VIPS) that can communicate learning on service delivery and antigen-agnostic issues to manufacturers for incorporation in their development plans. IPAC also discussed how research and deliberation on implementation issues can be coordinated across PDVAC, IVIRAC and IPAC.

iii. Immunization and Vaccine related Implementation Research Advisory Committee (IVIRAC) update. *(Raymond Hutubessy, WHO/IVR – presented for Information)*

IVIRAC provides guidance on implementation research relevant to immunization policies and practices, reviews implementation research, advises research groups, and reviews best practices related to research methods. IPAC was updated on IVIRAC's current agenda, including: firstly to minimize barriers through work on rotavirus vaccine impact, the global research agenda for HPV vaccines, and the global research on Vaccine Demand and Acceptance update; and secondly to maximize impact of vaccines in use through work on Malaria RTS,S Policy Decision Making Framework and impact modelling, the optimal intervals between measles SIAs model, the WHO Guide on standardization of economic evaluations of vaccines, the development of Full Public Health Value Proposition, TSE, and the standardization of vaccine delivery cost.

IPAC noted clear demarcations between the roles of the three Advisory Committees, with IVIRAC considering implementation research issues, PDVAC more upstream research and development issues, and IPAC focused on the programmatic aspects of implementation.

There are also useful synergies, such as the cross-cutting work of the TSE initiative. IPAC encouraged IVIRAC to continue to relay programmatic applications to IPAC once they had reached a sufficient level of maturity, so that the evidence-based approach to recommendations is maintained.

iv. Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) update. *(Kelly Moore, IPAC & PSPQ Standing Committee Member – presented for information)*

The PSPQ process works within WHO's Essential Medicines Programme to define characteristics that determine the programmatic suitability of vaccine products, define the process for assessing compliance with these characteristics, and indicate programmatic characteristic preferences to industry and other vaccine development stakeholders. The PSPQ Standing Committee, a standing report to IPAC, comprises two IPAC Members and three independent experts, and is responsible for reviewing applications where a vaccine falls outside standard PSPQ criteria, but has potential public health benefit, as referred by the PSPQ Secretariat. IPAC was updated that in 2018, prior to official submission for review by the PQ Secretariat, an advance opinion was requested from the Standing Committee on a pentavalent meningococcal conjugate vaccine. This request doubled as a training opportunity for new members on PSPQ Standing Committee criteria and processes. IPAC confirmed continuation of their representation on the PSPQ Standing Committee.

v. SAGE Decade of Vaccines Working Group – Assessing progress on Global Vaccine Action Plan (GVAP). *Christoph Steffen, WHO/DIR – presented for information)*

The SAGE Decade of Vaccines Working Group (SAGE DoV WG) facilitates a yearly assessment of progress of the implementation of the Global Vaccine Action Plan (GVAP) 2011-2020[3] and prepares the annual assessment report that is presented to the SAGE meeting in October, the WHO Executive Board in January, and to the World Health Assembly in May. As the GVAP comes to an end, it will be reported on to the WHA in 2020, and in 2022 to unveil the new strategy. GVAP's five main goals (Polio, Maternal and Neonatal Tetanus and Measles elimination, introduction of new vaccines, and increasing routine immunization coverage), six strategic objectives and 16 sub-objectives, are monitored through indicators largely based on data submitted by countries through the WHO-UNICEF Joint Reporting Form (JRF)[4]. IPAC heard that approximately 150 recommendations have been made through GVAP assessments, and the results for 2016 show that only the goal on new vaccine introduction is on track. The GVAP Secretariat is now aiming to reduce the number of recommendations being made and is discussing how to make them more impactful to achieve results.

Discussion:
IPAC Members recognized the tremendous achievement of having the GVAP report on the agenda of the World Health Assembly every year. It was noted that most efforts towards achieving the GVAP goals need to take place at country level and that the Regional Vaccine Action Plans developed by countries with support from WHO Regional Offices are key to holding countries accountable for the goals they have endorsed. IPAC also appreciated the increasing clarity and detail in the most recent assessment reporting.

IPAC agreed that in the setting of goals for the future strategy, balance needs to be achieved between setting aspirational and ambitious goals, setting achievable goals that

[3] http://www.who.int/immunization/global_vaccine_action_plan/en/
[4] http://www.who.int/immunization/monitoring_surveillance/routine/reporting/en/

countries can work towards and document achievements that contribute to high-level advocacy. IPAC Members suggested that a future global strategy could be reshaped so that not only can the annual reports serve to showcase the successes of immunization and garner international support, but also that countries can use the data for their own monitoring and advocacy. IPAC also suggested consideration in the new strategy of less frequent reporting, such as every other year, that could facilitate more in-depth and provocative analysis examining, for example, the causes of low coverage and high drop-out rates, which may be more useful to countries.

vi. Controlled Temperature Chain Working Group

(a) Progress towards GVAP Indicator. *(Rachel Bauquerez, WHO/EPI – presented for information)*

WHO defines the controlled temperature chain (CTC) as "a single excursion of a vaccine into ambient temperatures typically not exceeding a set threshold of 40°C, for a limited number of days before administration." The GVAP includes CTC within a strategic objective on research and development, measuring progress against the indicator "Number of vaccines that have either been re-licensed or licensed for use in a controlled-temperature chain at temperatures above the traditional +2°C - +8°C range". The CTC Working Group was established within IPAC in 2016 to expand on earlier work by the five year Project Optimize collaboration of WHO and PATH that successfully supported CTC re-licensing and deployment of a meningococcal A vaccine (MenAfriVac™). IPAC reviewed the main activity of the CTC-WG over the last year: the development of the Strategic Roadmap for Priority Vaccines 2017-2020[5], which identifies the way forward for vaccines to be considered for use in a controlled temperature environment. This document focuses primarily on the following four vaccine types selected by the CTC-WG and endorsed by IPAC in February 2017: Human Papilloma Virus (HPV) vaccine, Oral Cholera Vaccine (OCV), Hepatitis B birth dose (HepB-BD) and Tetanus toxoid containing vaccine (TT).

IPAC noted that progress against the GVAP CTC indicator remains on track following the recent prequalification of Shanchol® OCV for use in a CTC of 40°C for up to 14 days. IPAC also heard updates on progress by other priority CTC candidate vaccines. For the HPV vaccine, Gardasil® is already licensed and prequalified for use in CTC (up to three days at 42°C) and has been piloted in Uganda, with additional guidance under development. For HepB-BD, two different manufacturers have committed to relabelling their respective HepB-BD presentations, in order to be compatible with CTC minimum criteria (tolerance up to 40°C for at least three days). One product remains in the pipeline and another has been licensed for use up to four days at 45°C, or for up to 28 days at 37°C, and is currently under review for prequalification. HepB-BD has been shortlisted by Gavi for consideration in their next Vaccine Investment Strategy (VIS). If successful, this may help to increase demand for a CTC-approved product. For TT, no product has been re-licensed under CTC to date. One manufacturer has committed to relabelling its tetanus-containing vaccines for CTC compliance, but has yet to generate the full data required for this. More advocacy and financial resources are required to achieve further progress with this vaccine, noting that potential combined delivery with HPV may provide additional incentive.

As a cornerstone to its work, the CTC-WG favours open dialogue with manufacturers and the WHO Prequalification team to accelerate progress towards approving existing and new vaccines, acknowledging the cost and time commitments this represents for manufacturers, and the importance of continuing to work for clearer forecasts of demand

[5] http://www.who.int/immunization/programmes_systems/supply_chain/ctc_strategic_roadmap_priority_vaccines.pdf?ua=1

for CTC vaccine. Despite a current gap in funding, the CTC-WG, in conjunction with the main partners (PATH, MSF, Gavi and UNICEF), will continue to support countries in the implementation of CTC and generate additional evidence to inform guidance on this approach.

Discussion:
IFPMA expressed its satisfaction with the work WHO is doing in this area for which there are clearly expressed objectives and welcomed a continuation of an open and two-way dialogue.

(b)HPV/CTC Implementation

Lessons learned from the Pilot in Uganda.
(Andrew Bakanaiga, WHO Uganda - presented for information)

In order to assess impact and optimize the implementation methodology for using the CTC approach in the provision of HPV vaccine, a pilot study was carried out by the Uganda Ministry of Health, PATH and WHO in Uganda in Q4 of 2017. The pilot was conducted mainly in two districts (plus two control districts) with the objectives to: determine optimal conditions for integrating CTC into HPV vaccine delivery so as to improve coverage and equity and alleviate burden on healthcare workers; generate information and lessons learned to shape WHO's guidance to countries on appropriate use of CTC in HPV vaccination; and evaluate how to use the CTC flexibility for HPV vaccines and generate evidence on the experience and impact of delivering HPC vaccine.

IPAC was presented with the findings from the pilot, noting that: CTC was well understood and accepted in both districts and facilitated the work of EPI staff; CTC helps overcome poor cold chain practices and insufficient capacity, especially in reducing the risk of freezing of vaccines; the success of any CTC approach depends on effective training of healthcare workers prior to introduction, appropriate forecasting of vaccine and monitoring/supervision on the job; the CTC approach appears to have a positive effect on the number of girls vaccinated per session, but additional coverage data is necessary; and that the CTC implementation effort was undermined by a significant problem of unclear HPV target population and confusion around eligibility criteria, associated with poor forecasting of vaccine quantities and inadequate microplanning.

Implementation Guidelines
Anna-Lea Kahn, WHO/IVR presented for strategic guidance

Along with facilitating licensure of vaccines for CTC and piloting CTC deployment, WHO's commitment as outlined in the CTC Strategic Roadmap is to draft guidelines for implementation in a CTC of the designated priority vaccines. The purpose of these antigen-specific guidelines is to: empower countries to decide whether CTC is the appropriate choice; enable countries to implement CTC without external technical support; and ensure CTC offers more advantages than constraints. IPAC was updated on the current draft of **the HPV/CTC guidelines' objectives,** that is**:** to define standard operating procedures (SOPs) for implementation of HPV with CTC; assist country decision-makers and healthcare workers through all phases of HPV delivery using the CTC strategy, incorporate lessons learned from Uganda pilots; be adaptable for all HPV products approved for administration in a CTC, irrespective of product brand. IPAC also reviewed the **document development process,** that is: draft guidance has been prepared following on from the pilot implementation in Uganda, has undergone internal review and is currently in the process of two rounds of external review by the CTC-WG. Once the document is finalized, it will be submitted for endorsement by IPAC.

IPAC was asked to provide input on three main points where consensus within the CTC-WG had proven difficult, comprising: firstly whether the guidelines should be

comprehensive and detailed, or streamlined standard operating procedures (SOPs); secondly guidance on what constitutes acceptable wastage levels versus programmatic gains, recognizing that more cost-effectiveness data is needed to clarify trade-offs; and thirdly whether combined vaccine delivery (e.g. HPV + TT) should be encouraged, even though it potentially undermines the benefits of CTC by having a cold chain dependent vaccine. IPAC was also asked to consider three additional issues:

- Given the experience in Uganda, should CTC be implemented only after a country has delivery experience with the given antigen, e.g. HPV, or immediately to allow CTC application in constrained areas?
- Should the application of the CTC strategy be recommended nation-wide, or only at district level? Can the strategy be adopted only by select health facilities, or would this pose too high a risk of confusion and inefficient use of resources?
- As HPV vaccine is expensive and in short supply, should any leftover vaccine that has been taken out of the traditional cold chain for a CTC excursion be used to vaccinate older girls rather than discarding?

Discussion:
There was agreement among IPAC Members that the most important documents are those that support the national or subnational health planner, and the frontline healthcare worker; these could contain links to information sources for those health professionals interested in obtaining more information on the evidence base. As national level policy makers and National Immunization Technical Advisory Groups (NITAGs) also need to understand the CTC strategy and the scientific basis for its recommendation, such information could be provided separately or in an annex. Another option would be a generic guidance document for decision-makers that applies to CTC for all vaccines, and shorter documents for vaccine-specific indications to be used by healthcare workers.

The possibility of coupling delivery of HPV vaccine with other vaccines that need cold chain was discussed and IPAC members agreed that while the benefits of combining CTC with cold chain delivery appear limited, this should be a decision taken at national level based on the immunization schedule and proposed delivery strategy.

The Committee also noted that, when assessing whether or not to introduce the CTC strategy for HPV, countries should be empowered to also decide whether or not a trial introduction of HPV prior to introducing the CTC strategy is warranted. IPAC Members suggested that if the generic programmatic shortfalls highlighted in the Uganda pilot, especially problems with forecasting the total vaccine needed and lack of clarity over the target population, are overcome, then countries should be fully able to use the CTC strategy when they first introduce HPV vaccine. Routine monitoring arrangements could be expanded to include monitoring of CTC usage issues including wastage. Likewise, it should be decided at national level whether to apply the CTC strategy to HPV vaccination nation-wide or to limit it to certain geographic areas or populations.

Although the possible benefits of re-using left-over vaccine rather than discarding it are appreciated, on balance the Committee felt that such vaccine should not be returned to the cold chain after deployment in CTC; that is: that programmes should adhere to the original definition of CTC as allowing only one excursion outside the cold chain. IPAC noted that re-use of left-over vaccine is not recommended in other campaign-based usages, and there was concern among Committee Members that recommending this practice could divert attention from important improvements in micro-planning prior to introduction to assess demand and target population.

(c) Planning for OCV/CTC Pilots in Zambia and Uganda. *(Francisco Luquero, MSF-EpiCentre, and Lorenzo Pezzoli, WHO/WHE – presented for strategic guidance)*

Oral cholera vaccine (OCV) is usually administered in response to a cholera outbreak or during a humanitarian crisis. Its use is also being promoted preventively in cholera "hot

spots", that is: in settings that predictably experience cholera epidemics on a regular basis. Piloting CTC for OCV would be better placed in these non-emergency uses rather than in a humanitarian crisis situation. Zambia, Malawi, Haiti and Uganda are examples of countries containing cholera hotspots, with plans for OCV preventive campaigns in the near future. Those with potential to inform the CTC deployment of OCV are: Zambia, which plans to vaccinate with OCV in September and October 2018 and in April and June 2019; Uganda, which plans to vaccinate with OCV in July and October 2018; and Malawi, which plans to vaccinate with OCV in July and August 2018. It is anticipated that all upcoming campaigns can generate useful information for CTC pilot planning, with a formal CTC pilot possible in early 2019.

CTC can help address some of the challenges specific to OCV campaigns, given the vaccine is relatively more complicated than other vaccines in cold chain logistics and requires a two-dose schedule. Using OCV in CTC has the potential to increase the performance of the vaccination teams, reduce the time required to vaccinate an at-risk community, increase the vaccination coverage and reduce the cost of vaccine delivery. The fact that OCV is relatively expensive and often in short supply reinforces the need for accurate micro-planning and demand estimation.

IPAC was provided with reports on the limited experience with "off-label" use of OCV out of the cold chain during distribution, and while vaccine effectiveness studies have shown good protection of OCV using this strategy, the disadvantages of off-label use, in terms of liability born by the country and the lack of controlled and validated implementation measures, reinforce the importance of pursuing CTC deployment and licensing additional OCV products for use in CTC. As noted, the Shanchol ™ vaccine is now prequalified for use in CTC, and Eubiologics is also working on obtaining CTC labelling for their OCV product Euvichol. It was noted that the maximum 14 day excursion, as in the license for Shanchol™, is not ideal when the two dose schedule calls for a two week interval, especially given the desirability of allowing the second dose to be self-administered.

Discussion:
The Committee suggested that examination of existing data, including whether interpolation is possible, may help assess the potential for additional time out of the cold chain. It was noted that an additional barrier to extending the CTC duration is the vaccine vial monitor (VVM). While the VVM 30 can be exposed to 30 days at 37^{o}C before it reaches its endpoint, if OCV is stored up to the 40^{o}C that its licensure permits, the VVM 30 may reach its endpoint as early as day 14, thus requiring the vaccine to be discarded. This may require manufacturers seeking extended CTC durations to also seek other VVM types, the market for which is limited.

IPAC noted that, given many countries have significant experience of OCV preventive campaigns using the traditional cold chain, it will be important for OCV-CTC pilots to demonstrate that CTC can improve coverage, accelerate response times, and reduce operational costs. IPAC suggested that the CTC-WG, and others, could provide input to methods for future pilots, to assist with identifying core questions that will test the feasibility, acceptability, and cost savings in the CTC approach.

(d)The Hepatitis B licensure/programmatic needs challenge. *(Nora Dellepiane, CTC-WG Chair and IPAC Member – presented for strategic guidance)*

The Global Health Sector Strategy on Viral Hepatitis for 2016–2021 has set targets for global coverage of hepatitis B vaccine birth dose (HepB-BD) of 50% by 2020 and 90% by 2030, along with other approaches to prevent mother-to-child transmission. In 2016, SAGE also reinforced their earlier recommendation for vaccination within 24 hours of birth. As of 2016, 101 countries had a policy to administer hepatitis B vaccine birth doses to all infants and another 20 countries administer the birth dose only to infants born to mothers with chronic HBV infection. Seventy-three countries (38% of the WHO Member

States) do not have a HepB-BD policy. Hepatitis B vaccine is both highly freeze sensitive and highly heat stable. As a VVM30 suggests, the vaccine can be maintained at 37°C for 30 days without a harmful reduction in potency, some countries have elected to use the vaccine out of the cold chain (OCC); however this remains an off-label usage, not supported by vaccine manufacturers' licensing, and not acceptable to many countries. The challenges to the timely provision of HepB-BD relate to reaching newborns with an equipped, trained vaccinator within 24 hours of birth; most logistically difficult for births outside of health facilities, and in settings with infrequent births where multi-dose presentations and short re-supply times are less feasible.

WHO has been promoting the use of HepB-BD in a CTC to help overcome these barriers, and in 2016 SAGE urged all vaccine manufacturers to pursue regulatory approval for CTC use of their prequalified monovalent HepB vaccine. As reported, only one has succeeded so far. A major constraint is the lack of clarity in the demand forecast for a HepB-BD in a CTC. IPAC heard that the CTC Working Group is working on draft product profile characteristics for HepB-CTC which focus on time, temperature and dose per container. One currently proposed optimal operational target is 28 days at 40°C. At present, available thermostability data for vaccines that are potential candidates for CTC do not match this aspiration; for example: one is documented as stable for four days at 45°C or for 28 days at 37°C. The absence of data on stability at 40°C, raises questions regarding the potential interpolation of temperature data which cannot yet be answered. Other options under discussion include making a special variation to the standard CTC minimum temperature, for example to 37°C. Other CTC-WG discussions have suggested preferences for single dose containers, and/or possibly single dose compact Prefilled Autodisable Devices (cPADs) that could be used by lesser trained health workers based perhaps in the community.

IPAC guidance was sought on the following aspects of use of Hepatitis B vaccine in a controlled temperature chain: the potential market and value proposition for CTC qualified vaccines; comments on the suggested key product profile characteristics for Hep B birth dose (BD) in use in CTC; and recommended next steps.

Discussion:
IPAC Members noted that the success of bringing an affordable meningitis vaccine in a CTC (MenAfriVac) to market was due to the predictability in meningitis campaigns, with a clear demand that could be signalled to manufacturers. However, service planning for vaccination bound in time to an event that is inherently unpredictable (childbirth), is very difficult, especially in the African Region where 50% of births occur in the community. Although HepB-BD administration is a target in the African Regional Strategic Plan, to date, relatively few countries have introduced it due to the challenge of having a trained healthcare worker to administer the birth dose to infants within 24 hours.

The Committee also highlighted the challenge of supply, as much of the monovalent hepatitis B antigen is used to formulate the pentavalent HepB-Hib vaccine and some bulk manufacturers are discontinuing their production of monovalent HepB vaccines. UNICEF Supply Division have issued a new tender for HepB monovalent and have agreed with the WHO Prequalification Team that they will accept new applications of this product for prequalification to encourage increased production. IPAC Members also noted that the majority of settings in the region most advanced in HepB-BD, the Western Pacific, have been able to link vaccination to scaled up facility-based childbirth, where CTC is less applicable. Given that HepB-BD usages are limited in special settings such as community-based childbirth, this may reduce the incentive for manufacturers to engage in CTC re-licensing.

IPAC noted that the CTC-WG will need to continue work to better characterize the likely demand and feasibility of HepB-BD in a CTC, recognizing that this may require tighter focus on very specific usage scenarios such as community outreach.

Session III. Optimizing vaccine supply

IPAC noted that improved global monitoring of Immunization Financing shows a clearer picture of the shortfall between what is currently being spent and what needs to be spent to achieve immunization goals. The Committee noted the progress that is needed by national governments to take up immunization financing, and the importance of communicating the risk of failure in preventive health to decision-makers. IPAC also added to the discussion of global financing, the recognition of the risks posed by polio transition to operational budgets.

IPAC Members welcome the MI4A Initiative's provision of more nuanced data in the area of supply and access which is providing vital information to countries to increase their understanding of whom they are buying vaccines from and at what price. The benefits to Middle Income Countries (MICs) in particular was applauded. The Committee noted with concern continuing national stock-outs, and stressed the importance of engaging with countries to understand better the programmatic issues, such as poor supplies management, that may exacerbate this issue. IPAC recommended collation of different country responses to vaccine shortages and providing a menu of alternatives that can be employed in the face of global shortages; such as fractional dosing, improving forecasting, and modifying immunization session sizes.

IPAC was presented with updates on the global calculation of indicative wastage rates, including a refinement to the new method for estimation of immunization session sizes, previously reviewed and endorsed by the Committee. This was welcomed, with the well-recognized caveat that some wastage is unavoidable if coverage is to improve. IPAC was also presented with an update on the major revision to the Effective Vaccine Management (EVM) assessments (EVM 2.0). The Committee acknowledged the major role that EVM assessments have played in helping countries improve their supply chain. They also commended the different perspective in the EVM analyses that could facilitate evaluation of other aspects of service delivery such as waste management. IPAC urged that among the increased number of indicators, the focus remain on those with direct relevance to informing local improvement plans, and provided additional ideas on how to ensure trends remain comparable across assessments conducted under EVM 1.0 and 2.0.

i. Global Immunization Financing update. *(Claudio Politi, WHO/EPI – presented for information)*

IPAC was presented with an update on WHO's work on the monitoring of global immunization financing. At the global and regional level, the GVAP and the Addis Declaration[6] ask countries to commit to, and increase financing for, immunization. At the country level there are four key approaches countries can take to do this: efficient use of existing resources, mobilization of additional resources over time, increasing share of domestic resources, and ensuring country driven decisions and ownership.

The status of immunization financing globally is monitored through the GVAP immunization financing indicator that measures domestic expenditure for immunization per person targeted, based on data collected in the WHO/UNICEF Joint Reporting Form (JRF). Between 2010-2016, based on data from 127 countries, this figure increased globally from US$31 to US$39.[7] In 2016, globally, governments were funding around 71% of total expenditure on routine immunization (both vaccine and operational costs)

[6] http://immunizationinafrica2016.org/ministerial-declaration-english
[7] http://www.who.int/immunization/programmes_systems/financing/en/

although LMICs funded on average 26% of their immunization programme needs through domestic sources. Moving towards financial sustainability and introducing new vaccines requires government ownership and strong political commitment.

The main challenges in immunization financing at the global level, include an unfinished agenda on securing basic immunization, limited access to affordable vaccines by Middle Income Countries (MICs), relatively high prices for new vaccine, and problems for countries transitioning out of traditional support mechanisms such as Gavi, the Global Fund and support from the Global Polio Eradication Initiative (GPEI). At the country level issues relate to: limited fiscal space (the budgetary room that allows a government to provide resources for public purposes without undermining fiscal sustainability); inadequate budget allocation for the health sector in general; and the risk of either catastrophic health spending or inability to access health care by poor populations.

To translate the financing goals articulated in the GVAP into country plans, the comprehensive Multi-Year Plan (cMYP)[8] provides countries with an analytical and budgeting tool to assist in the area of planning, budgeting, financing and sustainability which can be used at national level to plan for, advocate for and secure financing for vaccine and operational costs of immunization. The cMYP is critical for securing appropriate funding for immunization both at the country level and in discussions with donors.

Discussion:
IPAC Members also noted that a significant threat to immunization operational funding is coming from the polio transition[9] as many countries' health systems have been built or strengthened around efforts to end the disease, and with the withdrawal of donor funding, will be dependent on domestic funding. Key areas such as disease surveillance, historically funded by the GPEI, may face serious budget cuts and no longer be able to operate. Countries are developing transition plans to enumerate costs and figures for what other donors or the countries themselves need to start financing.

The Committee also noted the additional pressures on countries as they transition out of Gavi support once their Gross National Income (GNI) per capita rises above US$ 41,580, and they take on full responsibility for their vaccine costs. Gavi provides support to countries to plan for and achieve financial sustainability for vaccine and immunization costs; they urged WHO and UNICEF to continue to support countries in this endeavour.

IPAC urged those working in immunization financing to strengthen the link between the Ministries of Health and Financing so that commitments made to introduce new vaccines (a key driver of increased immunization budgets), are supported by transparent information available to all concerned. The Committee pointed out that national governments have made commitments to increase health and immunization financing through the Abuja and Addis Declarations, and noted that efforts need to be made to bring these issues to Parliamentary bodies, where funding decisions are made, and not limit advocacy efforts to the Ministries of Health.

ii. Improving Vaccine Access. *(Tania Cernuschi, WHO/EPI – presented for strategic guidance)*

The WHO 13th General Programme of Work (GPW), approved by the Seventy-first World Health Assembly (WHA), foresees achievement of Universal Health Coverage (UHC) as one of three key goals aiming at saving, making safer and improving the quality of lives. A corner stone of the UHC is access to safe, effective, quality and affordable essential

[8] http://www.who.int/immunization/programmes_systems/financing/tools/cmyp/en/
[9] http://polioeradication.org/polio-today/preparing-for-a-polio-free-world/transition-planning/

medicines and vaccines for all, without suffering the risk of financial hardship. In response, the WHA mandated WHO to design an Access Roadmap, for 2019-23, in consultation with Member States to facilitate access to medicines and vaccines.

WHO's Market Information for Access to Vaccines (MI4A) initiative aims to advance UHC through enhanced access to safe, effective, quality, and affordable vaccines for all. This responds to specific requests from Member States and SAGE to address vaccine market information gaps. MI4A focuses on vaccines that have availability constraints, affordability issues, or that are subject to important policy or vaccine pipeline changes. In particular, MI4A aims to address the needs of self-procuring countries that do not benefit from international financing or procurement support. WHO is working with stakeholders to provide guidance and strategies to enhance affordability and availability of vaccines. Country fact sheets[10] have been developed to allow countries to see self-procuring prices, other products, and options from other manufacturers. Meningitis and HPV vaccines have been chosen for study in 2018, based on the current shortages of these vaccines and the importance of vaccination with these vaccines to reach elimination goals and respond to outbreaks and emergencies.

With respect to availability of vaccines, the global immunization community is far from reaching GVAP targets for reducing the number of stock-outs at country level. Although there is great variability between countries, globally, 35% of national-level stock-outs are reported as being due to global vaccine availability issues and 36% due to funding or procurement delays. Only 6% of countries report having national level stock management issues that contribute to vaccine stock-outs.

IPAC was asked to consider how best to engage countries in these initiatives, what kind of support countries need to leverage available information and analysis (noting that resources to engage with non-Gavi MICs and HICs are extremely limited), how best to use available fora to share information, and what might be other opportunities for engagement.

Discussion:
IPAC Members congratulated the MI4A Initiative for helping to bring the data on pricing, availability and procurement of vaccines out of the realm of research and health economics and make it available to programme managers and decision makers. IPAC noted that due to limited financial resources, MICs are lagging behind both high-income countries (HICs) and LMICs in introducing new vaccines, in increasing their routine immunization coverage, and are not conducting the preventive health actions needed to secure the health of their populations. The Committee expressed its hope that the support behind the WHO/GPW 13 will bring about additional change and more interest in this area.

The Committee noted with concern continuing national stock-outs, and stressed the importance of engaging with countries to understand better the programmatic issues, such as poor supplies management, that may exacerbate this issue. IPAC recommended collation of different country responses to vaccine shortages and providing a menu of alternatives that can be employed in the face of global shortages, such as fractional dosing, improving forecasting, and modifying immunization session sizes. Improved wastage management is also a contributor, with caveats that some wastage is unavoidable if coverage is to improve.

In terms of additional resources or fora to further intelligence in this area, IPAC Members suggested that the MI4A contact the Sustainable Immunization Financing Programme at

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

the Sabin Vaccine Institute, UNITAID and other entities involved in procuring commodities for MICs, as well as the Community of Practice in Immunization Value, Costing, Financing and Economics[11] initiated by the Bill & Melinda Gates Foundation.

iii. EVM 2.0 Progress. *(Souleymane Kone, WHO/EPI – presented for information)*

Update on Global Wastage Rates:

Improving vaccine forecasting by countries results in more accurate production from manufacturers, avoids global shortages, and facilitates procurement of accurate quantities of vaccine at country level, ensuring availability of potent vaccines at the service delivery level. Correctly estimating vaccine wastage is crucial in any vaccine forecast but systems for wastage monitoring at country level are weak, and the 2002 WHO global indicative vaccine wastage rates are generic and fail to account for national and sub-national variations. In 2016 a new model was developed to estimate more accurate open vial wastage, and in 2018 this has been refined to apply to normative immunization policies, such as universal coverage targets, session frequency, number of doses in schedule and number of service points (1:10,000 population being a common WHO target). This new approach, draws on the binomial distribution of session size methodology previously reviewed and endorsed by IPAC.

Based on this updated methodology, WHO will revise the global estimated wastage rates, and in consultation with countries and Regional Offices, develop a process for tailoring wastage rates for countries. Application of the new wastage rates will be submitted for endorsement by IPAC in 2019.

Update on the Status of EVM 2.0:

IPAC received an update on the major revisions to the Effective Vaccine Management (EVM) initiative; a joint WHO and UNICEF effort to provide guidance and tools to countries to assess the performance of their supply chain.[12] The EVM Assessment evaluates each level of the supply chain, from the national store down to the health facility level. The results of the assessment provide scores by programmatic area, the analysis of which then leads to an EVM Improvement Plan to bring about improvements in the supply chain. IPAC noted that 151 assessments have now been conducted in 89 countries, but of these, only 17 countries reached the target composite score of 80%.

Version 2.0 of the EVM assessment tool is intended to be a deeper and wider assessment process that will add assessment of waste management, warehousing practices, and include a more holistic view of managerial capacity. It is expected that EVM 2.0 will be better able to establish root causes of problems to guide action plans. EVM 2.0 can be administered using a mobile device and has other features that facilitate a faster more streamlined enquiry process. A WHO core technical team constituted in February 2018 is carrying out virtual and field tests in July and August of this year. A Global Partners' Consultation will be held in September 2018 and the final version of EVM 2.0 is expected to be launched for use by countries in December 2018.

IPAC was alerted to several challenges to rolling out EVM 2.0. Firstly, while the performance measurement scores between EVM 1.0 and EVM 2.0 are largely comparable, care needs to be taken in comparing quantitative scores that may now not accurately reflect true trends in countries' performance. Secondly, more investment and commitment from partners is needed to provide and disseminate guidance materials,

[11] http://immunizationeconomics.org/
[12] http://www.who.int/immunization/programmes_systems/supply_chain/evm/en/

conduct assessments, develop and support improvement plans and build capacity in countries to carry out self-assessments.

Discussion:
The Committee noted that the revised vaccine wastage rates and accompanying tool under development by WHO to help tailor vaccine wastage rates to realities in countries reflects a different approach to service planning, useful for informing a more efficient use of resources. IPAC Members cautioned those working in this field to exercise caution and not to encourage countries to focus solely on reducing their wastage rates, at the expense of not reaching children.

IPAC Members recognized the major value of EVM assessments to date in helping countries improve their supply chain. They also commended the different perspective in the EVM analyses that could facilitate evaluation of other aspects of service delivery such as waste management. The Committee urged that among the increased number of indicators, the focus remain on those with direct relevance to informing local improvement plans. The Committee also suggested that quick qualitative assessments in different categories (e.g. very good, good, poor) may also facilitate meaningful assessment of trends, for countries comparing assessments conducted under EVM 1.0 and 2.0.

Conclusion and closing remarks by the Chair

The IPAC Chair closed the meeting by summarizing key aspects of the discussions as noted above. He expressed his thanks to all participants, especially noted the engagement of staff from the Gavi Secretariat, the contributions from vaccine manufacturers, and from USCDC and UNICEF. He also thanked the Regional partners for providing a key country perspective to these global level discussions. On behalf of the Committee, he recognized the immense amount of work undertaken by WHO's IPAC secretariat and Working Groups, and by WHO staff working on immunization in general.

WHO's 5th Product Development for Vaccines Advisory committee (PDVAC) meeting
26–28 June 2018
Executive Summary

On 26–28 June, WHO's Product Development for Vaccines Advisory Committee (PDVAC) was convened for its 5th annual meeting. Progress was discussed in vaccine and monoclonal antibody (mAb) development for the 10 previously prioritized pathogen areas and also for 3 new pathogens with candidates in, or approaching, clinical development. Several cross-cutting topics were considered and two new vaccine product development initiatives were presented. Below, is a high-level summary of the major activities and advances in the product development of vaccines and other technologies, and in new initiatives, since the June 2017 PDVAC meeting.

Vaccines against pathogens prioritised by the Global Vaccine Action Plan:

Human immunodeficiency virus (HIV): Both vaccine (ALVAC//bi-gp120/MF59 and Ad26/4 mosaic + gp140/Alum) and broadly neutralizing monoclonal antibody (BnAb) (VRC01) candidates are in proof-of-efficacy trials in adults. Data are anticipated in the 2021 and 2020 timeframe, respectively. Both the vaccine candidates listed above are based on complex heterologous prime-boost regimens. The VRC01 BnAb study will assess proof-of-concept of the passive immunization approach and determine the serum level or neutralization titer of antibody required for protection. These data will inform optimization of the approach, which will likely be a combination of multiple BnAbs administered at a frequency to be determined. The development of these promising vaccine and BnAb approaches is in the context of epidemiologic changes, increased access to treatment and availability of other HIV prevention technologies, such as pre-exposure prophylaxis. In May 2018, WHO convened HIV experts for a consultation to evaluate the routes from proof-of-efficacy to policy decision, to inform on the access to, and use for future HIV vaccines and also mAbs for prevention. The report from that meeting is in preparation.

Tuberculosis (TB): WHO Preferred Product Characteristics (PPCs) for TB vaccines have been finalized and are publicly available. Since 2017, several vaccine candidates have advanced through the pipeline, including one recombinant Bacille Calmette Guerin (BCG) candidate (VPM1002), which is moving into a phase 2/3 prevention-of-recurrence study in India. Another candidate, known as MTBVAC, a genetically attenuated *Mycobacterium tuberculosis* isolate, is progressing from phase 1 to two phase 2a studies in infants and adults, in South Africa. The candidate H4:IC31 was evaluated for prevention of infection alongside BCG in a Phase 2b study, also in South Africa. The study population was previously BCG-vaccinated adolescents who had no evidence of latent infection. Although the primary objective of the study was not met for H4:IC31, a secondary analysis showed moderate efficacy of BCG revaccination measured by sustained QuantiFERON conversion. The development of H4:IC31 will be discontinued, but are ongoing with respect to the rationale for, and issues regarding, BCG-revaccination. Other candidates such as DAR901 (an inactivated whole cell *M. obuense),* H56:IC31 (an adjuvanted multi-component protein vaccine), and the GSK M72/AS01 subunit protein candidate are also are progressing through clinical development. Results from GSK M72/AS01 proof-of-concept evaluation are expected imminently.

Malaria: Significant progress has been made in the preparation for RTS,S/AS01 Malaria Vaccine Implementation Programme in Ghana, Kenya and Malawi, with earliest introductions through the Expanded Programme on Immunization (EPI) anticipated by early 2019. These pilot programmes will collect key evidence on the safety, programmatic feasibility and vaccine impact of RTS,S for consideration by WHO's Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee that advise WHO on vaccine and malaria policy

*** denotes pathogens prioritized by PDVAC**

recommendations, respectively. In parallel, a study evaluating pre-seasonal malaria vaccination strategy with RTS,S/AS01 is ongoing in Burkina Faso, which has a high seasonal malaria transmission rate. Another clinical study is evaluating a schedule that includes the addition of a fractional dose of RTS,S/AS01 with up to three annual additional doses. This will examine both protection against uncomplicated and severe malaria and protection against infection. The study is in 5–17 month olds in Ghana and Kenya, with interim results expected in 2021. Several other next-generation candidates are in clinical development (phase 2 or beyond) including pre-erythrocytic, blood-stage and transmission-blocking approaches, and some groups are considering passive protection with mAbs.

Influenza: In light of the ever-present epidemic threat from influenza, development of a universal influenza vaccine continues to be a major research and development (R&D) focus and remains a public health priority. A recent workshop organized by the US National Institute of Allergy and Infectious Diseases defined the required characteristics of a universal influenza vaccine and resulted in the development of strategic plan to guide future investments in influenza research. New technologies (particularly structural biology, rapid isolation of human mAbs, high-throughput sequencing, protein engineering, single-cell analysis, and their derivatives) have provided new development options for influenza vaccines. Several approaches are in development, and those undergoing clinical evaluation include candidates based on the hemagglutinin (HA) stem or head-stem chimera, matrix 2 ectodomain, HA rosettes, individual full-length HA nanoparticles, and virus-like particles (VLPs). In addition to vaccines, BnAbs that have the ability to cross react with the stem region of multiple HAs are being developed; these aim to protect against future drifted and pandemic strains of influenza.

Vaccines targeted for maternal immunization: In 2017, WHO estimated that 23% of the 2.6 million deaths that occurred in the neonatal period (0–28 days) were due to infectious diseases, most of which are potentially vaccine preventable. The current EPI vaccines provide little protection to neonates and improved strategies to protect neonates are urgently needed. Through initiatives such as the Maternal Immunization and Antenatal Care Situation Analysis and Advancing Maternal Immunization projects, WHO is working to assess the challenges and opportunities to implement routine maternal immunization services within the EPI or antenatal care systems. This is for delivery of approved maternal immunization vaccines, as well as to prepare the pathway for implementation of vaccines under development, such as respiratory syncytial virus and group B streptococcus.

Respiratory syncytial virus (RSV): The RSV vaccine pipeline is robust and diverse, with 47 candidates in development, including 19 vaccine and mAbs candidates that are in clinical trials. The most advanced candidate is Novavax's sub-unit F-protein based VLP, currently undergoing a phase 3 clinical study in both the Northern and Southern hemispheres. The result of an informational assessment using threshold criteria for a commercial product was announced in December 2017 and enrolment was completed in May 2018 after recruitment of 4,600 mother–infant pairs. Results of an interim analysis of the primary endpoint readout is anticipated in Q1 2019. A 'vaccine-like', single-injection, long-acting mAb approach is also in late-stage clinical development, with data from a phase 2b study expected in late 2018. An over-arching issue for both approaches relates to defining the most appropriate implementation strategy for these interventions, considering the absence of RSV seasonality in some settings, and the need to provide sustained protection through the first six months of life when disease is most severe.

Group B Streptococcus (GBS): WHO PPCs and technical R&D roadmap are now publicly available. A key component of the technical roadmap is the establishment of a serological correlate of protection (CoP), because the low incidence of the primary endpoint of invasive disease means that phase 3 clinical efficacy trials are likely to be complex and prohibitively costly. A GBS Assay Standardisation Group has been established to standardise the methodology for both antigen-binding and functional

*** denotes pathogens prioritized by PDVAC**

assay. This work could support a regulatory pathway based on a surrogate endpoint, which could be validated clinically through post-licensure studies. Currently two candidates are in the clinic, with the most advanced in phase 2 testing. Additionally, a health economic evaluation is underway of the potential value of GBS vaccines for global use in pregnant women.

Enteric pathogens:

Enterotoxigenic E.coli (ETEC): The leading ETEC vaccine candidate has progressed to a phase 2b efficacy study in adult travellers to Benin, with proof-of-concept data expected in 2019. This candidate has also demonstrated encouraging safety and immunogenicity in an age-descending phase 2 study in Bangladesh, where the youngest cohort was aged 6–11 months. However, the most recent burden of disease (BoD) estimates suggest that ETEC mortality rates are declining, in part due to the overall reduction in diarrhea mortality, which is creating uncertainty regarding the value proposition of ETEC vaccines. Current estimates are lacking for ETEC-specific BoD data from many countries in the African, Eastern Mediterranean and South American regions, which contributes to uncertainty in mortality estimates for this enteric pathogen. In addition, ETEC morbidity remains high, with an estimated 75 million cases of diarrhea annually.

***Shigella spp.*:** The vaccine pipeline of Shigella vaccines is diverse with both oral and parenteral approaches in clinical development. The most advanced candidates aim to elicit responses to the Shigella O-antigen and have data from phase 2 controlled human infection models (CHIMs), field safety and immunogenicity clinical studies. In May 2018, WHO convened a workshop to evaluate the role of CHIMs in the pathway to licensure and policy recommendation (meeting report in preparation). Three pathways were identified, including one for a travellers' vaccine, which could be accelerated significantly by the availability of CHIM proof-of-concept data. However the pathway for policy recommendation in low- and middle-income countries (LMICs) will likely require demonstration of safety and efficacy in the target population of young children. That, said, the LMIC licensure and recommendation may be supported and potentially accelerated if there are data from an existing licensed vaccine for travellers.

Non-typhoidal Salmonella (NTS): Progress towards an NTS vaccine was presented for the first time to PDVAC, stimulated by the 2015 Institute for Health Metrics and Evaluation ~~(IHME)~~ BoD estimates, which ranked it third with respect to all age diarrheal mortality, and also the observation that 43% of its BoD occurs in under 5 year-olds. In addition to heritable risk factors, acquired risk factors for invasive NTS disease in children in Africa include HIV infection, malnutrition and malaria. Emerging antimicrobial resistance (AMR) is of increasing concern, with many antibiotics becoming less effective treatment options. There are three common serovars of invasive NTS, and a tri-valent vaccine will be needed to broadly impact bacteremia. All of the current vaccine candidates are in preclinical development; however, two are expected to enter phase 1 studies in the coming year. The commercial incentive to develop these vaccines is lacking and changes in the rates of underlying conditions that affect invasive NTS risk further increase uncertainties of disease burden; that said, combination with the licensed typhoid vaccine may strengthen the value proposition for development and use of NTS vaccines.

Second generation rotavirus vaccines: As of 2017, 92 countries have introduced oral rotavirus vaccine. Although effective in reducing hospitalization and disease severity, the residual burden of rotavirus-associated diarrhea remains high in populations in which the vaccine has been introduced. Next-generation, non-replicating parenteral vaccines are in development, and aim to achieve improved efficacy, safety (although the latter will be difficult to evaluate), lower cost of goods sold, potential for combination, and optimized scheduling compared to the current oral vaccines. The

*** denotes pathogens prioritized by PDVAC**

most advanced parenteral vaccine candidate is expected to enter a phase 2b/3 efficacy study imminently, with efficacy data expected as early as 2020.

Other PDVAC prioritized pathogens:

Group A Streptococcus (GAS): There are many types of very common and also rare acute GAS infections, and also common and rare chronic sequelae. This suggests there is a clear public health need for a preventative GAS vaccine, considering that 33 million people live with rheumatic heart disease and there are approximately 300,000 deaths per year. In April 2018, member states of the WHO unanimously adopted a "Global Resolution on Rheumatic Fever and Rheumatic Heart Disease". The value proposition for a vaccine as an intervention strategy needs to be further articulated, as evidenced by the sparse pipeline of only three early-stage candidates. A CHIM is undergoing optimization and will likely inform, and may incentivize, product development. WHO PPCs and technical R&D roadmap documents will soon be publicly available.

Herpes simplex virus (HSV): WHO PPCs for prophylactic and therapeutic HSV vaccines have been drafted and will soon be ready for public consultation. Since the 2017 PDVAC meeting, significant progress has been made towards articulating the full public health vaccine (FPHVV) of HSV vaccines, particularly with respect to improving BoD estimates. A key consideration has been the potential impact of HSV vaccines on the reduction of HIV susceptibility and transmission. Publication of the first global estimates of HSV-associated HIV infections, as well as the revised global genital ulcer disease estimates are expected in late 2018. Whilst the greatest public health need is for a prophylactic vaccine, the therapeutic candidates, which are envisaged for high income country (HIC) use, are the most advanced. The development of two of these has recently been placed on hold or discontinued.

Neisseria gonorrhoeae (GC): There are 78 million new GC infections annually, with the greatest impact on women and neonates in LMICs. AMR significantly compromises the management and control measures for GC infection and, for this reason, GC has been identified as a high priority pathogen by WHO; R&D of new antibiotics and vaccines is urgently needed. A retrospective case-control study of the use in one population of one type of meningococcal B (MenB) outer membrane vesicle vaccine (MeNZB) recently provided initial proof-of-concept for a GC vaccine by demonstrating 31% efficacy against GC in in adolescents and adults. It is hypothesized that, the vaccine induced cross-reactive antibodies to outer membrane protein and lipopolysaccharide of the MenB and GC strains. However, there remain several questions for GC vaccine development, including understanding the appropriate use and implementation strategy, and the full public health value of GC vaccines, including the identification of critical data needs.

Chikungunya virus (CHIKV): Two candidates are now in phase 2 clinical proof-of-concept field testing for this low mortality but high morbidity epidemic virus, which has an increasing geographic range. A major challenge for vaccine development is the feasibility of phase 3 vaccine efficacy studies, because outbreaks are sporadic, hard to predict and usually cease within 6–8 months or less. The Coalition for Epidemic Preparedness Innovations, with the Indian Government Department of Biotechnology, convened a workshop on CHIKV in Delhi, on February 5–6, 2018, with the objective to create opportunities for cross-sectoral and cross-geographical R&D collaborations, innovation and data sharing. Several recommendations were identified; including the development of international reference reagents, validating virological and serological assays and standardizing neutralizing antibody assay/reference serum. These–will be key to identifying a potential CoP, and efforts are already underway to to establish a WHO reference reagent. A WHO collaborative study expected to commence early in 2019.

*** denotes pathogens prioritized by PDVAC**

Cross-cutting initiatives:

ETEC etiology estimates: A meta-analysis of quantitative PCR data from five recently conducted studies to estimate the etiology-specific attributable fraction of moderate-to-severe diarrhea episodes in sub Saharan Africa and South Asia in children under 5 years was presented by the Bill and Melinda Gates Foundation (BMGF). ST is the heat-stable toxin of ETEC. The majority of these data, and the revised estimates are not yet published, but suggest that the attributable fraction and under 5 mortality due to (ST) ETEC is lower than previous BoD estimates, and that other enteric pathogens have a more significant association with growth faltering in the first two years of life. Within the broader diarrheal disease vaccine development community, there remain concerns with respect to the robustness of pathogen-burden estimates, and the lack of transparency as to how burden estimates are derived, particularly since they are used for the basis of funding prioritization.

International Vaccine Task Force (IVTF): The World Bank created the IVTF in the wake of the Ebola crisis to promote clinical research, in general, and vaccine trials, in particular, for all countries, but especially in LMICs, in the inter-epidemic periods. This is so countries will be ready to respond when needed. This well-funded initiative represents an opportunity for global collaboration to identify gaps and priority needs in clinical trial resources and capacity that could significantly benefit the development of all vaccines and interventions against priority pathogens for use in LMICs.

Antimicrobial resistance (AMR): The threat of AMR and its contribution to mortality in developing countries is important to characterize in order to quantify the potential impact of vaccines and their role as a key intervention in its reduction. Disease-targeted analyses to model and estimate the potential vaccine impact on AMR are being developed and could help better articulate the value of vaccines that are of interest to PDVAC.

Total Systems Effectiveness (TSE) and the Vaccine Innovation Prioritization Strategy (VIPS): WHO, Gavi, Unicef, PATH, The US Centre for Disease Control, the BMGF and others are working together to develop new approaches to identify and prioritise vaccines and vaccine-related innovations that meet the preferences and priorities of LMICs. The intent of these initiatives is to communicate a common strategic vision regarding preferred products and attributes to vaccine manufacturers. TSE is an approach to identify the public health value of different vaccine products from a country perspective, which is intended to rationalise global market shaping and investment for R&D of both pipeline and existing products. As such, TSE will help to inform a novel strategic framework known as the VIPS. VIPS may leverage TSE to assess and communicate priority vaccine product innovations, and to provide greater clarity to manufacturers, technology developers and partners to make investment decisions.

Vaccine delivery by microarray patch (MAP): MAPs, also referred to as microneedle patches, are a novel methodology that have the potential to transform the way that vaccines are delivered within immunization programs. If successfully developed, MAPs could overcome several programmatic challenges, including the need for a stringent cold chain up to the point of delivery, missed opportunities to vaccinate due to reluctance to 'waste' vaccine by opening a multi-dose vial and the need for safe reconstitution, handling and sharps disposal. WHO is interested to understand how MAPs can improve ease of use and increase equitable coverage of vaccines in LMIC contexts, and the need for accelerated product development of MAPs for delivery of measles and rubella (MR) vaccines has been highlighted by SAGE. To this end, WHO held a consultation in April 2018 to evaluate the technical, economic and programmatic challenges of MR-MAP product development, to establish assumptions where they are known, and to propose areas of priority focus. The report from this meeting is in progress.

*** denotes pathogens prioritized by PDVAC**

WHO Preferred Product Characteristics (PPCs) and WHO Full Public Health Value of Vaccines (FPHVV): PDVAC has made great progress developing PPCs for each of its priority pathogens. Following the 2017 PDVAC meeting, several stakeholders, including vaccine development funders, wanted to better understand the value proposition of at least some of the vaccines that PDVAC prioritizes and for which it has produced, and is producing, PPCs. PDVAC, in collaboration with WHO's Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC) is developing an approach to best estimate and describe the FPHVV. This approach considers the aspects that would need to be assessed to address both the direct benefits, demonstrated in licensing trials, and also the broader impacts and indirect benefits of the vaccine. For some pathogen targets, it can be difficult to make a strong case for vaccine development based on perhaps prevention of mortality, but a valuable vaccine for LMICs could make a huge impact on factors not usually measured in clinical trials such as morbidity, educational achievement and economic development. This concept was presented to SAGE on Immunization in April 2018. An early and improved articulation of the FPHVV, that includes participation of LMICs public and private partners, would better inform development of PPCs and FPHVVs.

PDVAC Recommendations:

Human immunodeficiency virus (HIV): Develop PPCs for both vaccines and mAb approaches, through stakeholder convening and in collaboration with partners, especially those in LMICs. As part of the ongoing consideration for policy evaluation and implementation, evaluate the acceptability and programmatic fit of vaccine and BnAb approaches within existing interventions for both adult and mother-to-child-transmission.

Tuberculosis (TB): WHO's Initiative for Vaccine Research (IVR) will continue to collaborate with the TB vaccine development community through expert working groups to define priority research avenues and favourable investments for this major public health priority.

Malaria: IVR advised to collaborate with the Global Malaria Programme to develop WHO strategy and prioritization framework for next-generation malaria vaccines, evaluate the potential role and use case (public health need) for mAb approaches in the context of RTS,S and pipeline vaccines, and develop guidance on the product development pathway for vaccines that decrease transmission, all of which should be including in an update of the Malaria Vaccine Technology Roadmap.

Influenza: WHO will continue to monitor development under the Universal Influenza Roadmap and identify gaps in product development that need to be addressed.

Respiratory syncytial virus (RSV): Develop PPCs for mAb approach, including assessment of implementation strategy and requirements for global use, in the context of a potential vaccine for maternal immunization. Collaborate with RSV Vaccine and mAb manufacturers to communicate data, analysis and evidence required to support SAGE policy recommendation.

Group B Streptococcus (GBS): Whilst planning and preparing for a phase 3 study, support initiatives aimed at evaluating and establishing of CoP that may enable an accelerated route to licensure. In parallel, the subsequent evidence that will need to be acquired through post-licensure studies to support a policy recommendation needs to be articulated.

Enterotoxigenic E.coli (ETEC): PDVAC acknowledges that one major funder has deprioritized funding for ETEC vaccine development, however ETEC remains a priority pathogen in LMICs and PDVAC will continue to advocate for, and support, the development of a vaccine. A key component

*** denotes pathogens prioritized by PDVAC**

of this effort should focus on improving the understanding and credibility of BoD estimates (see 'cross cutting issues').

***Shigella spp.*:** Shigella remains a priority pathogen for PDVAC, with the primary strategic goal being to develop safe, effective, affordable vaccines to reduce diarrhea, dysentery and morbidity caused by Shigella in children aged under five years, in LMICs. PDVAC recommended further investigation into the reported burden estimates in adolescents and adults, and this would be included in the activities proposed under the enteric burden of disease estimates (see cross-cutting issues).

Non-typhoidal Salmonella (NTS): Include NTS in the proposed evaluation of BoD estimates (see cross-cutting issues). Continue horizon scanning, and revisit when clinical data become available. Communicate the need to evaluate NTS through WHO AMR task force.

Second generation rotavirus vaccines: Leverage the TSE approach to evaluate the public health impact of potential enteric or other parental combinations that could be enabled by a successful next-generation vaccine, to help inform the prioritization of and value proposition for these candidates.

Group A Streptococcus (GAS): PDVAC commended the progress that has been made over the last year with respect to the vaccine roadmap, and in particular the product development pathway. Further investment in GAS efforts is warranted to maintain momentum. The GAS Roadmap recommendation to form a consortium of global stakeholders to advance GAS vaccine development is fully endorsed by PDVAC. CHIM development will be followed with interest to understand its potential impact in decision making and identification of correlates.

***Herpes simplex virus (HSV*):** Considering the changes in the HSV therapeutic pipeline, and progress in development of HIV vaccine and BnAb candidates, PDVAC appreciates the challenge of developing the FPHVV assessment for HSV vaccines on the basis of its potential impact on HIV transmission. PDVAC recommended evaluating the LMIC need and potential demand for both a therapeutic and prophylactic HSV vaccine that has an impact on genital ulcer disease and sexual reproductive health as the basis for its FPHVV.

Neisseria gonorrhoeae (GC): Develop a statement of interest for GC vaccines with respect to PHPVV and considerations for PPCs (not yet prioritized by PDVAC).

Chikungunya: Communicate for the need to utilize the WHO reference serum, once available, to enable comparison of neutralization assay data, which is needed to support identification of a CoP.

Cross-cutting issues:

Enteric BoD estimates: In order to increase transparency, credibility and acceptance of BoD estimates, existing guidelines for good modelling practices for decision making should be adhered to, as stipulated by International Society For Pharmacoeconomics and Outcomes Research and IVIRAC. PDVAC recommended that a joint IVIRAC/PDVAC independent working group be established to evaluate diarrheal burden models, particularly to assess the level of uncertainty of regarding ETEC mortality estimates.

Anti-microbial resistance (AMR): Vaccine impact on AMR should be considered as a key criterion in PDVAC's prioritization of pathogens. Tools to model the impact of vaccines on AMR, are needed to help define the FPHVV of these vaccines.

*** denotes pathogens prioritized by PDVAC**

Heterologous prime-boost regimens: In the context of the leading HIV and TB vaccine candidates, there is a need for development of WHO technical standards and norms guidance on heterologous prime-boost regimens to prepare for regulatory and policy evaluation.

Passive immunization: Evaluate the technical, regulatory and commercial barriers to development, licensure and availability of mAb, specifically for use in LMICs.

Total Systems Effectiveness (TSE) / Innovation Prioritization Strategy (VIPS): PDVAC recognizes the potential utility of TSE to assess and articulate the public health value of vaccines, beyond the conventional commercial return on investment. The TSE approach could represent an important mechanism to understand end user (country) product preferences, and thereby rationalize R&D priorities and investment. PDVAC is highly supportive of the VIPS initiative and four PDVAC members have been identified to participate in the VIPS technical steering committee. Early and full participation of LMICs public and private partners will facilitate the full public health value and use assessment of vaccines, novel delivery technologies and mAbs in LMICs.

Vaccine delivery by microarray patch (MAP): MAPs are perceived as potential game-changers to achieve the coverage, equity and ultimately the eradication goals of current MR immunization strategies. PDVAC supports continued efforts and activities to inform the public health value for this innovative delivery technology, particularly in the case of MR-MAP product development.

*** denotes pathogens prioritized by PDVAC**

The potential role of the Controlled Human Infection Model (CHIM) in advancing licensure and introduction of next-generation O-antigen-based vaccines against *Shigella*

Cal MacLennan (BMGF) and Birgitte Giersing (IVR WHO)
Background for PDVAC presentation at
October 2018 SAGE meeting

1

Background

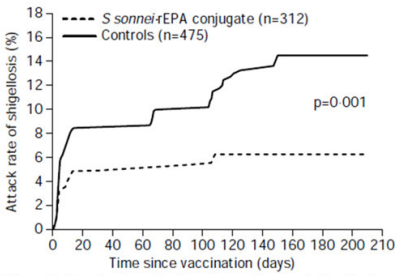


Figure 2: **Attack rates of culture-proven *S sonnei* shigellosis in recipients of *S sonnei* conjugate vaccine and controls in groups A–D**

20 years ago, a 1st generation NIH 'lattice-type' *S.* sonnei conjugate vaccine (S. sonnei-rEPA) gave 74% efficacy among Israeli military. Protection was strongly associated with the IgG antibody response to LPS O-antigen…

…but many years later, the same vaccine failed to protect children <3 years. Loss of protection closely associated with decreased induction of LPS O-antigen IgG *(Passwell JH et al Vaccine 2010)*

Hypothesis: a 2nd generation vaccine that induces higher levels of IgG to O-antigen will protect young children…

…meanwhile: the NIH team demonstrated that conjugates with shorter O-antigens and 'sun-type' configuration induce higher levels of O-antigen IgG in mice. *(Robbins JB et al PNAS 2009)*

2

Rationale for new O-antigen-based candidates

- WHO 2017: the strategic goal for Shigella vaccines for use in LMICs is to develop a safe, effective, affordable vaccine to reduce diarrhea, dysentery and morbidity caused by Shigella in children under 5 years of age
- New vaccines build on historical proof-of-concept efficacy studies with *S. sonnei*-rEPA
- Must protect the target population of young children in LMICs
- Need for multivalent vaccine for sufficient global health coverage: *Shigella sonnei,* and *Shigella flexneri* 2a, 3a and 6

3

Serum O-antigen IgG correlate of protection and threshold titer

- Evidence from historic vaccine efficacy studies and natural infection studies in the field support serum O-antigen IgG as a correlate of protection.
- Immunologic data from vaccine failures can help indicate the O-antigen IgG level where protection to infection is lost, helping establish the O-antigen IgG protective threshold.

4

New candidate *Shigella* O-antigen-based vaccines are currently in clinical development

- Limmatech (GSK) bioconjugate - *Shigella* O-antigen of wild-type length covalently coupled in sun-type format to rEPA within genetically-engineered *E. coli*
  - Monovalent *S. flexneri* 2a bioconjugate immunogenic in phase 1 US adults & protected in CHIM study
- GSK Vaccines Institute for Global Health (GVGH) outer membrane vesicle vaccine 'GMMA' (Generalized Modules for Membrane Antigens)
  - Monovalent *S. sonnei* GMMA induced less serum O-antigen IgG in phase 1 in French/UK adults compared with *S. sonnei*-rEPA in Israeli adults
- Institut Pasteur synthetic O-antigen tetanus toxoid conjugate – truncated O-antigen (15 monosaccharides). Sun-type format
  - S. flexneri 2a synthetic O-antigen conjugate induced high levels of serum O-antigen IgG in phase 1 Israeli adults

5

Shigella CHIM studies

- Established in three centres in US – currently limited to *S. sonnei* and *S. flexneri* 2a
- Performed in naive adults
- Considered a Go/No Go stage-gate in clinical development
- May enable identification of immunological correlates, surrogates and threshold levels of protection, to be validated through field efficacy studies
- Further support serum O-antigen IgG as a correlate of protection.
- Provide opportunity to link vaccine efficacy to immunological thresholds (comparators) in clinical studies.
- Potential role in vaccine regulatory approval, particularly for a travellers indication

6

Immunogenicity studies in target population

- Are candidates sufficiently immunogenic to confer protection in LMIC children?

Must evaluate immunogenicity in this target population, as soon as safety has been established in naive adults

This requires a safety and immunogenicity study in descending age groups (to <12 months) in LMICs.

7

Serum O-antigen IgG threshold

- Establishing protective threshold O-antigen serum IgG titers in the CHIM that is associated with protection in the target population would inform vaccine candidate prioritization and help accelerate clinical development pathways.
- Depends on the ability to 'bridge' immunologic responses in LMIC children to those in protected individuals from the historical efficacy studies
- Informed by CHIM, historic efficacy and field infection studies to be directly comparable
- Requires a standardized O-antigen ELISA and global reference reagents

8

Efficacy and/or immunologic data to guide serum O-antigen IgG notional surrogate threshold titers

Strain	Historical efficacy	CHIM data	Convalecent sera in LMIC U3's
Sonnei	✓	✓ (planned)	Under evaluation
Flexneri 2a		✓	Under evaluation
Flexneri 3			Under evaluation
Flexneri 6			Under evaluation

9

Strategy for progression

- O-antigen IgG notional surrogate needs to be established for S. sonnei and S. flexneri 2a components of a quadrivalent vaccine
- Aligning data from CHIM, historical efficacy studies, and convalescent serum samples from naturally-acquired shigellosis could help determine threshold titers for protection
- Use above information to leverage a large phase 2 safety and immunogenicity study in the target population as the basis of accelerated licensure
- Evidence of efficacy in LMIC children will likely be needed for policy decision to introduce into most LMIC countries
- Engagement with regulatory bodies and global health policy makers is needed to assess the acceptability of utilizing *Shigella* CHIM to accelerate vaccine licensure and introduction.

10

Policy implications for consideration

- Is there a benefit for LMICs in encouraging accelerated licensure of travellers vaccines for Shigella, based on CHIM?
- What role do CHIM studies play in policy- decision making for and access to *Shigella* vaccines in LMICs?
- What are key enabling activities that should be prioritized to advance *Shigella* vaccine development to licensure and introduction?

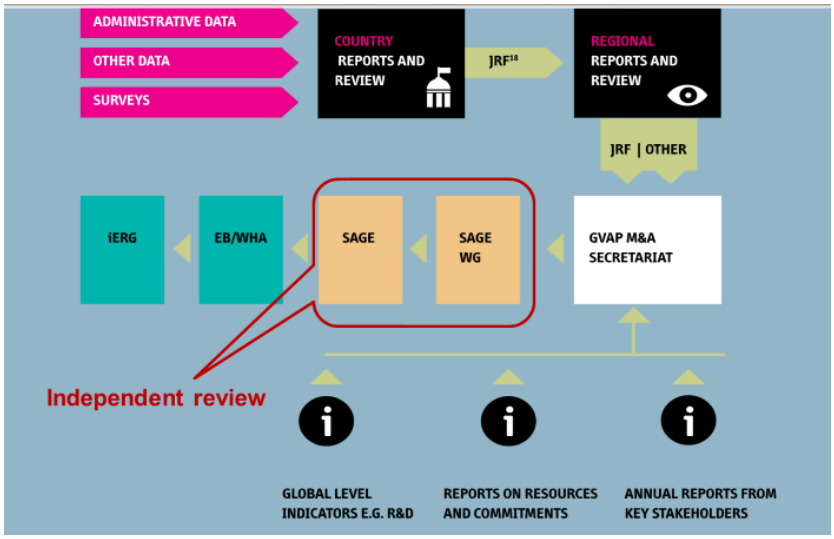
11

SAGE Oct 2018
Session 4: Global Vaccine Action Plan (GVAP) - Session 4 (14.35-17.20) 2h15 min

Session chairperson: Noni MacDonald
Session WHO technical focalpoint: Christoph Steffen

1. Background

The Global vaccine action plan was adopted by the World Health Assembly in 2012 and its monitoring and evaluation framework in 2013.



GVAP monitoring and evaluation framework

Within the monitoring framework, SAGE and the SAGE Decade of Vaccines (DoV) working group have been tasked to carry out the annual review of progress towards GVAP goals and strategic objectives. The SAGE DoV WG has been established in March 2013 and has currently 12 expert members, as well as representatives from WHO (at HQ and regional level), UNICEF, GAVI, the Bill and Melinda Gates Foundation, and the US National Institute of Allergy and Infectious Diseases as well as a Gavi Civil Society Organization (CSO) constituency representative.

2. Purpose of the session/ high-level Content summary

Agenda item 1: *Discussion of the draft SAGE GVAP progress report.* (1h25 min)
This session aims to present and discuss the draft SAGE GVAP 2018 progress report, as it has been prepared by the DOV WG. The working group has reviewed the material collected in the draft 2018 GVAP secretariat report and the regional progress reports and met at the end of August to develop the draft 2018 SAGE assessment report. The session is for discussion. The expected outcome is the revision and amendment of the report which will be finalised within a week after the SAGE session. This year's report also contains a review on the research and development indicators, which are reported on every other year.

Note: Conversely to previous years, this year's report will not be submitted to the WHO governing bodies. GVAP will be back on the agenda of EB/WHA in 2020 and 2022.

Agenda item 2: ***Presentation of high-level post 2020 global immunization perspective*** (45 min)
SAGE will also be presented with a high-level perspective on the development of a post 2020 immunization strategy and discuss the articulation with the current GVAP reporting and monitoring process.

3. Documentation list:

A. Yellowbook:

- **Executive 2018 SAGE GVAP session summary**
- ***Draft SAGE GVAP 2018 Assessment report*** (approx. 26 pages)

  This is the main document that will be discussed in the session.

B. Web:

-
- **Executive 2018 SAGE GVAP session summary**
- ***Draft 2018 GVAP secretariat report***

  This is the detailed report describing the progress on each of the goals and strategic objectives of the GVAP. It is the basis for the DOV WG to develop the SAGE assessment report.

- ***Annex to GVAP Secretariat Report 2018: 6 Regional Vaccine action plan progress reports***

  This are the detailed reports describing the progress in each WHO regions towards the goals and objectives of the respective regional vaccine action plans.

- ***National Immunization Coverage Scorecards 1998-2017***

  These are, in graphical format, the summary of vaccine coverage trends over 20 years in every country based on the data from WHO UNICEF Estimates of National Immunization Coverage (WUENIC).

IMMUNIZATION TODAY
AND IN THE NEXT DECADE

2018 ASSESSMENT REPORT OF THE GLOBAL VACCINE ACTION PLAN

STRATEGIC ADVISORY GROUP OF EXPERTS ON IMMUNIZATION

World Health Organization

Draft version – 21 September 2018

Immunization saves an estimated **2–3 million lives** every year

EXECUTIVE SUMMARY

Immunization has proven the test of time as one of public health's most cost-effective interventions. In 2017, the number of children immunized – 116.2 million – was the highest ever reported. The Region of the Americas achieved maternal and neonatal tetanus elimination, leaving only 15 countries yet to achieve elimination. Since 2010, 113 countries have introduced new vaccines, and more than 20 million additional children have been vaccinated.

Nevertheless, this year starkly illustrates **how easily hard-won gains are lost.** Because of low coverage nationally, or pockets of low coverage, multiple WHO regions have been hit with large measles and diphtheria outbreaks causing many deaths. The continued detection of circulating vaccine-derived poliovirus is further evidence that national immunization programmes are not achieving the goal of reaching every child.

To spur action, the Global Vaccine Action Plan set ambitious goals, and it remains the case that most targets will not be met by the end of the Decade of Vaccines in 2020. DTP3 and first-dose measles vaccine coverage have plateaued globally at 85%. Progress towards the eradication of wild poliovirus and the elimination of measles, rubella, and maternal and neonatal tetanus is currently too slow to be achieved by the end of the decade.

This picture provides a backdrop for discussions of the future of immunization after 2020, the final year of the Decade of Vaccines. The next decade is likely to be **volatile and uncertain.** Continuing mass urbanization and migration, population growth, geopolitical uncertainty and conflict, and natural disasters and environmental disruption will present major challenges to national immunization systems.

To meet these challenges, the immunization community must seek to **maintain its hard-won gains but also aim to do more and to do things better,** which may involve doing things differently. Equity must continue to be a strong driver, to ensure that everyone enjoys the benefits of immunization, including the most disadvantaged, marginalized and hard-to-reach populations, particularly those displaced or otherwise affected by natural disasters and conflict.

Integration will be central to achieving future goals. Partnerships have been key to the successes of the Global Vaccine Action Plan, and will be critical to the future. **Immunization is a central pillar of universal health coverage,** providing an infrastructure on which effective and equitable health systems can be constructed. Through this integration, immunization can contribute to multiple Sustainable Development Goals as well as **global health security and the battle against antimicrobial resistance.**

Countries will be at the heart of a future immunization strategy. Regions will have a key role to play in supporting the development of national immunization systems, while global immunization partners will continue working together to create an enabling environment for immunization.

As attention now turns to strengthening immunization post-2020, 2017's outbreaks are a sobering reminder that no country can take its eye off the ball: effective national immunization systems require ongoing nurturing, political commitment and public support. All countries need to see immunization systems as core to their health systems, and all citizens need to see immunization as a basic human right. In their absence, countries, regions and the world as a whole are less healthy, less safe and less prosperous. We become complacent at our own peril.

An additional
4.6 million
infants were vaccinated in 2017 compared to 2010

INTRODUCTION

The Global Vaccine Action Plan, launched in 2011, set out goals and objectives for the immunization community for the decade to 2020. Its vision was of a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases.

The Global Vaccine Action Plan, developed by the immunization community and endorsed unanimously by the global health community at the World Health Assembly (WHA), set ambitious goals and targets to catalyse a concerted global drive to minimize the burden of vaccine-preventable diseases in every country. Global immunization partners – WHO, Gavi, the Vaccine Alliance, the Bill and Melinda Gates Foundation, UNICEF and the US National Institute of Allergy and Infectious Disease – pledged to work together and with other immunization stakeholders to make this happen.

The Global Vaccine Action Plan includes five goals and six strategic objectives. A set of specific indicators and targets was developed to support monitoring and evaluation, with progress reported annually through a comprehensive Secretariat Report and this summary Assessment Report. Reporting on research and development (R&D) indicators takes place every two years, including this year.

There will never come a point at which immunization is no longer required. Every year, more than 130 million new babies are born – each equally deserving of protection against vaccine-preventable diseases. Exciting opportunities exist to extend the benefits of immunization to additional age groups, and to introduce new vaccines and vaccine delivery technologies. Hence, as the Decade of Vaccines draws to a close, a new plan is needed to guide countries and immunization partners through the next decade.

To ensure continuity, development of a new strategy needs to begin before the end of the Decade of Vaccines in 2020.

Hence, as well as reviewing progress against Global Vaccine Action Plan targets and objectives, this Assessment Report also suggests a pathway towards the development of a post-2020 strategy, building on lessons learned during the Decade of Vaccines. It also reflects on the key contextual factors and themes that will shape a successor global immunization strategy.

1. HIGHLIGHTS OF THE YEAR

- 116 million infants received the recommended three doses of DTP worldwide in 2017, the most ever
- The number of under-vaccinated children fell by over 1.8 million between 2010 and 2017
- Three additional countries achieved maternal and neonatal tetanus elimination – including Haiti, enabling the Region of the Americas to achieve elimination
- The number of functional National Immunization Technical Advisory Groups (NITAGs) has increased by 140% since 2010
- The Western Pacific Region has achieved its lowest ever incidence of measles and its first two countries were verified as having eliminated rubella
- Immunization activities in the South East Asia Region averted an estimated 622,000 measles deaths in 2017
- The African Region has seen a 130% increase in government expenditure on immunization since 2010
- In the Region of the Americas, 33 out of 49 countries have established a platform for immunization of pregnant women
- The Eastern Mediterranean Region maintained DTP3 coverage at 81%, despite eight out of 22 countries being affected by humanitarian emergencies
- Two countries in the European Region increased their measles vaccine coverage by more than 10%

But...

- 19.9 million children were under-vaccinated in 2017
- Four out of six regions experienced significant measles outbreaks
- Several countries and one region lost their measles elimination status
- Two out of six regions suffered major diphtheria outbreaks
- A major outbreak of yellow fever in Brazil has been challenging to control
- 11 countries that had previously achieved 90% DTP3 coverage failed to reach this target in 2017
- Circulating vaccine-derived poliovirus was detected in three regions
- Only seven countries reported no vaccine hesitancy in 2017

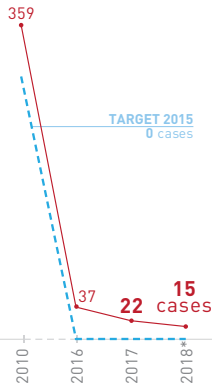
UNICEF procured over
2.4 billion
doses of vaccines for 100 countries in 2017

2. KEY INDICATORS

The following graphics summarize the current status of key coverage and other indicators in 2017.

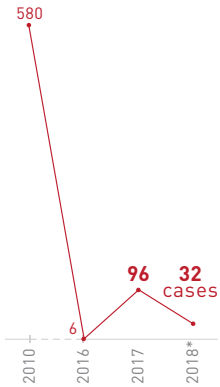
WILD POLIOVIRUS AND CIRCULATING VACCINE-DERIVED POLIOVIRUS CONTINUE TO BE DETECTED

Number of new wild poliovirus infections



*4 September 2018

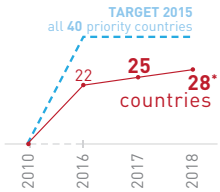
Number of new cases of circulating vaccine-derived poliovirus



*4 September 2018

THREE ADDITIONAL COUNTRIES ACHIEVED MATERNAL AND NEONATAL TETANUS ELIMINATION IN 2017 BUT GLOBAL ELIMINATION BY 2020 IS UNLIKELY

Number of priority countries verified for maternal and neonatal tetanus elimination

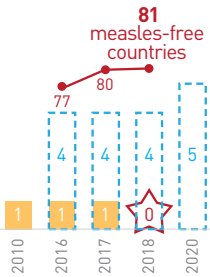


*Anticipated

MEASLES OUTBREAKS IN 2017 LED THE REGION OF THE AMERICAS TO LOSE ITS MEASLES ELIMINATION STATUS IN 2018

Number of regions and countries achieving elimination

MEASLES

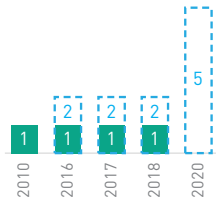


TARGET 2020
Five WHO regions

2018
Measles is again endemic in all regions

Number of regions achieving elimination

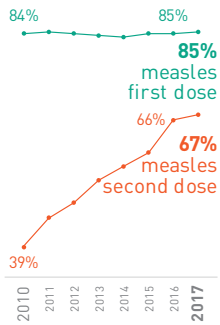
RUBELLA



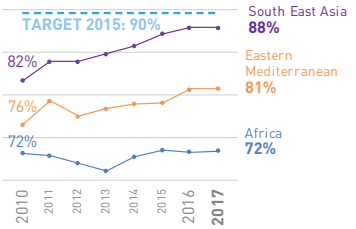
TARGET 2020
Five WHO regions

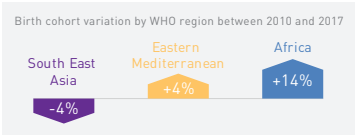
2018
Only one region rubella-free

GLOBAL COVERAGE OF FIRST-DOSE MEASLES VACCINE HAS PLATEAUED BUT SECOND-DOSE COVERAGE HAS INCREASED SIGNIFICANTLY

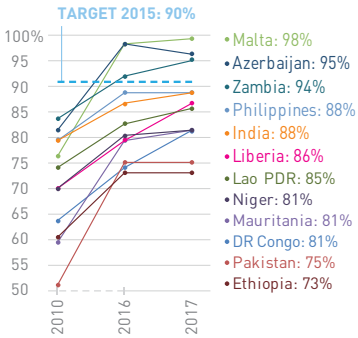


DTP3 COVERAGE HAS INCREASED SIGNIFICANTLY IN THE EASTERN MEDITERRANEAN AND SOUTH-EAST ASIA REGIONS AND BEEN MAINTAINED IN THE AFRICAN REGION DESPITE A BIG INCREASE IN ITS BIRTH COHORT





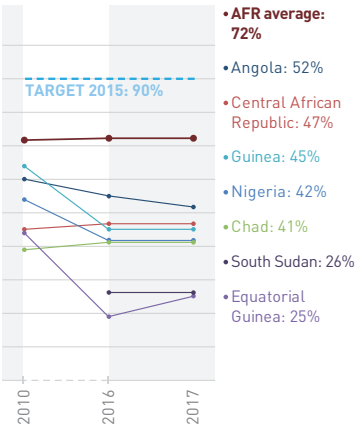
COUNTRIES ACHIEVING THE GREATEST INCREASES IN DTP3 COVERAGE 2010–17



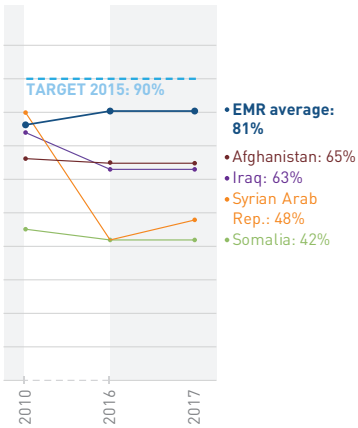
Excluding countries with a population less than one million.

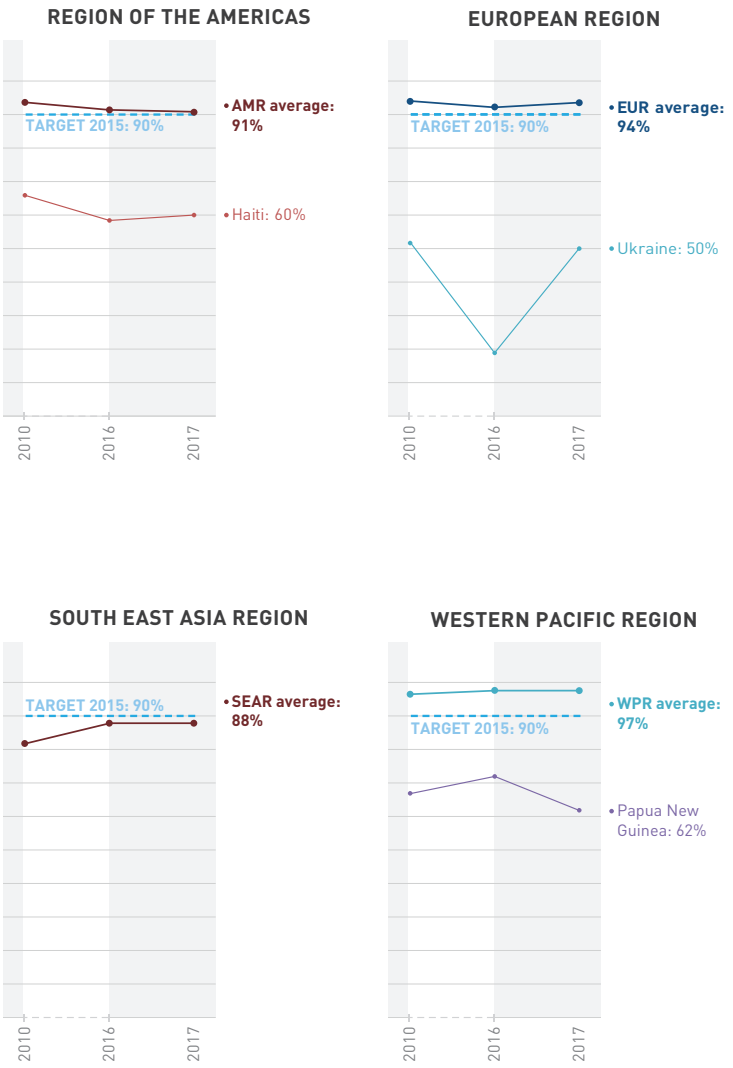
COUNTRIES SHOWING THE MOST MARKED DEVIATION FROM REGIONAL DTP3 COVERAGE

AFRICAN REGION



EASTERN MEDITERRANEAN REGION

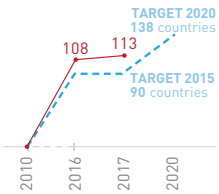




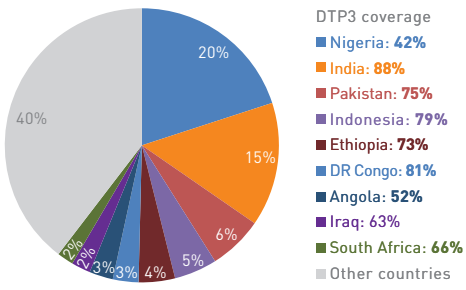
Note: only countries with DTP3 coverage below 65% have been represented.

NEW VACCINE INTRODUCTIONS REMAIN ON TRACK BUT AT RISK OF STALLING

Number of low- and middle-income countries that have introduced at least one new or underutilized vaccine since 2010



COUNTRIES IN WHICH THE 20 MILLION UNDER-VACCINATED CHILDREN LIVE AND THEIR RESPECTIVE DTP3 COVERAGE RATES



3. FRAGILE GAINS

A surge in outbreaks during 2017 is a timely reminder that hard-won gains are easily lost, even in countries with well-established health systems. Without constant attention, national immunization systems can easily deteriorate, particularly when faced with political and economic upheaval.

Outbreaks: Measles elimination took a step back in 2017. Although the incidence of measles has more than halved since 2010, it increased in 2017 from 19 to 25 cases per million, with increases seen in four out of six WHO regions. Significant outbreaks occurred across the globe, and a major outbreak in Venezuela, also affecting other countries in the Region of the Americas, led to the re-establishment of endemic measles transmission in Venezuela (but not so far in other countries in the region).

Outbreaks in North America and in Europe emphasize that measles can easily spread even in countries with mature health systems. Due to ongoing outbreaks, measles is again considered endemic in Germany and Russia. Measles outbreaks have been seen in countries reporting good national vaccine coverage, evidence of immunization gaps and highlighting the need to ensure high sub-national coverage, particularly among vulnerable populations.

There are also concerns about the widespread use and quality of supplementary immunization activities (SIAs). While nearly 200 million children were reached through SIAs in 2017, in less than half were coverage rates in excess of 95% achieved. Although they can be an important way of immunizing remote populations and rapidly addressing coverage gaps, SIAs are costly and labour-intensive; strengthening routine immunization systems would reduce the need for SIAs, as well as the costs associated with treatment of measles and resulting lost productivity – the cost of dealing with an outbreak can be 20 times the cost of the vaccinations that could have prevented it.

More positively, global coverage of a second dose of measles-containing vaccine (MCV2) increased to 67% in 2017 and 86% of countries have introduced MCV2 into their national immunization programmes. However, coverage rates globally remain inadequate to effectively control measles.

In 2017 and 2018, measles outbreaks have occurred in the Region of the Americas, the Eastern Mediterranean, the European and the South East Asia Regions

Between 2000 and 2016, measles vaccination prevented an estimated

20.4 million deaths

Although four additional countries were verified as having eliminated rubella, and global coverage for rubella-containing vaccine exceeded 50% for the first time in 2017, coverage varies markedly between regions and 24 countries have still to introduce a rubella vaccine into their national immunization programmes.

Polio: Although the number of cases of wild poliovirus declined in 2017, polio eradication remains highly challenging. Intensive and innovative activities have been undertaken to immunize remote populations in northern Nigeria and surrounding areas; no new wild poliovirus cases were detected in the African Region in 2017 but surveillance gaps remain a concern. Data from the first half of 2018 point to the persistence of wild poliovirus circulation in the other endemic area, spanning Afghanistan and Pakistan.

Equally concerning is the continuing detection of circulating vaccine-derived poliovirus in 2017 and 2018, in the Democratic Republic of the Congo, Nigeria, the Syrian Arab Republic, Somalia and Papua New Guinea. This highlights worrying inadequacies in national immunization systems that leave countries at risk of importation and the emergence of circulating vaccine-derived poliovirus, and ill-equipped to monitor and maintain polio-free status in the future.

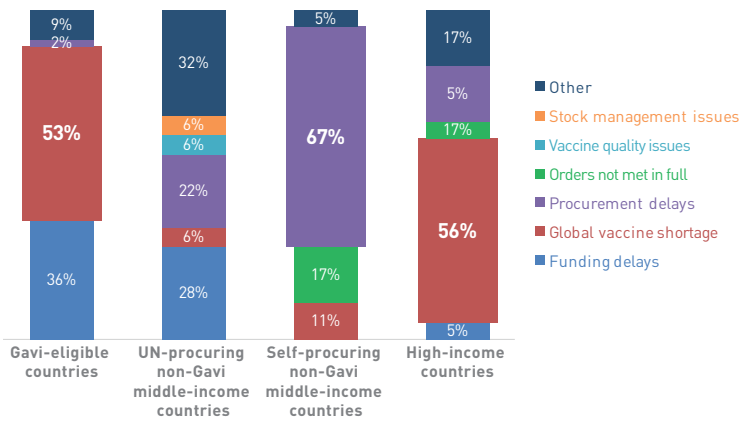
The extension plan for the Global Polio Eradication Initiative is a welcome development – polio eradication must be completed. The potential for the extension plan to deliver synergistic benefits should be energetically explored – as well as securing and sustaining polio eradication, the plan should provide important opportunities to strengthen national immunization systems, including surveillance.

The WHA recommendation that polio transitions should go in tandem with eradication is also timely. Uncertainties in polio transition planning, and the potential impact of polio transitions on national immunization systems, including surveillance infrastructures, are a significant concern. There is an urgent need to finalize and implement national polio transition plans, ensuring that rigorous investment cases are developed that, in addition to securing and maintaining poliovirus eradication, also strengthen national immunization systems.

Vaccine supply: Fewer countries experienced stockouts in 2017 (70) than in 2016 (73), but numbers remain well above the 2020 target (25). The causes of stockouts remain diverse. High-income and Gavi-eligible countries were particularly affected by global vaccine supply issues, while procurement delays were significant in middle-income countries. Gavi-eligible and UN-procuring countries were also affected by funding delays. Some 69 countries were affected by sub-national stockouts, which in 78% of cases led to an interruption of immunization services.

The proportion of vaccine doses of assured quality has risen from 72% in 2010 to
96% in 2017

CAUSES OF STOCKOUTS VARY
BETWEEN DIFFERENT CATEGORIES OF COUNTRY



These data point to the need to understand the origins of funding and procurement delays, as well as to strengthen forecasting, procurement practices, budgetary management and stock management within national immunization systems. Global vaccine shortages remain a concern; as well as contributing to gaps in coverage, they have the potential to undermine trust in immunization programmes. They are being addressed through initiatives such as the **Market Information for Access to Vaccines (MI4A),** one aim of which is to provide more clarity on global supply and demand to ensure vaccine availability. There are also encouraging signs of growing vaccine manufacturing capacity in low- and middle-income countries, underpinned by strong political support in many such countries.

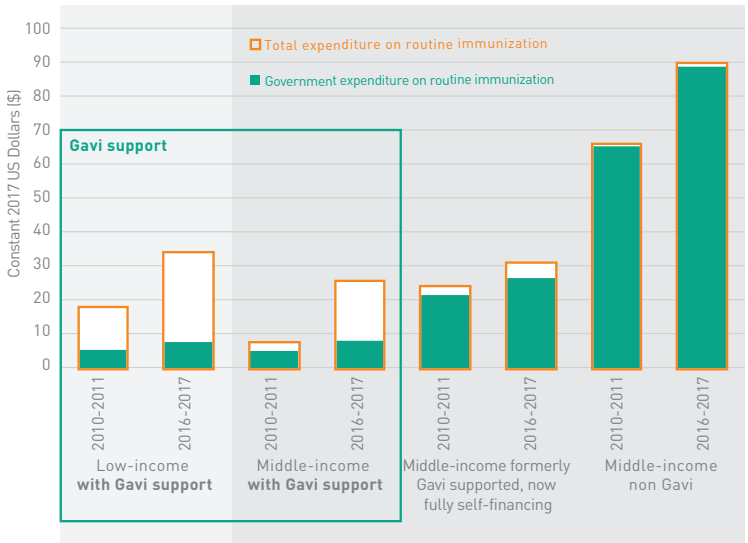
National ownership and political commitment: Achieving high coverage is fundamentally dependent on the effectiveness of people-centred national immunization systems. While national wealth inevitably has some influence on population access to immunization services, it is far from the only factor. Countries are making political decisions on resource allocation. Significant variation is seen in national commitments to immunization systems, and in immunization system performance as a function of national wealth. Countries such as Bangladesh, Cuba, Burundi, Eritrea and Rwanda show excellent coverage despite limited resources.

Currently, no global target exists for measles or rubella elimination at a national level. Despite this, several countries have made strong national commitments to strengthen their measles and rubella immunization programmes. Opportunities exist for other countries to follow their example and develop a similar national commitment to enhance MCV1, MCV2, rubella, poliovirus and other vaccination.

Globally, expenditure on national immunization systems has been growing, but this masks significant regional and national variation. Expenditure growth has exceeded 60% between 2010 and 2017 in the Western Pacific, African and South-East Asia Regions but has been lower elsewhere. Among Gavi-eligible countries, donor funding contributed significantly to increased expenditure, although government contributions also increased – by 130% in the African Region. The typically high cost of new vaccines means that self-sufficiency and introductions are hard to achieve simultaneously. Hence, although absolute government expenditure has grown, as a proportion of total expenditure it has fallen from 78% to 57%.

TOTAL EXPENDITURE ON IMMUNIZATION AND SOURCES OF EXPENDITURE VARY SIGNIFICANTLY BETWEEN DIFFERENT CATEGORIES OF COUNTRY

Annual expenditure on routine immunization per live birth



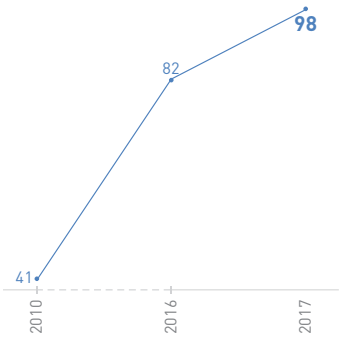
The MI4A/V3P database now includes vaccine price data for 84% of the world's countries and 95% of the world's birth cohort

57 additional
countries have established functional NITAGs since 2010

It is now widely recognized that enhanced access to immunization in countries is only partly dependent on financial support for vaccine procurement. Countries also need technical assistance to develop their national immunizations systems, based on a full system-wide assessment spanning issues such as procurement and financial management, demand and hesitancy, and the logistics of vaccine delivery and administration to recipients. Global immunization partners and regions are playing a key role in needs analyses and in the provision of peer support, while Gavi has also increased its emphasis on technical assistance. However, middle-income countries remain less able to benefit from technical support (see below).

Ultimately, the development of effective national immunization systems depends on high levels of political commitment. It is important that this commitment is not merely symbolic, but translates into concrete strategies and action plans. It is equally importantly to guard against complacency – high coverage is a goal that must be achieved each and every year.

THE NUMBER OF COUNTRIES WITH FUNCTIONING NITAGS INCREASED BY 20% IN 2017



TARGET 2020
All 194 countries have a functional NITAG

Central to country ownership are functioning **National Immunization Technical Advisory Groups (NITAGs),** which showed further encouraging growth in 2017. NITAGs are a national asset: they act both as a technical resource and as an independent advisory body enabling national authorities and policymakers to make evidence-based decisions. A total of 134 countries now report the existence of a NITAG and 98 report a NITAG meeting six functionality process criteria – a 20% increase over 2016. The development of NITAGs is being supported by Regional Immunization Technical Advisory Groups (RITAGs) and a Global NITAG Network, which held its inaugural meeting in 2017.

Sub-regional NITAGs, as established in the Caribbean, may be an answer to the difficulties experienced by small countries which are unlikely to have sufficient technical capacity for individual national groups. There is also a need to move beyond process indicators to assess the effectiveness of NITAGs and their contribution to national policymaking and practice.

Demand and hesitancy: Immunization programmes need to be designed so that individuals and communities understand the value of vaccines and demand immunization. Stimulating demand – the active seeking of services – requires attention to multiple issues, including community engagement, service quality and accountability, and responses to adverse events or other challenges. Engaging with civil society will help to generate a positive environment for immunization, while framing immunization as a basic human right and central to the development agenda can be an important driver of political accountability.

A wide range of stakeholders – communities, frontline health workers, Civil Society Organizations (CSOs) and 'immunization champions' – have important roles to play in fostering demand. Ensuring the quality of service delivery is essential – parents' experience at clinics and their interactions with health workers can significantly influence their future vaccination choices.

Working to stimulate demand will also help to prevent hesitancy. Since 2014, the number of countries reporting data on hesitancy has steadily increased, reaching 83% in 2017, while the number of countries undertaking an assessment of hesitancy has risen to 37%. Only seven countries reported a complete absence of hesitancy, evidence that the issue has become a truly global challenge.

Hesitancy linked to lack of awareness/knowledge continues to decline, and risk/benefit concerns remain the most often-cited reason for hesitancy (but represent less than 30% of the total responses, illustrating the wide diversity of issues underlying hesitancy). Of particular concern is the increasing politicization of immunization. Immunization has been exploited to mobilize political support, while in some cases vaccine refusal is being driven by extreme political agendas that prevent populations from being immunized. In addition, social media accounts have been used to provoke debate about immunization safety to undermine trust in national authorities.

New ways of analysing country responses are now needed to provide a clearer picture of demand and hesitancy issues at a national level, recognizing that the latter covers a spectrum of attitudes from outright rejection to passive acceptance, and is subject to multiple influences from groups with widely differing agendas. Further work is required to understand hesitancy issues at national and sub-national levels (many hesitancy issues are highly context-specific). Deeper insights into the factors influencing immunization decision-making should underpin the development of tailored strategies to promote local demand for immunization services and to address specific hesitancy issues. The European Region, for example, is capturing learning on national strategies to address hesitancy and demand-related challenges which may hold lessons for other regions.

To meet the need for more evidence on the factors affecting uptake and demand for immunization services, UNICEF is working with WHO, the US Centers for Disease Control and Prevention, and the Bill and Melinda Gates Foundation to establish a Hub for Vaccination Acceptance and Demand. The Hub will harness the expertise and resources of a wide range of immunization stakeholders, building a global resource for addressing demand-related challenges and coordinating technical support to countries.

By the end of 2017, Gavi had enabled
58 countries
to introduce pneumococcal vaccine, which has saved the lives of more than
500,000 children
in poor countries

4. EQUITY

A core principle of immunization is that everybody has an equal right to immunization services, no matter who they are or where they are from. Despite some progress, this goal is far from being achieved.

A Strategic Objective of the Global Vaccine Action Plan was that the benefits of immunization should be equitably extended to all people. Equity was broadly conceived to encompass access irrespective of geographic location, age, gender, disability, educational level, socioeconomic level, ethnic group or work condition.

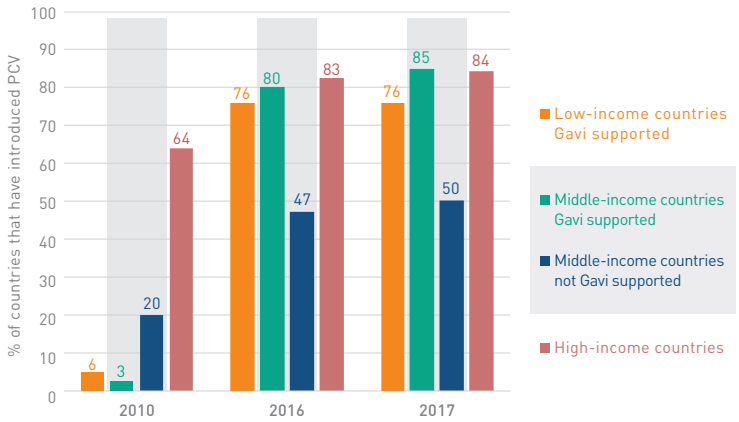
International inequalities: Vaccine coverage rates continue to vary substantially between countries and regions. Six countries achieved 90% DTP3 coverage for the first time in 2017, but 11 that had hit this target in 2016 fell below it in 2017. Eight countries had DTP3 coverage of less than 50% in 2017. As a result, nearly 20 million children were under-vaccinated in 2017.

As well as factors such as conflict, national wealth inevitably influences immunization system performance, as judged by vaccine coverage. However, the correlation is far from absolute – many low- and middle-income countries achieve unexpectedly high coverage given their economic status and a number of higher-income countries are under-performing. While the support of partners such as Gavi has obviously had a major impact, the 'over-performing' countries clearly indicate that low coverage is not inevitable. Furthermore, the recent gains achieved by countries such as Costa Rica, India, Kazakhstan and Zambia illustrate that innovative actions, driven by high-level political commitment, can have a major impact on coverage.

Support from Gavi has had an enormous impact in enabling many low- and middle-income countries to introduce new vaccines. However, there are widespread concerns that **middle-income countries** ineligible for Gavi support are not making anticipated immunization gains.

Middle-income countries account for almost three-quarters of the world's poorest people and have a birth cohort three times the size of that of low-income countries. Non-Gavi middle-income countries are diverse, and many face complex immunization challenges. These countries, which are almost entirely self-financing, do not benefit from Gavi preferential pricing, nor are they eligible for Gavi-financed technical support. Even with expanding immunization budgets, non-Gavi middle-income programmes are showing strain, as can be seen in the slow pace of adoption of vaccines such as pneumococcal conjugate vaccine (PCV). This is a situation of concern today, but also highlights future risks to sustainability for Gavi-transitioning and fully financing countries that have yet to contend with non-preferential pricing.

MIDDLE-INCOME COUNTRIES THAT ARE NOT GAVI-SUPPORTED LAG BEHIND IN PCV INTRODUCTION



There is also a growing realisation that economic constraints are only one obstacle to the availability of vaccines in middle-income countries (and low-income countries). Often, technical assistance to build effective, robust and sustainable national immunization programmes is of at least equal importance. This points towards models in which international support is based on national capacities and development needs rather than just income levels.

Reflecting this perspective, the African Region has developed a categorization system based on the capacity or maturity status of immunization programmes within its countries. This has been used to develop a 'maturity grid' in which countries are placed in one of four tiers according to the maturity of their immunization programmes. This categorization is being used to shape tailored programmes of support for countries as well as a long-term plan to develop countries' immunization capacities in a stepwise fashion. Other agencies have developed similar categorization criteria to ensure more targeted support for countries.

Within-country inequalities: No new data are available on sub-national differences in coverage associated with socioeconomic status. This remains an important gap to be addressed. The number of countries achieving 80% DTP3 coverage across all districts remained unchanged at 39 (20%).However, 74 countries (38%) do not report data of high enough quality for sub-national comparisons to be made. More granular data collection is essential if sub-national variations in coverage and coverage gaps are to be addressed.

A recent analysis of childhood immunization coverage in 10 Gavi priority countries identified several factors associated with inequalities in coverage. These included mother's education level, mother's age at birth and birth order, but not sex of child. Household economic status had a significant impact on likelihood of immunization. Although urban–rural divides in coverage were seen, these appeared to reflect the impact of poverty.

The majority of vaccine-preventable deaths globally now occur in middle-income countries

In Nigeria, children of older, well-educated, well-off mothers in the south were

300 times more likely to be vaccinated

than children with teenage, uneducated, poor mothers in the north-west

Socioeconomic inequalities tended to be highest in countries with lowest national coverage (although Chad has both low national coverage and low variation in coverage, while Tanzania has both relatively high coverage and low variation). In countries with higher coverage, urban-rural inequalities were typically lower, and inequalities instead tended to reflect exclusion of marginal populations. Some countries report district-level or even lower-level data, providing a more granular view of inequalities to guide corrective actions.

A growing set of toolkits are available to increase coverage in underserved populations and pockets of unvaccinated children in remote districts. In addition, UNICEF and the Bill and Melinda Gates Foundation have established a high-level **Equity Reference Group (ERG),** which will review innovative ideas, new approaches and best practices, and make recommendations for guidance, policies and programming to reduce inequities.

The ERG, which includes global experts from within and outside the immunization community, has identified three priority populations – the urban poor, children affected by conflict and insecurity, and children living in remote rural areas. Nevertheless, further efforts may be required to cope with the profound challenges presented by mobile populations, including economic migration, urbanization, and displacement by conflict or natural disasters.

CSOs have a potentially critical role to play in expanding access. As well as contributing to the delivery of immunization services, enhancing access to communities in volatile sociopolitical situations and among hard-to-reach communities, they can also play key advocacy roles locally and nationally, and hold governments and delivery partners accountable.

Maternal and neonatal tetanus: Immunization against maternal and neonatal tetanus, targeted for elimination by 2020, is often used as a measure of equitable access, as the infection disproportionately affects the most disadvantaged. By the end of 2017, 25 out of 40 priority countries had achieved maternal and neonatal tetanus elimination. In 2017, three additional countries (Ethiopia, Haiti and Philippines) achieved elimination, while two countries, Kenya and Chad, completed activities to prepare for validation in 2018.

An investment case has been completed for the remaining priority countries and will be used to mobilize resources for the completion of global maternal and neonatal tetanus elimination. The estimated cost is US$200m. A business case for use of compact pre-filled auto-disable (Uniject) devices to reach remote populations was not approved by the Gavi Alliance Policy and Programme Committee, following an unfavourable analysis of its likely cost-effectiveness. Alternative strategies will need to be developed to reach currently excluded populations, especially in remote rural settings.

Countries yet to achieve elimination include many affected by conflict, major disease outbreaks or environmental challenges. There is a realistic prospect that nine countries (Angola, Chad, Democratic Republic of the Congo, Kenya, Mali, Papua New Guinea, Guinea, South Sudan and Sudan) will achieve elimination by 2020, with firm political commitments and partner support. Achieving elimination on schedule in the remaining countries, Afghanistan, Central African Republic, Somalia, Nigeria, Pakistan and Yemen, appears unlikely without a significant change in the speed of progress.

Since 2014, an additional
10 countries
have eliminated maternal and neonatal tetanus, averting an estimated
81,000 newborn deaths

13 million children
are under-vaccinated as a result of conflict

On average,
44,500 people
were forced to abandon their homes every day in 2017

5. HUMANITARIAN EMERGENCIES

In a volatile and uncertain world, geopolitical instability and natural disasters can devastate health systems, undermine the performance of national immunization systems, and generate substantial numbers of displaced people. Special mechanisms are needed to deal with the exceptional circumstances generated by humanitarian crises.

In 2017, conflict continued to affect multiple global regions. Civil strife can severely undermine public health infrastructure, including immunization services, while mass displacement of people creates challenges for neighbouring countries as well as internally. The UN estimates that more than half the population of Syria has been displaced, at least 6 million internally and 5 million externally. Lebanon hosts 2.2 million Syrian refugees (who now account for one fifth of its total population) and Jordan more than 1.2 million. Globally, the UN estimates that 68.5 million people have been forced to flee their homes due to war, violence and persecution in 2017 – nearly 1% of the total global population.

Within the **Eastern Mediterranean Region,** 30 million people were displaced during 2017. An estimated 60% of hospitals in Syria have been closed, destroyed or rendered only partly functional; 50% of hospitals in Yemen are non-functional. Around 60% of health workers in Syria have either left the country or beenkilled. Under these circumstances, dedicated healthcare staff and international aid agencies have had remarkable success in maintaining coverage levels in Syria and Yemen. DTP3 coverage rose in Syria by 6% to 48% and dropped only slightly in Yemen to 68% (although there are some questions about the reliability of data collected under such difficult circumstances).

Around a million displaced **Rohingya** from Myanmar – more than half of them children – presented a major challenge to the Bangladesh public health system. International partners have worked with the Government of Bangladesh and national agencies to immunize refugees and prevent infectious diseases, with remarkable success – 4.5 million vaccine doses have been delivered to displaced Rohingya. Despite challenging conditions, outbreaks have been restricted to diphtheria, triggering a further mass vaccination campaign against diphtheria.

In the Region of the Americas, a deteriorating socioeconomic situation in **Venezuela** has had a significant impact on its health infrastructure, including its immunization services.The resulting measles and diphtheria outbreaks have also spread to other countries in the region. Having been free of diphtheria for 24 years, Venezuela has now experienced more than 1600 suspected cases between 2016 and the middle of 2018. The resurgence of measles has also led the region to lose its measles elimination status, just two years after it was secured in 2016.

Humanitarian relief operations have provided emergency immunization supplies among displaced populations, with an increasing emphasis on delivery of multiple vaccines (and additional interventions) to maximize every opportunity to reach displaced individuals. In 2017, the WHO published **Vaccination in Humanitarian Emergencies: Implementation Guide** to provide practical guidance and advice to immunization task forces. The new guide complements an updated version of Vaccination in Acute Humanitarian Emergencies: A Framework for Decision Making. The year also saw Gavi announce a **fragility, emergencies and refugees policy,** to enable it to respond more flexibly to challenging national circumstances.

Over the longer term, there is a need for a coherent and comprehensive global policy on protracted humanitarian crisis situations that also takes into account the challenges faced by countries hosting large numbers of displaced people and the need to track the immunization status of individuals as they move between and within countries. Delivery of immunization services to vulnerable groups is likely to depend on use of a variety of different models, tailored to local circumstances.

A further challenge will be maintaining public health function in emergency outbreak situations. As well as its severe direct impact, the 2014–16 Ebola outbreak also had a major impact on wider public health in affected countries. One consequence was a significant reduction in childhood immunization, potentially leading to as many vaccine-preventable deaths as caused by Ebola directly. Disrupted immunization programmes also provide opportunities for the emergence and spread of vaccine-derived poliovirus, as occurred in Guinea in 2014–15.

An estimated
258 million
people are living in a country other than their country of birth

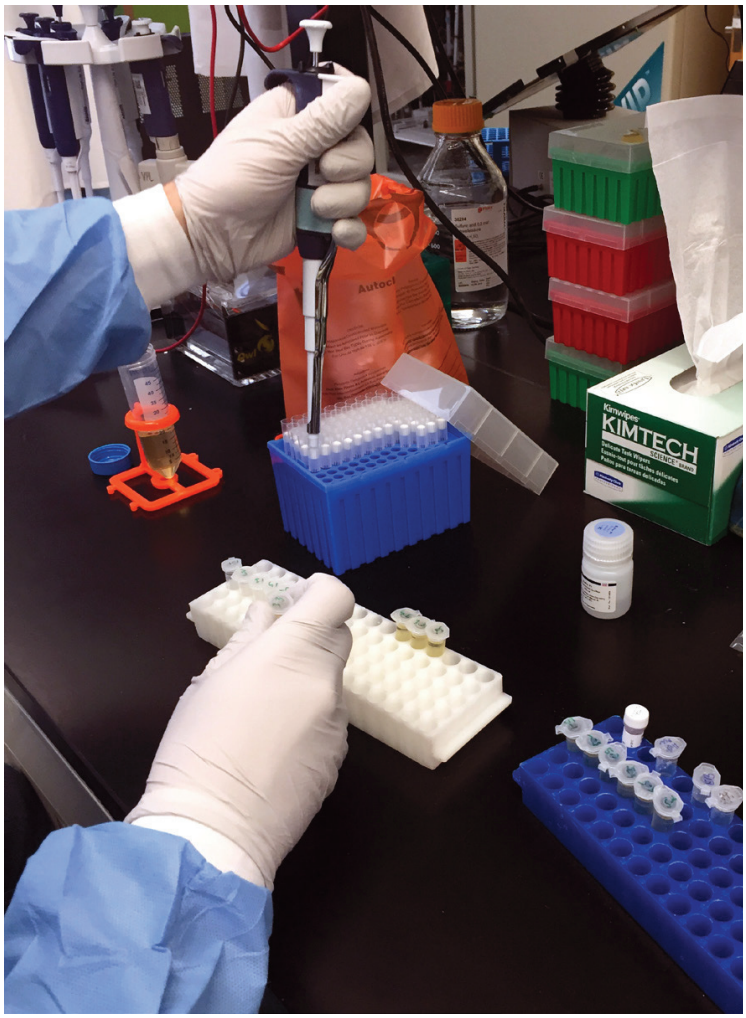
An estimated
445,000 people
died of malaria in 2016

Three African countries have begun pilot implementation studies of the RTS,S/AS01 malaria vaccine

In 2017, 1.8 million people became newly infected and 940 000 people died from HIV-related causes globally

6. RESEARCH AND DEVELOPMENT

Progress is being made in the development of new vaccines against infectious disease threats such as malaria, HIV/AIDS and tuberculosis (TB). Research also has the potential to play a much bigger role in the identification, development and evaluation of innovations to enhance access to and acceptability of vaccines and immunization services.



One of the five goals of the Global Vaccine Action Plan is to develop and introduce new and improved vaccines and technologies. The R&D focus is on potentially vaccine-preventable diseases responsible for a high global burden of disease, including malaria, HIV/AIDS, TB and seven other priority infections, and new technologies to facilitate vaccine delivery or wider use of vaccination.

The most advanced **malaria vaccine,** RTS,S/AS01 (Mosquirix®), has achieved a positive scientific opinion from the European Medicines Agency and is undergoing pilot implementation studies in three African countries. There are some concerns about its efficacy and safety, and further studies may be required to evaluate alternative dosing regimens and schedules. Encouragingly, multiple other vaccine candidates are at various stages of clinical evaluation, targeting different points in the malaria parasite life cycle.

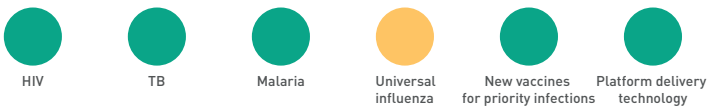
Vaccine development for HIV remains an immense technological challenge, not least because of its great variability and mutability. However, the field has taken heart from the RV144 trial in HIV, the first to demonstrate protective efficacy, albeit modest. The laboratory identification of broadly neutralizing antibodies – recognizing multiples strains of HIV – has provided further impetus. As well as enabling studies that are informative for vaccine design, broadly neutralizing antibodies could be manufactured and used directly in prevention. The HIV vaccine pipeline includes multiple candidate vaccines undergoing clinical and pre-clinical evaluation.

Although a vaccine for **TB,** BCG, already exists, the current forms offer incomplete protection and have several drawbacks. Different vaccines may also be required to achieve different objectives in TB, such as prevention of initial infection or prevention of activation of latent TB. A wide range of candidate vaccines are progressing through clinical evaluation, with several showing positive results in early phase clinical trials.

Progress towards a **universal flu vaccine** has been more challenging, although a variety of vaccine candidates are in early stages of clinical evaluation. One complication relates to the definition of 'universal' – sometimes used to refer to vaccines against just influenza A strains, against influenza A and B strains, or against these and 'exotic' strains acquired from other species.

Vaccine development efforts for these diseases face multiple challenges. Although new field-deployable vaccines are still some way off, progress has been highly encouraging and there are realistic prospects that new vaccines will be available for use within the next decade or so. Significantly, great progress is being made in understanding the biology of infectious agents, how they interact with hosts during infection, and which aspects of the host immune response correlate with protection – new knowledge that will support the identification, design and evaluation of enhanced vaccines. Furthermore, new vaccine platform technologies and innovative methodologies, such as controlled human infection studies (now being carried out in disease-endemic countries), are offering great potential to accelerate the development of new vaccines. Vaccine platforms that can form the backbone of multiple vaccines are providing further exciting opportunities for new vaccine development.

R&D INDICATORS ARE MOSTLY ON TRACK



The Global Vaccine Action Plan also identified seven other priority infections for which new vaccines are required. Significant progress is being made for many of these infections, with new products undergoing clinical evaluation. There is a need to determine whether the initial Global Vaccine Action Plan list is still appropriate and whether new priorities should be identified, building on the work of the **WHO Product Development for Vaccines Advisory Committee (PD-VAC)** and the R&D Blueprint.

Innovative **delivery technologies,** including needle-free injection systems, offer the prospect of more convenient, safer and people-friendly delivery of vaccines. Many different approaches are under development, including several that are now WHO prequalified and ready for implementation. Significant progress is also being made in **diagnostic technologies,** particularly simple-to-use, rapid, point-of-care diagnostics, with great potential in infectious disease surveillance and epidemiological studies that inform the design and scope of vaccine clinical trials and immunization programmes.

More than 50 HIV
vaccine trials have been launched since 2010

490,000 people
developed multidrug-resistant tuberculosis (MDR-TB) in the world in 2016

At least
13 TB vaccines
are currently undergoing clinical trials

The 2014–16 Ebola outbreak cost three African countries at least

US$2.8bn

The experience with RTS,S/AS01 (Mosquirix®) and other interventions has highlighted the challenges not just of navigating regulatory pathways but also of overcoming a **second translational gap** at the post-phase III implementation stage. This experience is highlighting the critical importance of adopting a 'total systems effectiveness' approach to determine the potential programmatic, public health and financial impact of new products, extending evaluation beyond safety, efficacy and performance, and more generally of linking product development to the practicalities of field deployment.

Recent years have also seen tremendous progress in the development of coordinated global responses to **emerging and re-emerging infections.** The 2014–6 Ebola epidemic illustrated that the world was poorly prepared to manage emerging disease outbreaks, and in particular to carry out clinical research on new vaccines or other interventions. The **WHO R&D Blueprint** initiative is coordinating global efforts to develop new products, including vaccines, for infections of epidemic potential, and to establish mechanisms for their timely and ethical clinical evaluation in outbreak situations. The **Coalition for Epidemic Preparedness Innovations (CEPI)** is a new global initiative developing vaccines for emerging pathogen threats.

A further noticeable trend has been the growth of **R&D and manufacturing capacity in low- and middle-income countries.** This is seen as an important way of addressing global supply and affordability issues (as well as contributing to the economic development of low- and middle-income countries). Nevertheless, there remains a need to develop research and translational capacity in such countries, to promote participation in and leadership of research, and to build national regulatory and other capacity to facilitate local innovation and industrial development.

While much attention is given to product development, research can play a wider role in immunization, generating evidence across multiple domains to improve access to vaccines and immunization services. **Implementation research and delivery science** have key roles to play in rolling out and scaling up new approaches to healthcare delivery. **Operational research** can identify improvements in immunization system functions and decision-making. ***In silico* modelling** can help to identify bottlenecks and hurdles, and provides a way to assess the likely impact of possible solutions. Research can also be used to evaluate initiatives to stimulate demand or address hesitancy. New innovations will be particularly required to deliver services to hard-to-reach populations, and need to be rigorously evaluated. Collectively, these approaches can ensure that immunization is a rigorous evidence-based discipline.

7. THE FUTURE

Implementation of the Global Vaccine Action Plan has taught us much and will provide invaluable lessons for immunization post-2020. A new strategy will need to consider profound changes in global context, a growing awareness of the difficulty of the challenges presented by infectious diseases, and the opportunities offered by new technologies and ways of working.

A volatile and uncertain world: The context for the next global immunization strategy will be a world in which volatility and uncertainty are the norms. Large-scale population movements are likely to be commonplace, with continuing mass urbanization and displacements due to conflict, deterioration of fragile states, and the consequences of natural disasters and global warming. History suggests that we will at some point encounter new infectious diseases that represent a global pandemic threat.

Tough challenges: Polio eradication has been a chastening experience. Smallpox eradication inspired hope that other infectious diseases could also be consigned to history, but the final steps in polio eradication have been hugely challenging. Effective control of measles and rubella demands very high and consistent levels of vaccine coverage. Reaching those remaining groups not fully benefiting from immunization will be challenging for many countries. Special efforts and investment will be required to access the most disadvantaged communities.

Complacency and the risk of regression: Just sustaining immunization gains year on year will remain a significant challenge, particularly given anticipated population growth, notably in the African Region. All our gains are at risk of being undermined by complacency – immunization is a commitment we need to make in perpetuity. As the disruption and cost of outbreaks illustrate, neglecting immunization is a false economy. Or, to put it more positively, immunization is an investment that will continue to deliver long-term health and economic benefits far in excess of its immediate costs.

Recognizing shared interests: In response to these challenges, the global immunization community needs to recognize the importance of shared interests and work towards common goals. As a public health intervention with unparalleled population reach, immunization can provide a springboard for universal health coverage and underpin enhanced primary care, thereby contributing to national development. It also provides key tools to ensure global health security and to tackle antimicrobial resistance. Multiple opportunities therefore exist to engage with additional sectors and potential partners.

Immunization at the heart of healthcare: Immunization is a central pillar of universal health coverage, and at the heart of comprehensive and sustainable primary healthcare systems. Other disciplines can build on the immunization community's ability to reach populations in need, driving coalescence of integrated patient-centred healthcare systems. The increasing relevance of immunization across the entire life course provides a further compelling argument for integration.

Building on partnerships: The successes of immunization owe much to partnerships, which must remain core to future work. Effective global models of collaboration have been established to tackle complex problems, supporting enhanced access and coordinated research. Additional partnerships can be envisaged, for example with development assistance communities, recognizing the core role of health protection and promotion in sustainable development, with the private sector, which makes a major contribution to immunization in many settings, and with a wider range of CSOs.

The global urban population is projected to increase by
2.5 billion
by 2050, with almost 90% of growth occurring in Asia and Africa

Vaccine-preventable diseases account for the deaths of more than

500,000 children

under five years of age in Africa every year

Immunization programmes in the Western Pacific Region have averted an estimated

7 million

deaths and

37.6 million

chronic hepatitis B cases among children born between 1990 and 2014

Putting countries in the driving seat: Effective, robust and sustainable national immunization programmes will be the building blocks of a future immunization strategy. It is essential that countries take ownership and pride in their national immunization systems, identifying strategies to strengthen their capacity with the appropriate technical support from regions, global partners and RITAGs. Central to this approach will be rigorously developed business cases for immunization that clearly articulate the justification for support, including anticipated health and economic gains as well as the risks of inaction – not least the human and financial impact of outbreaks. They also need to identify robust approaches to governance and accountability. The risk of corruption must be acknowledged and explicitly addressed – a zero tolerance approach is essential.

Strengthening the basics: Systematic strengthening of national immunization systems will need to recognize the complexity of immunization systems – spanning all areas from forecasting and procurement systems, through logistics, including delivery of vaccines to individuals, information management, and demand stimulation and hesitancy management. Integration with other elements of healthcare delivery will add further complexity, as will the need to embed strategies to ensure greater coverage of disadvantaged and hard-to-reach communities. Such work will require ongoing commitments to quality improvements at all levels in the system – there are no 'silver bullets'.

Addressing issues at the right level: While a future immunization strategy should have a country focus, regions and global initiatives will continue to play key enabling roles. Regions are best placed to develop locally tailored strategies to support countries, can recognize and respond to regional challenges, and can leverage regional assets to support individual countries. At the global level, partners can continue to advocate for immunization and coordinate financial support, undertake market shaping and other globally focused initiatives, and deliver training and other tools to facilitate immunization system strengthening. Within countries, immunization systems may need to incorporate sub-national strategies and mechanisms of devolved accountability.

Tailoring support: Countries vary in the maturity of their national immunization systems. International support for countries to develop their immunization systems should be based on national needs rather than simply measures of national wealth such as gross national income.

Building surveillance bridges: Infectious disease surveillance is central to immunization system function, as well as global health security. More needs to be done to strengthen laboratory capacity for both existing vaccine-preventable diseases and emerging infections, alongside support for community surveillance. More integrated approaches could also extend to national pharmacovigilance activities, to detect adverse events after immunization as well as reactions to other interventions.

R&D – maintaining the pipeline: Encouraging progress in new product development needs to be maintained, recognizing that all the 'quick wins' have likely been achieved and future product development will be challenging. Future vaccine introductions are likely to be more complex than in the past, with vaccines likely to have limited efficacy by themselves and consequently be used in conjunction with other interventions. These will present challenges to regulatory approval, health technology assessment and implementation. Strong links will be needed to ensure that R&D is guided by the needs and constraints of field use, but also that immunization programmes are aware of emerging new technological opportunities. Thought will also need to be given to issues such as financial sustainability of new product development and 'pull-through' to ensure continued investment, particularly for infections predominantly affecting resource-poor settings. Nimble approaches to R&D will be required to reflect rapidly changing epidemiology and emerging infectious disease threats. There is also much scope for research into vaccine scheduling and fractional dosing, as well as studies examining the impact of vaccine introduction on outcomes and disease burdens.

Research evidence: Research will also play a key role in enhancing the quality of national immunization systems, through implementation research, delivery science and operational research. Innovative new approaches will be needed to widen access to services or enhance other aspects of immunization system function, from novel diagnostics to new approaches to demand generation, all of which will need to be rigorously evaluated. Much of this work needs to be led at a country level, emphasizing the importance of building immunization research capacity in low- and middle-income countries.

Making better use of data: Major new opportunities exist to leverage the power of immunization data, particularly to inform programme actions. As well as their value in monitoring and evaluation, national and sub-national data can support more effective central planning and local micro-planning to address coverage gaps. Exploiting the potential of data will require investments in IT infrastructure and data management and analysis, as well as integration with other relevant national ehealth initiatives. Development of programme staff skills and data science capacity at a national level will also be critical. Enhancing the granularity of immunization data collection and data quality will be fundamental to improved planning and decision-making.

Exploiting existing and new opportunities: With no major new vaccines on the immediate horizon, now is the time to focus on strengthening immunization systems and ensuring best use is made of existing vaccines. There is still considerable scope to expand use of vaccines in age groups beyond infants and further extend use of MCV2, PCV, rotavirus vaccine, human papillomavirus (HPV) vaccine, and hepatitis B vaccine (HBV) birth dose. Multiple innovations in vaccine delivery and in controlled temperature chain distribution will open up new opportunities to deliver services to even greater numbers of people, particularly the vulnerable and hard to reach.

Fostering demand and addressing hesitancy: Public attitudes to immunization vary across a spectrum from active support and advocacy to vocal hostility. Stimulation of broad-based public demand for immunization creates resilience to threats like vaccine hesitancy and promotes political accountability at national and local levels to ensure the responsiveness and quality of services. A future immunization strategy must build countries' capacity for community engagement, demand promotion, and trust building. Countries need to be prepared to effectively respond to vaccine-related events that can quickly undermine public trust and disrupt national immunization programmes. Demand-related issues like vaccine hesitancy are complex, and subject to multiple influences, from genuine safety concerns to manipulation of public perceptions for political ends. The need is pressing to better understand the drivers of and barriers to vaccination uptake and to build national capacities to develop and implement tailored strategies to promote demand for immunization services.

Staying close to reality: A future immunization strategy should place people at its heart. The focus should be on people and communities. Future immunization systems need to reflect the realities of healthcare delivery, particularly in low-income settings, where contact with health systems may be rare and an opportunity to achieve multiple health goals. By involving communities in the design, implementation and monitoring of services, such services are likely to be more sustainable, more acceptable and more appropriate to the needs of those that need services the most. A key challenge will be to identify how global, regional and national strategies and principles can be converted into actions that make a real difference to the lives of people across the globe.

Government expenditure on immunization has increased by 130% in the Africa Region since 2010

8. CONCLUSION

More people than ever before benefited from immunization in 2017. Although the world remains off track to reach many of the goals set out in the Global Vaccine Action Plan, these were designed to be ambitious and stretching, and it is important not to lose sight of the great progress that has been made. Even so, the consequences of not achieving global goals have been vividly illustrated with the resurgence of measles and diphtheria and the persistence of poliovirus and maternal and neonatal tetanus.

The final years of the Decade of Vaccines provide us with an opportunity to drive forward immunization in pursuit of the Global Vaccine Action Plan goals. Past successes illustrate what can be achieved by countries prioritizing immunization, producing integrated development plans, and working with national, regional and global partners on their implementation. Despite many challenges, between 2011 and 2017, an additional 20 million children were vaccinated – but we can do even better.

Now is the time to learn the lessons from the Decade of Vaccines to shape a post-2020 strategy that enables the world to sustain its hard-won gains and expand the benefits of immunization to those currently missing out and to older age groups. The next chapter of immunization must also be one of integration, with immunization consolidating its position as a pillar of universal health coverage and primary healthcare, and contributing to the safer, healthier and more prosperous world envisioned in the Sustainable Development Goals.

9. RECOMMENDATIONS

Countries, regions and global immunization partners should commit to developing an integrated post-2020 global immunization strategy:

- A comprehensive review should be undertaken of progress, impact and implementation of the Global Vaccine Action Plan to inform a post-2020 strategy
- The monitoring and evaluation framework for the Global Vaccine Action Plan should be reviewed to inform the development of a revised post-2020 framework
- A new post-2020 strategy build on the lessons learned during the Decade of Vaccines and draw upon the key themes identified in this 2018 Assessment Report.

Global Vaccine Action Plan priorities, adapted to reflect changing contexts and lessons learned, should drive immunization activities until the end of the Decade of Vaccines:

- A major focus should be tailored country support to build and sustain robust and effective national immunization systems aligned with national plans for achieving universal health coverage
- A best practice framework should be developed to ensure equitable access to immunization services for migrant, displaced and disadvantaged populations, including those affected by humanitarian emergencies
- Nurturing individual and community demand for immunization should be given high priority within countries.

The contributions of research to immunization should be enhanced and expanded:

- Strengthened connections between vaccine R&D and field use and programmatic challenges should be encouraged to realize the full benefits of immunization
- More research should be undertaken to improve the performance of national immunization systems, including implementation and operational research as well as innovations in service delivery to reach underserved populations
- Immunization research capacity in low- and middle-income countries should be developed across all these areas.

Every $1
spent on childhood immunization returns
$44 in economic and social benefits

Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies
PREVENT

wellcome

PREGNANT WOMEN & VACCINES AGAINST EMERGING EPIDEMIC THREATS

Ethics Guidance for Preparedness, Research, and Response

The PREVENT Working Group

EXECUTIVE SUMMARY

Recent epidemics, including Zika virus, Lassa Fever, Ebola, and H1N1 influenza, have highlighted the ways in which infectious disease outbreaks can severely—and at times uniquely—affect the health interests of pregnant women and their offspring.[i] For some pathogens, pregnant women are at significantly higher risk of serious disease and death. Infection in pregnancy can also result in pregnancy loss or severe congenital harms. Even if the disease caused by the pathogen is no worse in pregnancy, the harms of infection in pregnant women can potentially affect two lives.

These serious and often disproportionate risks underscore the critical need to proactively consider the interests of pregnant women and their offspring in efforts to combat epidemic threats. This is especially true for vaccines, essential tools in the public health response to infectious diseases. Despite increasing support of maternal immunization strategies and efforts to develop certain vaccines specifically targeted to pregnant women, the vast majority of new vaccine products are rarely designed with pregnant women in mind. Moreover, widespread failure to appropriately include pregnant women in vaccine research means that evidence about safety and efficacy in pregnancy has been limited and late in coming. As a result, in numerous outbreaks and epidemics, pregnant women have been denied opportunities to receive vaccines that would have protected them and their offspring from the ravages of these diseases.

This way of treating pregnant women in vaccine research and deployment is not acceptable. Business as usual can no longer continue.

To ensure that the needs of pregnant women and their offspring are fairly addressed, new approaches to public health preparedness, vaccine research and development (R&D), and vaccine delivery are required. This Guidance provides a roadmap for the ethically responsible, socially just, and respectful inclusion of the interests of pregnant women in the development and deployment of vaccines against emerging pathogens. The Guidance is a product of the Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Working Group—a multidisciplinary, international team of 17 experts specializing in bioethics, maternal immunization, maternal-fetal medicine, obstetrics, pediatrics, philosophy, public health, and vaccine research and policy—in consultation with a variety of external experts and stakeholders.

We recognize the recommendations contained in this Guidance will not always be easy to follow. For some, it will require a new way of thinking about pregnant women and vaccines. For many, it will require a commitment of will and of financial resources. Addressing inequities in biomedical research and public health rarely comes cheaply or without hard work. In terms of the lives saved and the suffering averted, the resources and the effort needed to ensure that pregnant women and their offspring are treated fairly will be more than worth it.

i We use the term "women" throughout this document, and while we appreciate that individuals who do not identify as women can still become pregnant, transgender and gender non-conforming individuals face different (though also substantial and problematic) barriers to participating in clinical research and having their health needs met that lie beyond the scope of this work. We use the term "offspring" throughout this report to broadly refer to fetuses as well as any persons born whose interests may be affected by *in utero* exposures to pathogens or vaccine administrations.

VISION

The guidance aims to realize a world in which:

RECOMMENDATIONS

PUBLIC HEALTH EMERGENCY PREPAREDNESS

RECOMMENDATION 1

Health information systems and infectious disease surveillance systems should be strengthened and integrated to ensure that data relevant to maternal, obstetric, and newborn health outcomes can inform scientific and public health responses to emerging pathogenic threats.

- **DIRECTED TO:** public health authorities; the World Health Organization (WHO) and regional health organizations; developers and users of routine health information and global health security systems, including organizations with a focus on maternal and child health outcomes; organizations developing innovative approaches to data collection and surveillance; funders and sponsors of maternal health studies and global health surveillance

Routine health information systems and infectious disease surveillance systems are both essential to an appropriate and rapid response to emerging pathogenic threats. Collecting baseline data on maternal, obstetric, and newborn health can advance the interests of pregnant women and their offspring by enabling detection of increases in adverse events that may signal the presence of infectious disease threats. These baseline rates are also needed to help interpret whether adverse events surrounding pregnancy have any causal link to vaccination. Infectious disease surveillance systems should routinely include pregnancy status and maternal, obstetric, and newborn outcomes in case reports. These data, when integrated with baseline rates from health information systems, can help determine whether a circulating pathogen causes additional or more severe harms in pregnancy.

RECOMMENDATION 2

Evidence-based strategies to promote confidence about vaccination in pregnancy should be developed and implemented ahead of outbreaks, including stakeholder engagement with health care providers, women, their families, and their communities.

- **DIRECTED TO:** public health authorities; health care providers; professional medical associations; medical and health training programs; community leaders; civil society organizations and vaccine advocacy groups; research institutes; funders and sponsors; the media

For immunization programs to be successful, it is critical that populations have confidence in the benefits of a vaccine and its safety, and in the health benefits of vaccination more broadly. Inadequate confidence in vaccines can be especially pronounced among pregnant women and those who care for them. Evidence about safety in pregnancy is limited because of the historic absence of vaccine trials in pregnant women. Moreover, pregnant women and health care providers are understandably concerned about fetal harm, and they are frequently bombarded with mixed messages about what may or may not be harmful in pregnancy. Working now to better understand and address the various sources and drivers of vaccine confidence among pregnant women and their communities will be critical to ensure appropriate vaccine uptake by pregnant women during outbreaks and epidemics.

RECOMMENDATION 3

Communication plans should be developed for clear, balanced, and contextualized dissemination of vaccine study findings, recommendations for vaccine use in pregnancy, and any pregnancy-specific adverse events.

- **DIRECTED TO:** clinical investigators; scientific journal editors; funders and sponsors; public health authorities; global, regional, and local vaccine advisory groups; professional medical associations; regulatory authorities; civil society organizations and vaccine advocacy groups; the media

Because pregnant women, health providers, and the public often overestimate potential fetal harms associated with medications and biologics, effective communication in vaccine development and delivery is critical. In research studies, the required timely reporting of clinically relevant signals and findings on vaccine safety and efficacy in pregnancy to regulatory authorities is not enough. Effective communication to the public and to clinicians through a variety of channels, including traditional and social media, is essential. In an epidemic response that recommends vaccination in pregnancy, communication plans must be clear about any known risks to pregnant women and their offspring, and why the anticipated benefits of vaccination outweigh these risks. When immunization in pregnancy is not recommended, communication plans should be sensitive to fears and concerns about the pathogenic threat that pregnant women share with the rest of the population, and provide them with information about what alternatives, if any, are available to them. In both research and epidemic responses, one best practice for communicating reports of adverse pregnancy or birth outcomes is to present the findings alongside the best available information about the baseline rates of these adverse events, and to acknowledge that many of them have no known cause.

RECOMMENDATION 4

Research efforts that aim to advance vaccine development by using new technologies to study human immune system function and response should include investigations specific to pregnant women and their offspring.

- **DIRECTED TO:** clinical investigators; basic research scientists; funders

Because pregnancy can alter immune response and because both maternal and fetal immune responses may change over the course of gestation, it is important that these foundational studies examine the distinctive characteristics of maternal and fetal immune systems. Understanding these differences could critically inform the development and identification of new vaccines that are safe and effective in pregnancy.

RECOMMENDATION 5

Mechanisms for incentivizing vaccine development for emerging and re-emerging infections and mitigating existing disincentives should include and address pregnancy-specific concerns of vaccine developers.

- **DIRECTED TO:** policymakers; regulatory authorities; funders and sponsors; vaccine developers; civil society organizations and those who are positioned to influence vaccine research, adoption, and delivery, including WHO, the World Economic Forum, and the Coalition for Epidemic Preparedness Innovations (CEPI)

Vaccine developers and manufacturers face significant market challenges and uncertainties in pursuing products targeting emerging and re-emerging pathogens. These challenges can become even more complicated when vaccine products are studied in and ultimately offered to pregnant women—for whom there may be heightened concerns of legal and financial liability. Current mechanisms in place to encourage development of

beneficial biomedical products and protect developers and manufacturers against liability concerns—as well as new incentive programs being explored for vaccines against epidemic threats—need to be intentionally inclusive of the needs and interests of pregnant women.

RECOMMENDATION 6

To help ensure systematic and enduring change in the treatment of pregnant women in global vaccine policy and practices, the World Health Organization should convene a consultation of relevant stakeholders and experts. The Consultation should identify specific strategies to establish for pregnant women the presumption of inclusion in both vaccine research and deployment, including whether a dedicated, standing expert group is needed.

Throughout this Guidance we make multiple recommendations to help ensure that pregnant women and their offspring can fairly benefit from the protection that vaccines offer against emerging epidemic threats. These recommendations outline specific actions that need to be taken, but institutional change at every level—globally, regionally, and nationally—will be required to operationalize these new approaches and move advisory and decision-making bodies toward the new default of presumptive inclusion of pregnant women. To seed this institutional change and explore specific strategies for the systematic consideration of pregnant women in international policies and practices governing vaccine research and delivery, WHO should convene a multi-day, global Consultation of relevant stakeholders. The Consultation should provide a critical opportunity to discuss and determine the best strategies to systematically integrate consideration of the interests of pregnant women and their offspring throughout all relevant WHO-supported activities, including whether a dedicated, standing group of relevant and diverse experts is needed. The Consultation should also consider ways to support regional and national public health authorities who may wish to establish similar expert groups.

Institutional change at every level will be required to establish a new default of presumptive inclusion of pregnant women.

The Presumptive Inclusion of Pregnant Women

"Presumption of inclusion" does not entail the automatic or absolute inclusion of pregnant women in every vaccine study or every vaccine campaign. Instead, a presumption of inclusion changes the default position. It normalizes the position that pregnant women are to be included in vaccine deployment programs and vaccine R&D. With inclusion of pregnant women as the default position, the burden of proof, both scientific and ethical, falls on those who want to argue for their exclusion. There will certainly be cases where the exclusion of pregnant women from a particular vaccine trial or vaccine campaign will be justified, but starting from a presumption of inclusion helps instantiate and maintain a fundamental shift in the way pregnancy and pregnant women are viewed in the field of vaccines.

VACCINE RESEARCH & DEVELOPMENT

RECOMMENDATION 7

Suitability for use in pregnancy should be a strong consideration in development and investment decisions for vaccines against emerging pathogenic threats.

- **DIRECTED TO:** CEPI, U.S. Biomedical Advanced Research and Development Authority (BARDA), and other funders and sponsors; WHO emergency response teams, R&D Blueprint teams and TPP Working Groups; vaccine developers

If pregnant women, and the offspring they carry, are among those threatened by an emerging pathogen, then suitability for use during pregnancy should be an important vaccine development priority. Organizations investing in the vaccine pipeline against emerging pathogenic threats should try to ensure that, among candidates prioritized for development, at least some use platforms and adjuvants that would make them suitable for use in pregnancy. Early investment in options that are most likely to be acceptable in pregnancy can pave the way for pregnant women and their offspring to realize benefits from vaccine candidates that ultimately prove successful—and help ensure that they, like other population groups, will be protected against emerging infectious diseases. For pathogens that pose significantly greater threats in pregnancy—of fetal harm, maternal harm, or both—funding calls should designate greater investment priority to candidates likely to be suitable for use in pregnancy. When pregnant women or their offspring are at higher risk of harm, it would be particularly unjust for their needs not to be included in vaccine development priorities.

RECOMMENDATION 8

When pathogens pose a risk of severe harm to pregnant women or their offspring and the most promising vaccine candidates are likely to be contraindicated for routine use in pregnancy, investments should be made in alternative vaccine candidates that could be more readily used in pregnancy.

- **DIRECTED TO:** CEPI, BARDA, and other funders; vaccine developers

It is possible that the vaccine candidates that move most rapidly through the R&D pipeline are found to be problematic for use in pregnancy. Unless other vaccines with more favorable profiles for use in pregnancy are then prioritized, it is possible that pregnant women and their offspring will end up without any vaccine protection against the emerging pathogenic threat. This prospect is particularly dire when the target pathogen has more severe consequences in pregnancy. When pregnant women and their offspring suffer disproportionately compared with other population groups from an emerging infectious disease threat, justice calls for the vaccine enterprise to make every reasonable effort to bring to market a safe and effective product that pregnant women can use.

> **Pregnant women need to be on the agenda when decisions about investment and funding are made.**

RECOMMENDATION 9

Non-clinical studies that are a prerequisite for clinical trials in pregnant women, such as developmental toxicology studies, should be initiated early in the clinical development of promising vaccine candidates, before efficacy trials are planned.

- **DIRECTED TO:** CEPI, BARDA, and other funders and sponsors; vaccine developers; national regulatory authorities

Current regulatory guidance often requires that certain non-clinical studies must be completed prior to including pregnant women in clinical trials. Because pregnant women should be able to participate in large-scale efficacy studies conducted during outbreaks whenever the benefits outweigh the risks (see Recommendation 11), any non-clinical studies required prior to clinical evaluation in pregnant women should be conducted as soon as promising vaccine candidates move from phase 1 to phase 2 clinical trials.

RECOMMENDATION 10

Studies to assess immune responses to vaccines in pregnancy should be conducted before or between outbreaks whenever scientifically possible and ethically and legally acceptable.

- **DIRECTED TO:** CEPI, BARDA, and other funders and sponsors; vaccine developers; clinical investigators

Although much of the work to evaluate vaccines in pregnancy will be done during outbreaks and epidemics (see Recommendation 11), there will be some cases in which it will be both beneficial and feasible to generate immunogenicity data in pregnancy before or between outbreaks. Because immune system functioning is altered in pregnancy, it is possible that a vaccine will be less immunogenic or induce atypical immune responses in pregnant women, with potential implications for its effectiveness as well as the dosing and frequency required in pregnancy to generate sufficient protection. Such immunogenicity studies would be particularly valuable if a correlate of protection for the vaccine has already been established. In the absence of an outbreak or epidemic, it may be difficult to demonstrate that studies to assess immune response in pregnant women have a favorable risk-benefit profile. However, there may be instances in which the future exposure to a pathogen among a particular population is likely enough to conclude that the potential benefits of being protected would outweigh the risks associated with a particular candidate vaccine.

RECOMMENDATION 11

Clinical development plans for investigational vaccines against emerging and re-emerging pathogens should include studies designed to evaluate vaccines in pregnancy. Pregnant women should have opportunities to enroll in vaccine studies conducted during outbreaks and epidemics whenever the prospect of benefit outweighs the risks to pregnant women, their offspring, or both.

- **DIRECTED TO:** CEPI, BARDA, and other funders and sponsors; vaccine developers; clinical investigators and trial implementation partners; research ethics committees; national regulatory authorities

This recommendation rests on two claims of justice about the importance of treating pregnant women and their offspring fairly in the conduct of research on vaccines for emerging and re-emerging infections. The first of these justice claims pertains to pregnant women as a class: as a matter of equity, as well as public health, the evidence base for pregnant women should be as good as possible and generated as contemporaneously as possible to the evidence for the general population. The second, independent reason motivated by justice is that pregnant women, as the moral equals of others,

should have fair access to the prospect of direct benefit that may ensue from receiving an experimental vaccine. For both of these reasons, it is critical that vaccine research conducted during outbreaks include appropriate plans for research with pregnant women when there is a reasonable judgment that the prospective benefits of enrollment outweigh the risks.

RECOMMENDATION 12

Vaccine studies that include women of childbearing potential should have plans to systematically collect data on immunogenicity and pregnancy-specific indicators of safety from participants who are unknowingly pregnant at the time of exposure or become pregnant within a relevant window following vaccine administration.

- **DIRECTED TO:** CEPI, BARDA, and other funders and sponsors; vaccine developers; clinical investigators and trial implementation partners; research ethics committees; national regulatory authorities

In trials enrolling women of childbearing potential, including vaccine trials conducted in outbreak contexts, it is predictable that some women not known to be pregnant at the time of enrollment will nevertheless be pregnant at enrollment, or become pregnant in the course of the trial. Historically, data from inadvertent exposures during pregnancy have been a key source of information regarding the safety profiles of vaccines in pregnancy. Having a plan to systematically generate evidence from participants who are unknowingly pregnant at the time of administration also enables capturing data from vaccine exposures earlier in pregnancy than would be likely in trials prospectively enrolling pregnant women. Wherever possible, systematic observational studies that are designed to capture inadvertent exposures to vaccine during pregnancy should also include longitudinal evaluation of safety, immunogenicity, and other relevant outcomes. Data from inadvertent exposures during pregnancy should be collected using standardized methods and case definitions and must be cautiously interpreted, particularly when adverse events occur in early pregnancy, as these very commonly occur unrelated to vaccine exposure.

RECOMMENDATION 13

Women participating in vaccine trials who become aware of a pregnancy during the trial should be guaranteed the opportunity, through a robust re-consent process, to remain in the trial and complete the vaccine schedule when the prospect of direct benefit from completing the schedule can reasonably be judged to outweigh the incremental risks of receiving subsequent doses.

- **DIRECTED TO:** clinical investigators and trial implementation partners; vaccine developers; research ethics committees; national regulatory authorities

In vaccine trials that include prospectively enrolled pregnant women, participants who become pregnant after enrollment should be provided the opportunity to continue to receive vaccine doses after a renewed consent process. In trials that exclude pregnant women from prospective enrollment, determinations about continued dosing should be based on assessment of the potential benefits and harms specific to the circumstances of the pregnant participant, including possible risks associated with receiving an incomplete vaccination series and the risks already incurred from the first vaccination. In both cases, a robust re-consent process will be essential to allowing pregnant women to determine whether they want to receive additional doses. Regardless of whether they choose or are permitted to continue with the vaccine schedule, participants who become pregnant should be provided all study-related benefits and ancillary care to which they would otherwise be entitled.

RECOMMENDATION 14

When a pregnant woman of legal standing to consent is judged eligible to enroll or continue in a vaccine trial, her voluntary and informed consent should be sufficient to authorize her participation.

- **DIRECTED TO:** clinical investigators and trial implementation partners; research ethics committees; national authorities in charge of governance and oversight of human subjects research

As a matter of respect, and as a key aspect of ensuring fair access to investigational vaccines, the consent of pregnant women who are judged eligible to participate in or continue receiving doses in a vaccine trial should be sufficient for participation. Pregnant women are the moral equals of other self-governing adults. Further, requiring the consent of additional actors can present a material barrier to the benefits research may offer to the offspring. At the same time, researchers should support pregnant women who wish to involve partners, family members, and other personal supports in decisions to join or remain in vaccine trials.

RECOMMENDATION 15

Experts in maternal and perinatal health, pediatrics, and research ethics should be involved in decisions about funding; trial design; research ethics oversight; and the generation, analysis, and evaluation of evidence on vaccine use in pregnancy.

- **DIRECTED TO:** funders and sponsors; vaccine developers; clinical investigators; research ethics committees; national health authorities in charge of research governance and regulations; data safety monitoring boards

Pregnant women deserve that decisions affecting them will be made in careful, thoughtful, and evidence-based ways, involving the most informed experts possible. Experts in obstetrics and gynecology, maternal-fetal medicine, pediatrics, and neonatology, especially those who have experience with infectious diseases, immunology, and maternal immunization, have specialized knowledge that is critical to properly identifying and addressing the needs and interests of pregnant women and their offspring in research and development.

RECOMMENDATION 16

Whenever possible, the perspectives of pregnant women should be taken into account in designing and implementing vaccine studies in which pregnant women are enrolled or in which women enrolled may become pregnant.

- **DIRECTED TO:** clinical investigators; vaccine developers; research ethics committees; community advisory boards; funders and sponsors; public health authorities

Community engagement and participatory-based approaches to biomedical research have been increasingly recognized as good practice in the design and conduct of human subjects research. In the context of vaccine studies enrolling pregnant women, soliciting the perspectives of pregnant women from the communities in which the research will be conducted offers a way to demonstrate respect, and can be critical to the success of a study. The perspectives of pregnant women can improve various aspects of study design by, for example, determining what information and outcomes are most important to pregnant women, ascertaining culturally relevant considerations for the consent process, and establishing the appropriate frequency and location of study visits based on the daily demands on women's lives throughout pregnancy and after delivery.

VACCINE DELIVERY DURING THE EPIDEMIC RESPONSE

RECOMMENDATION 17

Pregnant women should be offered vaccines as part of an outbreak or epidemic response. Pregnant women should only be excluded if a review of available evidence by relevant experts concludes that the risks to pregnant women and their offspring from the vaccine are demonstrably greater than the risks of not being vaccinated.

- **DIRECTED TO:** public health authorities; national immunization programs; recommending and advisory bodies, including professional medical associations, SAGE, and other relevant WHO advisory committees; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; organizations involved in vaccine delivery in the outbreak response, including UNICEF, MSF, and International Federation of Red Cross

Because pregnant women are the moral equals of others, and because there is nothing about being pregnant that would make them or their offspring less susceptible to the harms of emerging pathogenic threats, the default position of advisory bodies and public health authorities should be that pregnant women are offered vaccines alongside other affected populations during an epidemic response. Any recommendations or decisions not to use vaccines in pregnancy during an outbreak or epidemic requires justification of exclusion based on a reasonable determination that the risks to pregnant women and their offspring from vaccination are demonstrably greater than the likely benefits of being protected from the pathogen. This determination should be made by relevant experts, including those in maternal, perinatal, and pediatric health. ***The absence of evidence and the mere theoretical or even documented risk of fetal harm is generally not sufficient to justify denying pregnant women access to a vaccine in an outbreak or epidemic.*** Even when the risk of fetal harm from the vaccine is significant, if the likelihood and severity of harms from the pathogen are high enough for pregnant women and their offspring, then the benefits of vaccination may still outweigh the risks.

RECOMMENDATION 18

When there is a limited supply of vaccine against a pathogenic threat that disproportionately affects pregnant women, their offspring, or both, or when only one vaccine among several is appropriate for use in pregnancy, then pregnant women should be among the priority groups to be offered the vaccine.

- **DIRECTED TO:** public health authorities; national immunization programs; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; WHO; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross

It is not uncommon in outbreak and epidemic settings for vaccine demand to exceed supply. For some pathogenic threats, pregnant women and their offspring may be among the hardest hit groups; in these cases, as with any other high-risk group, they should be a priority in the allocation of a vaccine that is in short supply. Additionally, even when the threat is no worse for pregnant women than it is for other affected population groups, vaccinating a pregnant woman protects not only the pregnant woman but also her offspring. Particularly for high-consequence pathogens with significant mortality rates, there may be considerable additional benefit in vaccinating pregnant women.

During an epidemic, the default should be to offer vaccines to pregnant women alongside other affected populations.

RECOMMENDATION 19

When vaccines are offered to pregnant women during outbreaks or epidemics, prospective observational studies should be conducted with pregnant women and their offspring to further advance the evidence base for use in pregnancy.

- **DIRECTED TO:** vaccine manufacturers; public health and regulatory authorities; national immunization programs; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross; researchers; funders; groups that oversee research with human subjects, including research ethics committees

Implementing prospective observational studies in pregnant women and their offspring who receive the vaccine as part of the outbreak or epidemic response provides an important opportunity to narrow the evidence gap between pregnant women and other population groups. If such studies are not conducted, decision-makers in future outbreaks and epidemics will be faced with the same evidence gap as current decision makers—an unacceptable outcome from both an equity and a public health perspective. Moreover, safety data obtained from evaluating a vaccine derived using a novel platform in pregnant women may inform future decision-making regarding the suitability of that platform for development of vaccines against other pathogens.

RECOMMENDATION 20

When vaccines are offered to pregnant women during outbreaks and epidemics, the consent of the pregnant woman should be sufficient to authorize administration whenever the pregnant woman is of legal standing to consent to medical care.

- **DIRECTED TO:** public health authorities; national immunization programs; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross; clinicians and obstetricians; pregnant women and communities

As a matter of respect, and as a key aspect of ensuring fair access to vaccines during an outbreak or epidemic, when vaccines are offered to pregnant women, their consent should be sufficient to authorize administration. Women should be presumed to have authority for decisions about their own medical care. Women are no different from men in this respect, and pregnant women are no different than women who are not pregnant. All adults, regardless of gender or pregnancy status, have rights of self-determination over decisions that affect their bodies and their health. Pregnant women who wish to engage or consult with their partners or other family or friends in making their decisions about vaccination should be supported in doing so.

Ensuring that pregnant women have vaccines to protect them and their offspring will require generation of evidence from pregnant women.

RECOMMENDATION 21

When evidence supports a determination that the risk of serious maternal or fetal harm from the vaccine outweighs the vaccine's benefits, pregnant women should be a priority group for access to alternative preventative or treatment measures.

- **DIRECTED TO:** public health authorities; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross; providers

Despite the best possible research and development efforts, the available vaccine for a given outbreak or epidemic may have sufficiently severe pregnancy-specific risks, even compared with the risks posed by the pathogen, that it is not made available to pregnant women. The moral objective remains, however, of giving pregnant women and their offspring as close to an equal chance of avoiding the harms of infection as the rest of the population. If they cannot be protected by immunization, then pregnant women, along with any other population group that cannot receive the vaccine, should be given preferential access to alternative preventive interventions and treatments.

RECOMMENDATION 22

When vaccines against emerging pathogens are not recommended for use in pregnancy, inadvertent vaccine exposures during pregnancy should be anticipated and mechanisms put in place for the collection and analysis of data from pregnant women and their offspring on relevant indicators and outcomes.

- **DIRECTED TO:** public health and regulatory authorities; vaccine manufacturers; national immunization programs; funders and sponsors

Even when pregnant women are intentionally excluded from the vaccine response effort, it is reasonable to expect that some of the women who are vaccinated will be unknowingly pregnant at the time of vaccine administration, or will become pregnant within a relevant window of its administration. Collecting data about outcomes in these women and their offspring in the midst of an active outbreak or epidemic will be difficult and costly, but there are two sets of ethical and public health reasons why it is critically important to do so. First, collecting data from unintentional exposures to vaccine in pregnancy during an outbreak or epidemic affords an important opportunity to gather evidence about novel vaccine technologies and thus to help ensure that pregnant women are not left behind as vaccine technology advances. Second, research and public health communities have a responsibility to pursue evidence about the likelihood and nature of any associated risks pregnant women and their offspring face from these unintended exposures to inform personal and clinical decision-making.

litigation (particularly when many affected have few re… at public … no-fault compensation systems increase public confidence in vaccination.[93] WHO, with support from partners at CEPI, World Economic Forum, and Harvard Global Health Institute, is currently exploring the establishment of a global no-fault compensation program that would specifically cover serious adverse events resulting from the use of non-licensed vaccines for emerging diseases with epidemic potential. We encourage those working on this compensation mechanism to explore ways this program can include features specific to vaccine administration in pregnancy—such as allowing for two claimants in the event that both the woman and her offspring suffer vaccine-associated adverse events.

Policymakers, regulatory authorities, sponsors, funders, civil society organizations, and those who are positioned to influence vaccine research and adoption should work together to identify global and country-specific incentive mechanisms for development and delivery of vaccines that pregnant women can use in the event of an outbreak, while exploring … g pregnant women.

RECOMMENDATION 6

To help ensure systematic and enduring change in the treatment of pregnant women in global vaccine policy and practices, the World Health Organization should convene a consultation of relevant stakeholders and experts. The Consultation should identify specific strategies to establish for pregnant women the presumption of inclusion in both vaccine research and deployment, including whether a dedicated, standing expert group is needed.

Standard approaches to determining when pregnant women can be offered vaccines in the context of both research and delivery have too often operated on a presumption of exclusion—that pregnant women cannot or should not be eligible. This default mindset of exclusion, often without scientific or ethical justification, has done a great disservice to pregnant women and their offspring and

Box 6: The Presumptive Inclusion of Pregnant Women

"Presumption of inclusion" does not entail the automatic or absolute inclusion of pregnant women in every vaccine study or every vaccine campaign. Instead, a presumption of inclusion changes the default position. It normalizes the position that pregnant women are to be included in vaccine deployment programs and vaccine research and development. With inclusion of pregnant women as the default position, the burden of proof, both scientific and ethical, falls on those who want to argue for their exclusion. There will certainly be cases where the exclusion of pregnant women from a particular vaccine trial or vaccine campaign will be justified, but starting from a presumption of inclusion helps instantiate and maintain a fundamental shift in the way pregnancy and pregnant women are viewed in the field of vaccines. The presumption thus serves to reframe decisions about investments in vaccine research and development and about the design of vaccine delivery efforts in ways that are profoundly important from the standpoints of both public health and equity.[vii] (See also Box 9).

must be changed. It has resulted not only in unjustifiably excluding pregnant women from specific vaccine trials or specific vaccine deployment efforts, but also in obscuring the interests of pregnant women from focal consideration in investments in vaccine research and public health programming, more broadly.

Throughout this Guidance we make multiple recommendations to help ensure that pregnant women and their offspring can fairly benefit from the protection that vaccines offer against emerging epidemic threats. These recommendations outline specific actions that need to be taken, ***but institutional change at every level—globally, regionally, and nationally—will be required to operationalize these new approaches and move advisory and decision-making bodies toward the new default of presumptive inclusion of pregnant women.***

To seed this institutional change and explore specific strategies for the systematic consideration of pregnant women in international policies and practices governing vaccine research and delivery, WHO should convene a multi-day, global Consultation of relevant stakeholders.[vii]

Consultation participants should include representatives from regional regulatory networks and national regulatory authorities (NRAs), such as: the African Vaccine Regulatory Forum (AVAREF); the Pan American Pharmaceutical Regulation Harmonization Network (PANDRH); the Developing Country Vaccine Regulators' Network (DCVRN); European Medicines Agency (EMA); U.S. Food and Drug Administration (FDA); and other NRAs, as well as from national ethics committees.

Experts in obstetrics and gynecology, maternal-fetal medicine, pediatrics, and neonatology, especially those with experience in infectious diseases, immunology, maternal immunization, and research and public health ethics should be present (see Recommendations 15 and 17), as well as stakeholder representatives from industry, implementation partners in research and emergency response, and funders.

The Consultation should provide a critical opportunity for representatives across relevant WHO programs, initiatives, clusters, teams, and advisory committees to discuss and determine the best strategies to systematically integrate consideration of the interests of pregnant women and their offspring throughout all WHO-supported activities relevant to vaccine R&D, maternal immunization, and emergency preparedness and response.

One such strategy that should be considered at the Consultation is the establishment of a Joint Pregnancy Expert Group on Immunization (JPEG). Structured as a standing body of interdisciplinary experts, the JPEG could provide guidance on use in pregnancy for both routine vaccination and vaccination in public health emergencies. This interdisciplinary expert group could jointly report to existing WHO advisory groups, such as the Strategic Advisory Group of Experts (SAGE) on

vi. This is consistent with various CIOMS International Ethical Guidelines on equitable distribution of benefits and harms of research, which state that: inclusion and exclusion criteria should not be based on potentially discriminatory criteria unless there is a sound ethical or scientific reason; for research in disease outbreaks, adequate justification is given whenever particular populations are excluded; and when under-representation of groups results in or perpetuates health disparities, equity may require special efforts to include members of those groups in research.

vii. Although the focus of this recommendation is on specific vaccine products and maternal immunization, particularly in outbreak contexts, the Consultation may be a useful platform to explore broader strategies to address the interests and unmet needs of pregnant women and their offspring as they pertain to the development and delivery of a wider range of biomedical interventions.

Immunization and the proposed Strategic and Technical Advisory Group (STAGE) on Maternal Health.[viii]

We believe there are compelling reasons for establishing JPEG. Creating a standing body at the World Health Organization devoted to pregnant women and vaccines will bring global focal attention to maternal immunization. The JPEG will send an unmistakable signal to the global health community that pregnant women and their offspring, no less than other members of the population, should be permitted to benefit from the advances in health that vaccines offer, and that there are responsible ways to ensure that they do.

Moreover, making determinations about what is in the best interests of pregnant women and their offspring during an emerging outbreak or epidemic often entails multiple and complex assessments and the synthesis of rapidly emerging data from many settings. It is unrealistic and inefficient to expect every locality to have the resources to be able to convene the expertise necessary to assess vaccine use in pregnancy during an outbreak or epidemic. However, absent an appropriate and timely process for making these assessments, pregnant women and their offspring will continue to be seriously disadvantaged—with the default being their exclusion from programs that deliver beneficial vaccines in emergency responses.

The Consultation should also include consideration of ways to support regional and national public health authorities who may wish to establish similar groups of relevant and diverse experts to advise their National Immunization Technical Advisory Groups (NITAGs), Regional Immunization Technical Advisory Groups (RITAGs), and emergency response teams. In addition, the Consultation should address approaches to facilitate communication and collaboration between national, regional, and global advisory groups on pregnancy during outbreaks.

viii. The JPEG could be modelled after the similarly structured Joint Technical Expert Group (JTEG) on malaria vaccines, which was convened by the Immunization, Vaccines, and Biologicals Department (IVBD) and the Global Malaria Program (GMP) to provide advice on malaria vaccine development to both SAGE and the Malaria Policy Advisory Committee (MPAC). For more on the JTEG, see Kaslow DC, Biernaux S. RTS, S: Toward a first landmark on the Malaria Vaccine Technology Roadmap. Vaccine. 2015 Dec 22;33(52):7425–32 and WHO Initiative for vaccine research/global malaria programme joint technical expert group (JTEG) on malaria vaccines entering pivotal phase 3 trials & beyond (April 2009–February 2016). Terms of References. Accessed 8 Aug 2018. Available from: www.who.int/immunization/research/committees/jteg/en.

engagement platforms already being planned for the research, such as a community advisory board. Another option is to conduct dedicated formative research with pregnant women or to establish an advisory board for the trial that is composed of pregnant women and their family members.

Because a number of standard protocols for vaccine efficacy trials are being developed in advance of epidemics to enable rapid implementation, there should be ample opportunity to engage pregnant women as well as other stakeholders in the development of these protocols.[25,138,139]

III. VACCINE DELIVERY DURING THE EPIDEMIC RESPONSE

RECOMMENDATION 17

Pregnant women should be offered vaccines as part of an outbreak or epidemic response. Pregnant women should only be excluded if a review of available evidence by relevant experts concludes that the risks to pregnant women and their offspring from the vaccine are demonstrably greater than the risks of not being vaccinated.

- **DIRECTED TO:** public health authorities; national immunization programs; recommending and advisory bodies, including including professional medical associations, SAGE, and other relevant WHO advisory committees; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; organizations involved in vaccine delivery in the outbreak response, including UNICEF, MSF, and International Federation of Red Cross

Because pregnant women are the moral equals of others, and because there is nothing about being pregnant that would make them or their offspring less susceptible to the harms of emerging pathogenic threats, ***the default position of advisory bodies and public health decision-makers should be that pregnant women are offered vaccines alongside other affected populations during an epidemic response.*** Any recommendations or decisions not to use vaccines in pregnancy during an outbreak or epidemic requires justification of exclusion based on a reasonable determination that the risks to pregnant women and their offspring from vaccination are demonstrably greater than the likely benefits of being protected from the pathogen.

An assessment of the comparative risks and benefits of vaccination in pregnancy during an outbreak should take into account the same 6 considerations identified for the appropriateness of including pregnant women in research: 1) the likelihood of infection; 2) the likelihood and severity of harms to pregnant women and their offspring from infection; 3) the likelihood that the vaccine will protect against the potential risks of infection in both pregnant women and their offspring; 4) the likelihood and severity of risks to pregnant women and their offspring from receiving the vaccine; 5) the availability of safe and effective alternative prevention options; and 6) the availability of safe and effective treatment options. However, at the time of implementing a vaccine campaign, compared with the trial context, there is typically more evidence available to inform these assessments. Table A provides more detail about these considerations, with side-by-side comparisons of the two different contexts.

Risk-benefit assessments should be informed by expert review of the best available evidence. The establishment of an WHO standing body of interdisciplinary experts dedicated to advising on vaccine use in pregnancy, as proposed for consideration in Recommendation 6, can help fulfill this requirement. So, too, would

be the establishment of any regional or local counterparts.

The considerations in Table A are likely to play out differently for different combinations of pathogenic threats and vaccine countermeasures. Advisory committees, decision-makers, and the experts they engage will need to weigh the evidence available at the time as best they can to reach informed and fair judgments.

In some cases, there may be substantial data from intentional administrations or inadvertent exposures during pregnancy in the context of clinical trials or in earlier outbreaks to establish the safety of the vaccine in pregnant women. Alternatively, the vaccine may be new but developed using a platform and/or adjuvant that has been widely and safely used in other maternal immunizations.

In other cases, it may be advantageous to offer pregnant women vaccines with non-ideal characteristics for pregnancy because the protective benefits of the vaccine outweigh risks. ***The absence of evidence and the mere theoretical or even documented risk of fetal harm is generally not sufficient to justify denying pregnant women access to a vaccine in an outbreak or epidemic. Even when the risk of fetal harm from the vaccine is significant, if the likelihood and severity of harms from the pathogen are high enough for pregnant women and their offspring, then the benefits of vaccination may still outweigh the risks.*** (See Box 12) For example, while the live-attenuated yellow fever vaccine is not routinely offered to pregnant women, it is widely endorsed for use during epidemics to protect pregnant women and their offspring against the far greater risks of yellow fever infection.

Box 12: Theoretical Risks of Live Vaccines in Pregnancy versus Documented Associated Harms

Routine administration of live vaccines to pregnant women has been generally contraindicated because of concerns about fetal harm.[123,140] However, not all live vaccines pose equal concern. Concern is greatest for those live vaccines that replicate systemically and could potentially cross the placenta. Despite unintended exposures during pregnancy to several of these types of live vaccines (e.g., rubella, yellow fever, and smallpox vaccines) in hundreds to thousands of women, convincing evidence of fetal harm has only been demonstrated for smallpox vaccine (a small increased risk of birth defects [2.4% vs. 1.5%] among women vaccinated in the first trimester; a total of 21 cases of fetal vaccinia reported in the literature).[119,123,141,142,143,144,145] For this reason, offering yellow fever and smallpox vaccines to pregnant women at high risk of infection has been advised, based upon the assessment that potential benefits far outweigh risks.[108,123] When novel live vaccines are being developed for emerging pathogens, it will be impossible to prospectively assess the risk of fetal harm through transplacental transmission of live-attenuated vaccine candidates that replicate systemically. To ensure that pregnant women have access to vaccines with reassuring safety data, investments should be made in vaccine candidates that are most likely to be acceptable in pregnancy (Recommendations 7 and 8). In addition, since situations will likely arise in which women are unintentionally exposed to these types of live vaccines during pregnancy, it will be critical to systematically collect data on pregnancy-specific indicators of safety to inform a risk-benefit assessment (Recommendations 12 and 22).

Consider also the rVSV-ZEBOV Ebola vaccine. This vaccine would likely not be viewed as appropriate for use in pregnancy outside the context of an Ebola outbreak. Currently, however, it is the only Ebola vaccine that has successfully completed efficacy trials.[146] Given the harms associated with Ebola infection in pregnancy, including maternal mortality ranging from 70–90% and near 100% fetal demise, the potential benefits of offering the vaccine clearly outweigh the potential harms in the context of a high incidence outbreak setting.[2,3]

RECOMMENDATION 18

When there is a limited supply of vaccine against a pathogenic threat that disproportionately affects pregnant women, their offspring, or both, or when only one vaccine among several is appropriate for use in pregnancy, then pregnant women should be among the priority groups to be offered the vaccine.

- **DIRECTED TO:** public health authorities; national immunization programs; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; WHO; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross

It is not uncommon in outbreak and epidemic settings for vaccine demand to exceed supply. Numerous groups have proposed criteria for determining how to ethically set priorities among different groups of potential vaccine recipients.[147,148,149,150] Most acknowledge that groups who face greater risks of harm from the infection have a greater claim on vaccines than those who face lesser risks. For some pathogenic threats, such as Lassa fever, pregnant women and their offspring may be among the hardest hit groups and should, like any other high-risk group, be a priority in the allocation of a vaccine that is in short supply.

An additional argument in favor of placing a priority on pregnant women in vaccine scarcity settings is that vaccinating a pregnant woman protects not only the pregnant woman but also her offspring. Particularly for high-consequence pathogens with significant mortality rates, there may be additional benefit when pregnant women are vaccinated. It is not only their lives, but the lives of the children they bear that stand to be saved. This argument applies even when the threat is no worse for pregnant women than it is for other affected population groups.

Yet another context in which pregnant women may justifiably be made a priority is when more than one vaccine is available to combat an outbreak or epidemic, but one vaccine is distinctly preferable for use in pregnancy. Here, it may be appropriate to allocate the preferable vaccine first for administration to pregnant women, as well as to any other group who might benefit from that vaccine's specific characteristics.

As is the case with all allocation criteria for scarce resources in a public health emergency, the reasons why some groups are prioritized should be communicated clearly to the public. Transparency is crucial to sustaining public trust during epidemics.[8,10,23]

Table A: Considerations for Assessing Risks & Benefits of Including Pregnant Women in Vaccine Research & Delivery

Considerations	Specific Dimensions of the Consideration & Expanded Definition	
	Research Context	**Deployment Context**
1. Likelihood of infection	» Likelihood of exposure » Susceptibility to infection o Susceptibility of the pregnant woman o Potential for vertical transmission of pathogen to the offspring	» Likelihood of exposure » Susceptibility to infection o Susceptibility of the pregnant woman o Potential for vertical transmission of pathogen to the offspring
	For certain pathogens, pregnant women may be at increased risk of exposure given the routes of transmission combined with social and behavioral norms. For example, pregnant women may be more likely to be exposed to infections that can be transmitted sexually because of decreased condom use in pregnancy. There is also evidence from past SARS and Ebola outbreaks that pregnant women may be more likely to have exposures to certain infections given their increased contact with health care settings for antenatal care.*	
2. Probability and severity of harms of infection to pregnant women and offspring	» Types of maternal, obstetric, and child harms o Morbidity o Mortality o Pregnancy loss o Pre-term labor o Short- and long-term congenital harms » Probability and severity of these harms often vary based on gestational timing of infection and may vary between pregnant woman and offspring (see below)	» Types of maternal, obstetric, and child harms o Morbidity o Mortality o Pregnancy loss o Pre-term labor o Short- and long-term congenital harms » Probability and severity of these harms often vary based on gestational timing of infection and may vary between pregnant woman and offspring (see below)
	Maternal and Obstetric: Some pathogens cause high rates of mortality and severe morbidity, with short-term and potential long-term effects on a woman's health. In some cases, the severity of effects is significantly heightened in pregnancy, with variable virulence across different stages of gestation. Additionally, infection may result in pregnancy loss, which can have adverse health and psychological consequences for women. Offspring: For certain pathogens, the primary concern is the congenital harm from fetal infection during pregnancy. However, a broader range of pathogens can have detrimental congenital effects – with short- or long-term ramifications – as a result of maternal infection. Even if the pathogen never crosses the placenta, harm to the fetus can arise from maternal health consequences of infection, particularly if the pathogen causes symptoms such as a high fever, anemia, or obstetric complications such as premature labor and delivery or maternal death.	
3. Prospect of immune protection from vaccine	» Based on data from clinical trials (phases 1 and 2) o Magnitude and frequency of immune responses o Correlate of protection (if known)	» Based on data from clinical trials (phases 2, 3, 4) o Magnitude and frequency of immune responses o Efficacy against disease endpoints relevant to pregnant women and their offspring o Correlate of protection (if known) o Special considerations relevant to pregnant women and their offspring (e.g., placental transfer of antibody; sterilizing immunity against pathogens that can infect fetus)

Table A: Considerations for Assessing Risks & Benefits of Including Pregnant Women in Vaccine Research & Delivery

Considerations	Specific Dimensions of the Consideration & Expanded Definition	
	Research Context	**Deployment Context**
	Data related to the magnitude and frequency of relevant immune responses may suggest that a vaccine candidate will protect against disease caused by the pathogen. Depending on the studies completed prior to large-scale efficacy trials, there may be more or less evidence that a vaccine will induce an adequate immune response. This can be especially true for vaccines being developed against emerging threats, given accelerated pathways for clinical testing that may differ from standard approaches. Data from prior studies, including pre-clinical and clinical trials that assess immunogenicity and other indicators of efficacy (e.g., challenge trials in non-human primates), will provide varying degrees of evidence about anticipated protective effects of a vaccine.	Indicators from prior studies, including pre- and post-licensure studies on immunogenicity, efficacy, and effectiveness, can provide information on the protective effects of a vaccine. There are efficacy indicators that may be particularly important during pregnancy — for example, sterilizing immunity may be required to fully protect against congenital Zika syndrome. Additionally, if immunogenicity studies have been done in pregnancy, this can further inform the anticipated protection a vaccine will confer and whether there are any clinically meaningful differences in how the vaccine performs in pregnant women.
4. Likelihood and severity of vaccine-associated harms to the pregnant woman or offspring	» Safety and reactogenicity o Based on data from prior studies of the specific vaccine candidate o Based on evidence from vaccines using similar platforms » Probability and severity of these harms may vary based on gestational timing of vaccine administration and may vary between pregnant woman and offspring (see below)	» Safety and reactogenicity o Based on data from prior studies of the specific vaccine candidate, including observational studies from previous deployments of the vaccine in response to past outbreaks o Based on evidence from vaccines using similar platforms » Probability and severity of these harms may vary based on gestational timing of vaccine administration and may vary between pregnant woman and offspring (see below)
	Maternal and Obstetric: Adverse events (AEs) following vaccine administration range from common mild events (e.g., transient arthralgia) to very rare severe events (e.g., Guillain-Barré syndrome, anaphylaxis). Data on the likelihood and severity of vaccine-associated AEs should be considered against the probability and magnitude of benefit of protection from the pathogenic threat. Available evidence informing whether the vaccine and/or the pathogen may increase the risk of pregnancy loss should also be considered. Offspring: Some vaccine candidates employ platforms and adjuvants with a long history of fetal safety. Others, like replication-competent vaccines, may raise particular concerns in pregnancy based on theoretical risks of the vaccine virus causing harm to the fetus. Although convincing evidence of fetal harm has only been demonstrated for smallpox vaccine (see Box 12), biological plausibility and potential fetal harms should be considered among other factors in the risk-benefit assessment for any vaccine platform. For many vaccine components and platforms, particularly novel ones like nucleic acid-based vaccines, there is limited evidence available on potential associated fetal harms. As the evidence base grows, the best available data should be used to assess the known likelihood and severity of congenital harms across candidate platforms.	

Table A: Considerations for Assessing Risks & Benefits of Including Pregnant Women in Vaccine Research & Delivery

Considerations	Specific Dimensions of the Consideration & Expanded Definition	
	Research Context	**Deployment Context**
5. Availability of safe and effective alternative prevention options	» Relevant considerations for alternative preventives o Safety (generally and in pregnancy) o Efficacy (generally and in pregnancy) o Durability, sustainability, and adherence factors o Availability and accessibility in the area(s) where research is being conducted	» Relevant considerations for alternative preventives o Safety (generally and in pregnancy) o Efficacy (generally and in pregnancy) o Durability, sustainability, and adherence factors o Availability and accessibility in the area(s) affected by the epidemic
	The availability and effectiveness of alternative forms of prevention will vary based on the type of epidemic threat and the context in which the outbreak is occurring. In some cases, there may be available and acceptable alternatives that pregnant women can use for prevention in an outbreak that may be preferable, depending how they compare to the vaccine. In other cases, the alternative prevention options may be inadequate or their availability may be limited, and receiving the vaccine may be preferable to relying on alternative strategies. In some instances, the best alternative preventative interventions for the general population may have well-established risks in pregnancy and should be avoided in favor of safer options.	
6. Availability of safe and effective treatment options	» Relevant considerations for treatments o Safety (generally and in pregnancy) o Efficacy (generally and in pregnancy) o Availability and accessibility in area(s) where research is being conducted	» Relevant considerations for treatments o Safety (generally and in pregnancy) o Efficacy (generally and in pregnancy)
	The existence, availability, effectiveness, and safety profiles in pregnancy of therapeutic options may influence assessments of whether study participation offers the prospect of net benefit. For certain emerging pathogens, there may not yet be any effective treatment. When treatments exist, they may not have evidence of safety, dosing, and efficacy for use in pregnancy — and in some cases, treatment options may be known teratogens. Even when safe and effective options exist, their availability within a given epidemic context may limited.	The existence, availability, effectiveness, and safety profiles in pregnancy of therapeutic options may influence assessments of whether pregnant women and their offspring are better off receiving or foregoing vaccination during an epidemic or outbreak. For certain emerging pathogens, there may not yet be any effective ways to treat the infection. When treatment options exist, they may not have evidence of safety, dosing, and efficacy in pregnancy – and in some cases, treatment options may be known teratogens. Even when safe and effective options do exist, their availability within a given epidemic context may be limited.

*Sources: Davey DJ et al., Risk perception and sex behaviour in pregnancy and breastfeeding in high HIV prevalence settings: Programmatic implications for PrEP delivery. PloS one. 2018 May 14;13(5):e0197143; WHO, Addressing sex and gender in epidemic-prone infectious diseases, 2007

RECOMMENDATION 22

When vaccines against emerging pathogens are not recommended for use in pregnancy, inadvertent vaccine exposures during pregnancy should be anticipated and mechanisms put in place for the collection and analysis of data from pregnant women and their offspring on relevant indicators and outcomes.

- **DIRECTED TO:** public health and regulatory authorities; vaccine manufacturers; national immunization programs; funders and sponsors

For most immunization efforts in response to outbreaks, women of childbearing potential will comprise a significant subset of the target population. Even when pregnant women are intentionally excluded from the vaccine response effort, it should be expected that some of the women who are vaccinated will be unknowingly pregnant at the time of vaccine administration or will become pregnant within a relevant window of its administration. Collecting data about outcomes in these women and their offspring in the midst of an active outbreak or epidemic will be difficult and costly. However, there are two sets of ethical and public health reasons why it is critically important to do so.

First, collecting data from unintentional exposures to vaccine in pregnancy during an outbreak or epidemic affords an important opportunity to gather evidence about novel vaccine technologies and thus to help ensure that pregnant women are not left behind as vaccine technology advances. Gathering data from women who are unknowingly pregnant when they receive vaccine and subsequently from their offspring could be critical and uniquely informative to building an evidence base on safety and efficacy in pregnancy of novel vaccine technologies, given that these data may be difficult to otherwise obtain. For example, studies of oral cholera vaccine given to women unintentionally during pregnancy in Bangladesh, Guinea, Malawi, and Zanzibar were instrumental in establishing the safety profile of the vaccine in pregnancy and shifting the WHO recommendation in support of including pregnant women in oral cholera vaccine campaigns.[160]

The second set of reasons has to do with the importance of having evidence for both personal and clinical decision-making about the likelihood and nature of any risks to pregnant women or their offspring associated with vaccine administration in early pregnancy. Research and public health communities have a responsibility to pursue evidence that will allow for the best possible counseling on the implications of unintentional exposures during pregnancy. The price of ignorance in the face of unintended exposures is significant. We know from the experience with live-attenuated rubella vaccines that hundreds of women inadvertently exposed during pregnancy chose to terminate their pregnancies, presumably due to concerns about unknown fetal harm.[74,161,162,163] Yet worries about vaccine-associated congenital rubella syndrome turned out to be unfounded, with not a single case documented from thousands of unintentional exposures worldwide.[123] Furthermore, pregnant women who are vaccinated prior to finding out they are pregnant will want to know not just whether the vaccine is safe, but how likely it is that the vaccine they received will protect them and their fetus from infection. Such information may guide decisions about how aggressively to pursue other protective measures and whether they should receive another dose of vaccine after delivery to ensure protection in future epidemics.

Box 14: Active and Passive Vaccine Surveillance Systems to Advance the Evidence Base on Vaccines in Pregnancy

Existing vaccine surveillance programs for monitoring adverse events following immunization (AEFI) can be useful tools to study both intentional and unintentional vaccine administrations in pregnancy (Recommendations 19 and 22). Various countries and regions have mandatory requirements for passive reporting of any adverse events potentially associated with immunization, including the U.S. Vaccine Adverse Event Reporting System (VAERS), the EU EudraVigilance, and the Chinese National AEFI Information System (CNAEFIS). Although the ability to draw conclusions from passive surveillance systems is limited due to potential reporting bias and unknown denominators, these systems can serve as important mechanisms to identify safety signals for vaccination in pregnancy that require further study. They are especially useful and cost-effective for monitoring vaccines over the longer term, enabling the detection of rare adverse events that may occur in a very small percent of the vaccinated population. These passive surveillance systems can be leveraged to enhance the evidence base on vaccine use in pregnancy by adding more targeted questions about pregnancy status, gestational timing of immunization, and pregnancy-specific outcomes to the data collection forms.

For newer vaccines, active surveillance mechanisms can be critical tools to build upon pre-licensure safety data once the vaccine is introduced to the broader population, without some of the methodological shortcomings inherent in passive systems. In the U.S., various active vaccine surveillance programs, such as the Post-Licensure Rapid Immunization Safety Monitoring (PRISM), Vaccines and Medications in Pregnancy Surveillance System, and Vaccine Safety Datalink, are being used to build the safety profile of vaccines in pregnancy.[164,165,166] The example of PRISM also highlights the potential benefits of strengthening health information systems and how growing use of electronic medical records can enhance post-market studies—including those focused on safety in pregnancy. In recent years, there has been increasing focus on the systematic surveillance for AEFI for pregnant women and their offspring.[167,168,169,170] A recent global survey identified 11 active surveillance systems across countries in various income brackets and geographic regions to detect serious AEFI in pregnant women or their infants, with 4 of these systems specifically focused on inadvertent vaccine administrations in pregnancy.[169]

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Executive Summary: Polio

Background

The polio eradication program in 2018 has continued to strive for eradication of Wild Poliovirus Type 1 (WPV1) endemic areas. In 2018, as of 4 September 2018, 15 WPV1 cases have been reported worldwide (12 in Afghanistan, 3 in Pakistan), compared to 10 for the same period in 2017 (6 in Afghanistan, and 4 in Pakistan). In addition to WPV1 detected from paralyzed persons, WPV1 continued to be found in environmental samples: 64 samples in Afghanistan and 91 in Pakistan in the past 12 months. In Nigeria, there has been no detection of WPV1 since September 2016. No cases of WPV3 have been reported globally since November 2012.

Regarding circulating vaccine derived polioviruses (cVDPVs), there have been several outbreaks detected in the last 12 months: the most significant were cVDPV2 outbreaks in Nigeria, Democratic Republic of Congo (DRC), and the Horn of Africa. There has been a total of 10 separate cVDPV2 outbreaks detected since the tOPV to bOPV switch (April 2016) affecting 6 countries. In addition to cVDPV2, in 2018 a cVDPV1 outbreak has been detected in Papua New Guinea, and a cVDPV3 outbreak detected in Somalia. The remaining challenges to final eradication and cVDPV2 control are:

- Access issues in Pakistan and Afghanistan. In Afghanistan, transmission of wild poliovirus in the Northern and Southern transmission corridors has not been interrupted, with circulation maintained in Kandahar Province for more than 1 year. This ongoing transmission in the Southern & Eastern regions is mainly due to inaccessibility and a security ban on house to house campaigns in Kandahar Province, with approximately 1.3 million children inaccessible during the August 2018 campaign.

- Circulation of cVDPV in DRC is spreading to areas with conflict and bordering other countries.

The current Polio Eradication and Endgame Strategic Plan 2013-2018 will be extended through 2019. A new strategic plan and budget will be developed for the period 2019-2023 and funding will need to be secured.

The independent monitoring board (IMB) has completed an external review of the programme in the 3 endemic countries and the findings will be presented in September 2018, in London.

Purpose of the session and summary

This session will consist of three presentations: (1) global epidemiological overview, (2) report from the “Independent Evaluation Board” of the eradication program in Afghanistan, Pakistan and Nigeria; and (3) report from deliberations of SAGE Polio Working Group.

For this SAGE meeting, there are no items for endorsement but rather for information and discussion. The SAGE members will be invited to comment on the progress of polio eradication and on challenges and strategies to overcome the remaining obstacles to achieving final eradication.

SAGE members will also be invited to comment on the conclusions and recommendations of the IMB report.

As part of the SAGE WG presentation, an "Appraisal of Options for Certification of Global Poliovirus Eradication" will be introduced. This appraisal is one of the background documents to SAGE and discusses options for considering cVDPV status in the final declaration of WPV eradication. SAGE members will be invited to comment on the different options while understanding that the final decision on the requirements for certification lies with the Global Certification Commission.

Background documents in the yellow book

- Report from meeting of SAGE WG on polio (held on 4-5 September 2018)
    - This report provides summary of the deliberations of the SAGE WG

- Draft "Options appraisal for certification of polio eradication"
    - The document addressed the advantages and disadvantages of different options for certification of polio eradication (whether to limit the scope of certification only to the interruption of transmission of WPV alone or whether cVDPV should also be considered)

Background documents on the web

- Report by the Independent Monitoring Board (IMB) on polio eradication program evaluations in Pakistan, Afghanistan and Nigeria
    - This document will provide an assessment of the program from IMB's field mission to the remaining endemic countries

04-05 September 2018

16th Meeting of the SAGE Polio Working Group

Conclusions and recommendations

Note for the Record

World Health Organization

Background

The 16th face-to-face meeting of the SAGE Polio Working Group (WG) was held on 04-05 September, 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 review the GPEI programme update, including VDPV epidemiology and IPV supply
2. To provide inputs into draft options appraisal for certification of eradication
3. To discuss "readiness criteria" for bOPV withdrawal
4. To review Containment Breach Protocol
5. To review scientific data and availability of ID devices (adaptors and needle-free devices); and discuss guidance on use for the program
6. To review Hexavalent landscape analysis (for information)
7. To review country-based assessment of risk of poliovirus re-emergence

Minutes of the meeting and SAGE WG recommendations

Polio Eradication – Global Update

The WG reviewed the global epidemiology of wild poliovirus (WPV) and circulating vaccine derived polioviruses (cVDPV).

The public health emergency of international concern for poliomyelitis was re-confirmed on 15 August 2018.

In 2018, as of 4 September 2018, 15 WPV1 cases have been reported worldwide (12 in Afghanistan, 3 in Pakistan), compared to 10 for the same period in 2017 (6 in Afghanistan, and 4 in Pakistan). In addition to WPV1 detected from paralyzed persons, WPV1 continues to be found in environmental samples: 64 samples in Afghanistan and 91 in Pakistan in the past 12 months. In Nigeria, there has been no detection of WPV1 since September 2016. No cases of WPV3 have been reported globally since November 2012.

Regarding cVDPVs, there have been several outbreaks detected in the last 12 months: the most significant were cVDPV2 outbreaks in Nigeria, Democratic Republic of Congo (DRC), and the Horn of Africa (Table 1). There has been a total of 10 separate cVDPV2 outbreaks detected since the tOPV to bOPV switch (April 2016) affecting 6 countries. In addition to cVDPV2, in 2018 a cVDPV1 outbreak has been detected in Papua New Guinea, and a cVDPV3 outbreak detected in Somalia (Table 1).

Country	Wild poliovirus		cVDPV2		cVDPV3		cVDPV1	
	Onset most recent case	Total WPV1	Onset most recent case	Total cVDPV2	Onset most recent case	Total cVDPV3	Onset most recent case	Total cVDPV1
Nigeria	NA	0	27-Jul-18	8	NA	0	NA	0
DRC	NA	0	22-Jul-18	26	NA	0	NA	0
AFR	**NA**	**0**	**27-Jul-18**	**34**	**NA**	**0**	**NA**	**0**
Pakistan	18-May-18	6	NA	0	NA	0	NA	0
Afghanistan	17-Jul-18	20	NA	0	NA	0	NA	0
Syria	NA	0	21-Sep-17	4	NA	0	NA	0
Somalia	NA	0	10-Jul-18	3	23-May-18	3	NA	0
EMR	**17-Jul-18**	**26**	**10-Jul-18**	**7**	**23-May-18**	**3**	**NA**	**0**
PNG	NA	0	NA	0	NA	0	29-Jul-18	9
WPRO	**NA**	**0**	**NA**	**0**	**NA**	**0**	**29-Jul-18**	**9**
Global	**17-Jul-18**	**26**	**27-Jul-18**	**41**	**23-May-18**	**3**	**29-Jul-18**	**9**

Table 1: Global wild poliovirus cases and cVDPV cases[1], in previous 12 months[2], NA: Not applicable

[1]Excludes viruses detected from environmental surveillance

[2]Onset of paralysis 05 Sep. 2017 – 04 Sep. 2018

The SAGE WG was informed of the challenges to final eradication and cVDPV2 control:

- Access issues in Pakistan and Afghanistan. In Afghanistan, transmission of wild poliovirus in the Northern and Southern transmission corridors has not been interrupted, with circulation maintained in Kandahar Province for more than 1 year. This ongoing transmission in the Southern & Eastern regions is mainly due to inaccessibility and a security ban on house to house campaigns in Kandahar Province, with approximately 1.3 million children inaccessible during the August 2018 campaign.
- The cVDPV2 outbreak in DRC is of high concern as circulation is spreading to areas with conflict and bordering other countries. All efforts are to control this outbreak before the rainy season, with 2 SIAs planned, targeting 16 provinces in September and October 2018. Initially, the DRC government was slow to respond, as resources in the national health system have been stretched with concomitant outbreaks of Ebola virus disease, cholera and other infectious diseases in 2018. However, the GPEI and other international agencies have responded by deploying surge staff to the affected areas.

The current Polio Eradication and Endgame Strategic Plan 2013-2018 will be extended through 2019. A new strategic plan and budget will be developed for the period 2019-2023 and funding will need to be secured. The independent monitoring board (IMB) has completed an external review of the programme in the 3 endemic countries and the findings will be presented in September 2018, in London.

WG discussion:

– The WG emphasized that although the program has not reached an end to the circulation of endemic wild poliovirus type 1 and cVDPVs, we should not lose sight of what has been achieved. Specifically highlighted were:

    - WPV1 transmission is limited to a few endemic zones, with no spread of virus out of active transmission corridors between Afghanistan and Pakistan.
    - The surveillance has become more sensitive, especially because of the expansion of environmental sampling.
    - The progress in reducing the number of unreached children in Nigeria from 600,000 in 2016 to 200,000 in 2018, in a context of continuing high insecurity.
    - The exceptional response and apparent successful control of the cVDPV2 outbreak under very difficult circumstances in Syria.
- The working group expressed concern over reaching children in countries with inaccessible areas, which is essential to achieving the interruption of WPV. This concern was specifically stressed for Afghanistan and Nigeria.
- The WG viewed the development of the new strategic plan for GPEI (to cover the period 2019-2023), as an opportunity to strengthen strategic coordination and collaboration between GPEI, EPI and GAVI. There was consensus that to improve immunisation, we need to work across disease disciplines to strategically develop a primary healthcare system that can deliver high routine immunization coverage in those developing countries with the majority of under-vaccinated children. Better functioning primary healthcare systems can then serve as the basis for delivering specific health goals such as polio eradication or measles elimination. All partners and stakeholders must work together to help these priority countries take ownership for developing their primary healthcare systems.
- The WG discussed the poliovirus surveillance in a post-certification era and emphasised that preserving the functionality and high sensitivity of surveillance is critical during the transition.

Polio Vaccine Supply – Update as of September 2018

The WG was presented with an update on the IPV, mOPV1 and mOPV2 supply and stockpile outlook. Due to delays in manufacturer's scaling up production to meet committed quantities, 33 countries procuring IPV vaccines through UNICEF were unable to access IPV supply since the switch from tOPV to bOPV: 18 countries did not have access to IPV for routine introduction and 15 countries had supply interrupted post introduction.

In 2018, supply will meet UNICEF demand for at least 1 IPV routine immunization dose in all OPV using countries (85 countries) and two million doses for IPV full dose use in endemic zones to accelerate WPV eradication. However, other needs will not be met: such as for SIAs outside of endemic zones of around 3 million doses (e.g. Syria and Ukraine for campaigns, Uganda and Rwanda for refugee populations) and catch up of around 43 million doses (across 33 countries) to provide at least one dose of IPV to the cohorts of children that had been missed due to supply shortages.

There is a rich pipeline of manufacturers, with 9 new manufacturers expected to have their IPV WHO pre-qualification by 2022. UNICEF expects some additional supply by the end of 2019 from new supplier(s) and that total IPV supply will be sufficient to meet a 2-dose

schedule globally in 2023. With the increase of available manufacturers, the price of IPV should decrease.

Regarding mOPV1 production, following the June 2018 TAG meetings in Pakistan and Afghanistan, mOPV1 is planned to be used for some SNIDs. However, there are no contracts established with vaccine manufacturers. UNICEF has explored options to secure mOPV1 for immediate requirements of 23.7 million doses (2018). Due to i) production lead times and ii) licensure requirements in Pakistan, only one manufacturer can supply. While the full requirements can be met, supply of bOPV will be reduced with the same quantity.

The WG was updated on the mOPV2 stockpile availability. There is currently only one supplier for finished product: the 269 million doses of bulk under contract is fully used and the programme is accessing bulk outside of contract which will allow 45 million doses to be available for July 2019. Final discussions are ongoing with a second supplier for mOPV2 in finished presentation.

WG discussion:

- The WG discussed that the programme needs to establish clear communication with vaccine manufacturers and develop a supply requirements plan, especially if mOPV1 is to be reintroduced into the program outside endemic countries.
- Countries receiving mOPV2 for outbreak response need better accountability and better systems to be put in place for retrieving mOPV2 vials after SIAs.

Appraisal of Options for Certification of Global Poliovirus Eradication

In April 2018, the chairs of the expert committees, which advise and support the GPEI requested the Secretariat of the Global Certification Commission (GCC) to prepare an appraisal of options for certification of global poliovirus eradication. The document presented to the SAGE WG addressed the advantages and disadvantages of different options. The Options Appraisal will be considered by the GCC at its meeting in October 2018.

Options 1A and 1B limit the scope of certification only to the interruption of transmission of WPV alone and differ by whether to consider cVDPV status in the final declaration of WPV eradication. Both include a separate process for validating the absence of VDPVs. Option 2 proposes to frame the concept of certification as a multi-stage process including all polioviruses.

WG discussion:

- The WG welcomed the certification options appraisal as a suitable tool for reviewing the criteria for certification of eradication of polioviruses.
- The WG recalled that the 1988 World Health Assembly (WHA) resolution called for the global eradication of poliomyelitis, with later consideration that the certification of eradication referred to wild polioviruses: “elimination of indigenous wild polio virus transmission”; however, since then VDPVs have been recognized as viruses capable of establishing circulation. The WG agreed that the GCC should respond to the present

circumstances acknowledging the challenge of certifying absence of cVDPVs in the development of eradication certification criteria. The “absence of cVDPVs” denotes that no VDPV is being transmitted anywhere, and that all VDPVs are under containment.

- Through interactive discussion, the WG provided input into the appraisal paper, with the chair of the GCC in attendance. The 3 presented options and additional ones will be reviewed by the GCC in October 2018.

Certification of Wild Poliovirus Type 3

The GCC had proposed using the certification of WPV3 eradication as a trial run of final certification of polio eradication. Following the completion of the Options appraisal (above), the GCC Chair undertook a review of the strengths and weaknesses of sequential certification of WPV3 followed by WPV1 with a potential roadmap to certification of eradication.

The WG was presented with data on WPV3 epidemiology over the past decade. There has been no WPV3 detected through AFP or environmental surveillance globally since November 2012. During the same period, poliovirus surveillance efforts have increased in most high-risk areas. Since the last detected WPV3 cases in April 2012 in Pakistan and November 2012 in Nigeria, there have been over 150,000 and 92,000 samples, respectively, from AFP cases that have tested negative for WPV3 across AFRO and EMRO, while all other WHO Regions have obtained Regional Certification of absence of WPVs including WPV3.

The global certification of WPV3 eradication might be possible in 2019. This could be followed by the cessation of OPV3 use, further reducing the risk of VAPP and VDPV3, and creating the potential to validate disappearance of VDPV 2&3 by 2021.
The GCC will consider the option of sequential certification at its meeting in October 2018.

WG discussion and recommendations:

- The WG recognized that WPV3 is unlikely to be currently circulating and it is a valid option to work on certifying eradication of WPV3 ahead of WPV1 certification. The WG agreed that this could energize the programme and highlight progress.
- The WG considered the programmatic and ethical reasoning to move from bOPV to mOPV1, and recommended that advantages and disadvantages of such switch should be articulated. However, the Director of WHO’s Polio Department emphasized that certification of eradication of WPV3 does not automatically mean there has to be switch from bOPV to mOPV1. There is strong concern that the programmatic and communications implications of yet another switch might overwhelm the program.
- It was noted that a potential benefit of withdrawing OPV3 and validating the disappearance of cVDPV3 sooner would be to complete these activities before GPEI is reduced as a consequence of its winding down.

The Public Health Management of Facility-Based Exposure to Live Polioviruses

The safe containment of polioviruses is one of the objectives of the Polio Eradication and Endgame Strategic Plan 2013-2018, and the GAP III protocol describes the necessary conditions for poliovirus containment and requirements for safe handling of polioviruses in designated poliovirus-essential facilities (PEF).

The WG was presented with a draft Containment Breach Protocol, which has been developed to provide guidelines for a public health response to a human exposure or infection related to a breach of poliovirus containment. This protocol is primarily aimed at PEF hosting countries.

The main components and strategies used in the response to a breach of containment and prevention of potential establishment of further transmission include: risk assessment, isolation/quarantine of exposed persons and their family and contacts, infection control and disinfection, targeted vaccination, and intensification of surveillance.

For each country with PEF, it is necessary to consider what public health measures can be implemented within their existing national regulations.

WG discussion and recommendations:

- The WG was comfortable with the approach taken. The document could provide guidance for countries to develop specific protocols in the context of national legislation.
- The WG agreed that the document needed to be further refined and should be presented to SAGE WG for endorsement during its next meeting in early 2019.
- The WG highlighted some specific comments on sections of the guidelines, including:
    - The protocol should include recommendations about use of antiviral therapy.
    - The importance of communication strategies around breaches and ensuring the privacy of exposed persons in question should be highlighted in the protocol.
    - The WG suggested to include a clause in work-contracts for staff of PEFs, that a certain requirement or process would need to be followed if they are exposed to PVs.

Readiness Criteria for bOPV Withdrawal

In September 2017, the SAGE WG endorsed the concept of developing trigger and readiness criteria for bOPV withdrawal and proposed to continue discussions over the next 12-18 months.

The withdrawal trigger was stated as the certification of wild poliovirus eradication, followed by 4 readiness criteria:

1. Adequate population immunity, especially in high-risk communities
2. No poliovirus type 2 outside of containment

3. No persistent cVDPV1 or 3 circulation (circulation beyond the six months after the first notification)
4. Availability of sufficient IPV supply for all countries to adopt two IPV dose schedule (either IM or ID)

The proposed revised criteria removed #2 (no poliovirus type 2 outside of containment) because of iVDPV2 chronic excretors, and added criteria on iVDPV surveillance and management:

- Surveillance for PIDs established
- Therapeutic options for clearing infections among iVDPV available

WG discussion and recommendations:

- The WG agreed that the readiness criteria still serve a useful purpose.
- The WG agreed with the need for additional criteria for PID surveillance, with input expected to be provided from the iVDPV WG
- The WG emphasized that we need to ensure we learn from lessons of the tOPV to bOPV switch before bOPV withdrawal
- Regarding the planning and activation timeline, there was agreement:
    - The trigger point for withdrawal of bOPV is GCC certification, and should plan to withdraw 6-18 months after certification.
    - The programme needs to start planning for withdrawal well in advance of certification.
    - Possible early certification of WPV3 and its implications need to be considered
    - Potential regional withdrawal of bOPV could be considered

IPV Allocation Options for 2019-2020

The UNICEF IPV supply availability for 2019 is 71,650,000 doses. This exceeds the estimated requirement to cover routine immunization needs of 64,183,000, by an excess of 7,467,000 doses, however, other requirements for IPV outside of routine immunization include:

- SIAs with IPV planned in endemic countries in 2019: 5.9 million doses
- Request from Nigeria for fIPV use for cVDPV2 response: 1.6 million doses
- Additional doses for SIAs in outbreak countries/refugees: 3 million doses
- Approximately 42 million doses needed for catch-up campaigns to cover cohorts of children missed due to IPV shortage in Tier 3 and 4 countries,

An assessment conducted by Imperial College London for country prioritization of IPV catch-up immunization was presented.

SAGE WG was asked:

- Whether the allocation principles still apply
    1. Ensure routine requirements for all countries is met
    2. Requirements for objective 1 (eradication of WPV) are fully covered

3. After meeting these two requirements doses can be allocated for catch up immunization

- How to treat additional requests (Refugees in Rwanda & Uganda; catch up immunization in older age groups, Ukraine and Syria; etc)
- To reconfirm that IPV should not be used as a primary tool in response to cVDPV2

WG discussion and recommendations:

- WG members agreed with the prioritization order for IPV allocation as follows:
  1. Ensure that routine immunization needs in all countries are met. At the same time, ensure quarterly periodic (for example quarterly) national and sub-national monitoring of IPV supply and use.
  2. Ensure requirements for the acceleration of the interruption of wild poliovirus transmission are fully met (requests from endemic countries for SIAs to interrupt WPV)
  3. After these 2 requirements, excess doses should be allocated to populations that are IPV-unvaccinated since the switch, based on risk assessment

- SAGE WG emphasized that in the current climate of IPV supply constraints, countries need more accountability of IPV stock in the country. The WG expressed concern regarding Nigeria's request for additional IPV, when the country has received sufficient IPV to meet their birth cohort, yet coverage is only 42%. This highlighted the issue of requesting additional IPV supplies without adequate accounting of the supplies already received. SAGE recommended that countries provide periodic national and sub-national level reports of IPV stock, both for routine immunisation as well as for SIAs.
- Refugee groups were highlighted as an important group in requirement (3) that may be IPV-unvaccinated since the switch. SAGE WG recommended that a risk-ranking is conducted for refugee populations based on country of origin.
- Countries using fIPV should be prioritized for supply.
- The SAGE WG re-endorsed their previous statement on use of IPV (or fIPV) to control cVDPV2 outbreaks (from 15th SAGE WG meeting: *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.*)

Needle-free injector for administration of fIPV (Tropis): Review of field experience and immunogenicity data AND Prioritization of Tropis devices

WHO recently prequalified Tropis for delivery of intradermal vaccines including fractional IPV (fIPV), 0.1 ml volume. SAGE WG was presented with existing data from use of Tropis in pilot campaigns and immunogenicity studies. In summary, the data from Pakistan, Cuba and Gambia confirmed that Tropis is a device that is feasible to use in a vaccination campaign. It

provides for better comfort for children, is quicker to use than tradition BCG needle and syringe and is easy to train.

In Gambia, the number of doses per vial and the total storage and weight per 1,000,000 vaccinations were for BCG needle and syringe, ID adapter, and Tropis respectively: 50 doses per vial, 24.3m^3 and 3,477kg; 57 doses per vial, 89.0m^3 and 13,197kg; and, 63 doses per vial, 80.5m^3 and 6, 423kg.

In terms of immunogenicity, the studies in Gambia and Cuba concluded that the seroconversion rates achieved with fIPV administered with Tropis are non-inferior to those achieved with BCG needle and syringe.

Current procurement of Tropis will secure 5,000 devices (1 device ~20,000 doses), 5,000,000 disposable syringes and 1,000,000 vial adapters by April 2019. This would allow for ~2.5 million children to receive 2 doses of fIPV using Tropis.

When prioritizing the use of Tropis, the following criteria were suggested:

- Regulatory environment for use of fIPV
- Size of population
- Risk level

Economic analysis of campaign delivery of fIPV was presented. In this analysis, Tropis was the most expensive method for intradermal administration of fIPV, however it was still cheaper than using full dose IPV. Economic analysis of fIPV delivery was developed by PATH.

WG discussion and recommendations:

- SAGE WG emphasised that the performance and pre-qualification of Tropis device was an exciting development which could have applicability to other antigens.
- SAGE WG suggested that it is important to gain more implementation experience both in routine and campaign settings to guide future policy; this should be well documented.
- Tropis device should initially be allocated where it makes most programmatic sense and using the above proposed criteria; evaluation of use should be carried out at all times.
- SAGE WG added that the Immunization Practices Advisory Committee (IPAC) should be consulted.

IPV and Hexavalent Supplier Landscapes and Country-Based Assessment of Risk of Poliovirus Re-emergence for Gavi's post-2020 IPV considerations

In 2013, the GAVI Board decided to support introduction of IPV as part of GPEI's Endgame Strategy (2013-18) to facilitate the introduction of a single dose of stand-alone IPV into routine immunisation schedules in 71 GAVI countries. Substantial supply of whole cell pertussis hexavalent vaccine (wP -hexavalent) is expected in 2023-24, with one licensed product currently available and four other manufacturers' products in development. This

will provide options of how IPV antigens are introduced into routine immunisation schedules, and the logistical and programmatic advantages for wP-hexavalent versus pentavalent + IPV were presented.

The objectives of GAVI's review of wP-Hexavalent strategic position were presented:

- Analyse the parameters relevant to the potential value of wP-Hexavalent in the context of Gavi's support of the global polio eradication initiative (GPEI)
- Describe the decision pathways that Gavi would need to follow to potentially support the procurement of wP-Hexavalent
- Integrate programmatic, financial and supply considerations related to wP-Hexavalent into the overall Vaccine Investment Strategy (VIS) investment case to be presented to the Board for decision-making in November 2018

In accordance with GAVI'S next strategic period 2021-2025, the Gavi Board had agreed that any investments in IPV beyond 2020 should be considered as part of Gavi's periodic Vaccine Investment Strategy (VIS) to be presented at the end of 2018. The Board recommended that a tailored assessment approach be applied given IPV's low impact in terms of traditional metrics (i.e., lives saved and value for money) yet unique role in mitigating the re-emergence of poliovirus. In recognition of this, Gavi and WHO have developed a risk assessment to categorise countries as high, medium or low risk for poliovirus re-emergence, which has been stratified by country ability to co-finance vaccine cost.

WG discussion and recommendations:

- The WG welcomed the progress with wP-hexavalent vaccine and increasing options for IPV delivery into routine immunisation schedules.
- The WG welcomed Gavi support to help countries secure IPV.
- The WG were comfortable with the methodology and purpose of the risk assessment model that has been developed by Gavi and WHO. The WG suggested that the model should be periodically evaluated and updated.
- The WG expressed concern over the group of middle-income countries that are assessed as having a high-risk for polio re-emergence but are in Gavi-transition or fully-self-financing groups.

World Health Organization

16th Meeting of the SAGE Polio Working Group (WG)

Salle D, WHO, Geneva

September 4-5, 2018

AGENDA

Expected outcomes of the meeting:

1. To review the GPEI programme update, including the VDPV epidemiology and IPV supply situations
2. To provide inputs into draft options appraisal for certification of eradication
3. To discuss "readiness criteria" for bOPV withdrawal
4. To discuss Containment Breach Protocol
5. To review scientific data and availability of ID devices (adaptors and needle-free devices); and discuss guidance on use for the program
6. To review Hexavalent landscape analysis (for information)
7. To review country-based assessment of risk of poliovirus re-emergence

Day 1 (Sept 4)

09:00 - 09:15	Welcome and opening remarks	WG Chair
09:15 - 10:30	Programme update • Progress toward interruption of WPV and cVDPV2 • Progress with the other objectives of the Polio Eradication and Endgame strategic plan	M. Zaffran, WHO
	IPV Supply update and update on mOPV stockpiles (10 mins)	A. Ottosen , I. Lewis
10:30 – 11:00	**Coffee break**	
11:00 - 11:30	Presentation of draft options appraisal for certification of eradication	B. Burkholder
11:30 – 12:00	***Discussion***	
12:00 – 12:30	WPV3 certification of eradication "dry run"	D. Salisbury
12:30 - 13:30	**Lunch**	

13:30 – 14:30	Presentation of draft Containment Breach Protocol ***AND Discussion***	G. Tallis
14:30 – 15:30	"Readiness criteria" for bOPV withdrawal ***AND Discussion***	R. Sutter
15:30 – 16:00	**Coffee break**	
16:00 – 17:00	Discussions and wrap up of the day *(Working Dinner Restaurant: Cafe du Soleil, topic: plan for 2019-2023)*	

Day 2 (Sept 5)

9:00 – 9:30	IPV allocation options	A. Ottosen , I. Lewis
9:30 – 10:00	Tropis: Review of field experience and immunogenicity data	O. Mach
10:00 – 10:30	Prioritization of Tropis devices in the context of Tropis availability and IPV supply	J. Vertefeuille
10:30 – 11:00	**Coffee break**	
11:00 – 11:30	Hexavalent landscape analysis	D. Hein
11:30 – 12:00	Country-based assessment of risk of poliovirus re-emergence	S. Sosler
12:00– 12:30	Discussions	
12:30 - 13:30	**Lunch break**	
13:30 - 16:00	Closed session: Finalizing WG recommendations (Continued; **Coffee break at 15:30)**	WG members WHO secretariat

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Background materials that will be shared with WG members at least 2 weeks prior to the meeting:

- Draft options appraisal for certification of eradication
- Draft Containment Breach Protocol
- Draft Country-based assessment of risk of poliovirus re-emergence

List of Participants
16th Meeting of the SAGE Polio Working Group
4 – 5 September 2018
WHO-HQ, Salle D

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Appraisal of options for certification of global poliovirus eradication

The chairs of the committees which advise and support the Global Polio Eradication Initiative (GPEI) met on 16 April 2018 to harmonize and align the various committees' functions in the lead up to certification of WPV eradication[1]. As follow-up to the meeting, the chairs requested the secretariat of the Global Commission for the Certification of Polio Eradication (GCC) to prepare an appraisal of options for certification of global poliovirus eradication, particularly with respect to the relationship between wild poliovirus (WPV) eradication and circulating vaccine-derived poliovirus (cVDPV).

This paper presents options for consideration along with possible advantages/risks of each option, including the relative impact that each will have on the timeline and process of certification. Options 1A and 1B limit the scope of certification only to WPV and differ by whether to consider cVDPV status in the final declaration of WPV eradication. Both options include a separate, future process for validating the absence of VDPVs. Option 2 proposes to expand the concept of certification to a multi-stage process including all polioviruses.

A core assumption underlying the options is a distinction between the concepts of *certification* vs *validation of absence*. As has been the case to date for regional and type 2 global eradication considerations, *certification* implies a high degree of certainty that specific criteria have been met. Although providing an absolute guarantee of eradication would be problematic, modeling can provide some probabilities of undetected transmission which provide confidence in making such a determination. [2] Due to unknowns about transmission and/or substantial challenges to meeting certain criteria, *validation of absence* implies a lower level of certainty. This determination also does not guarantee zero transmission, but, reflective of a lower level of confidence, may be considered to denote elimination of a public health problem (e.g. like MNT). This paper does not attempt to provide all the details of the criteria expected to be met in order to declare either *certification* or *validation of absence*.

All the proposed options could include sub-options to sequentially address certification of first type 3 and then type 1.

General links between certification of eradication and containment are noted below. However, due to complexities of the interaction and the ongoing evolution of containment implementation, this paper does not attempt to provide specific details. Further relevant information on containment is provided as background in Annex 2.

[1] See Meeting Note. *Building consensus for certification of poliovirus eradication: meeting of the chairs of the committees with advice and support the GPEI*. Geneva, 16 April 2018.
[2] Eicher M, Dietz K. Eradication of poliomyelitis: when can one be sure that polio virus transmission has been terminated? Am J Epidemiol. 1996;143(8)816-22.

Proposed Options

1A - Certification of eradication based on the interruption of transmission of WPV alone followed later by separate process to validate the absence of VDPVs

1B - Certification of eradication based on the interruption of WPV transmission, with consideration of the context of ongoing or recent cVDPV outbreaks, followed later by separate process to validate the absence of VDPVs.
Proposed context at GCC meeting in Feb 2018:

- *Consider all types of cVDPV*: No detection of a persistent cVDPV2 outbreak from any population source in the previous 18* months; and no detection of a cVDPV 1 or 3 outbreak from any population source in the previous six* months.

Or (newly proposed for this paper):

- *Consider only types 1/3*: No detection of a cVDPV 1 or 3 outbreak from any population source in the previous six* months
  *time frame could be further discussed

2 – Certification of eradication in two stages: Stage 1 based on interruption of WPV transmission; Stage 2 based on evidence of no new VDPV emergence or circulation following OPV cessation.

Background--prior definitions of certification of eradication

Global

The 1988 World Health Assembly (WHA) resolution[3] calling for the global eradication of poliomyelitis by 2000 referred only to WPV eradication. While the potential impact of VDPVs may not have been appreciated at the time of the initial resolution, later relevant WHA documents in 2012 and 2015 specifically highlighted WPV eradication and directly referred to cVDPV only in the context of heightened surveillance.[4]

Consistent with this perspective, the initial meeting of the GCC in 1995 defined eradication as "eradication of all wild polioviruses".[5] Following the first confirmed outbreak of cVDPV on the island of Hispaniola in 2000, the GCC in 2001 re-affirmed that its objective was "to certify eradication of wild poliovirus, including completion of the containment process" , but also recognized " that the full benefits of polio eradication will only be realized in the absence of VDPV circulation" and called on WHO to " develop a process for verifying the absence of VDPV circulation after certification of wild poliovirus eradication."[6]

[3] http://www.who.int/ihr/polioresolution4128en.pdf
[4] See http://apps.who.int/gb/ebwha/pdf_files/wha65/a65_r5-en.pdf and http://polioeradication.org/wp-content/uploads/2016/07/A68_R3-en.pdf
[5] Report of the 1st meeting of the Global Commission for the Certification of the Eradication of Poliomyelitis. Geneva: World Health Organization; 1995. WHO document WHO/EPI/GEN/95.6.
[6] Report of the 6th meeting of the Global Commission for the Certification of the Eradication of Poliomyelitis. Geneva: World Health Organization; 2001. WHO document WHO/V&B/01.15.

An overview of the global certification process published in the Bull WHO in 2004[7] summarized the main criteria set by the GCC and noted the prerequisites for global polio-free certification included the absence of **wild** poliovirus, isolated from cases of acute flaccid paralysis (AFP) (suspect polio), healthy individuals, or environmental samples, in all WHO regions for a period of at least three years in the presence of high- quality, certification-standard surveillance; and the containment of all **wild** poliovirus stocks in laboratories through completion of the requirements of the WHO global action plan for laboratory containment of wild polioviruses.

The 2015 GCC declaration that WPV2 had been eradicated worldwide did not consider the presence or absence of cVDPV2 (i.e. consistent with option 1A). However, the declaration was a pre-condition to OPV2 withdrawal, which also was dependent on cessation of persistent cVDPV2 (defined as circulation for greater than six months). Implementation of containment under GAPIII was not included as a pre-requisite for the declaration but was initially considered a criterion for tOPV withdrawal.

In February 2018[8], the GCC re-examined its procedures and recommended the following criteria for certification of WPV eradication:

- No WPV transmission detected from any population source for the previous three years,
- Adequate global poliovirus surveillance
- Safe and secure containment of WPV retained in facilities, such as laboratories and vaccine manufacturing facilities

Additionally, the GCC recommended that the announcement of the eradication of WPV should take into consideration the epidemiology of cVDPVs at that time with the following conditions (reflected in Option 1B):

- No detection of a persistent cVDPV2 outbreak from any population source in the previous 18 months; and
- No detection of a cVDPV 1 or 3 outbreak from any population source in the previous six months.

Regional

Certification of four WHO regions as polio free occurred with consideration of WPV eradication only and irrespective of cVDPV transmission. All four have detected cVDPVs post-certification (See **Table 1**).

Table 1: post regional certification cVDPV outbreaks

Region	Year certified	cVDPV outbreaks
Americas (AMR)	1994	Hispaniola, 2000-01
Western Pacific (WPR)	2000	Cambodia 2005-6; China 2004, 2012; Philippines 2001; Lao PDR 2015-16; PNG 2018
European (EUR)	2002	Ukraine 2015
South-East Asia (SEA)	2014	Myanmar 2015

[7] Smith J, Leke R, Adams A, Tangermann RH. Certification of polio eradication: process and lessons learned. Bull WHO. 2004; 82:24-30

[8] Report from the Seventeenth Meeting Global Commission for the Certification of the Eradication of Poliomyelitis, Geneva, 26-27 February 2018. http://polioeradication.org/wp-content/uploads/2018/04/polio-eradication-certification-17th-meeting-global-commission-for-certification-of-poliomyelitis-eradication-20180412.pdf

The options presented in this paper are specifically for global certification and exclude regional certification.

Key considerations

1. Program Strategic and Operational Perspectives

The current program strategies for the GPEI outlined in the *Polio Eradication and Endgame Strategic Plan 2013-18* (PEESP) include:

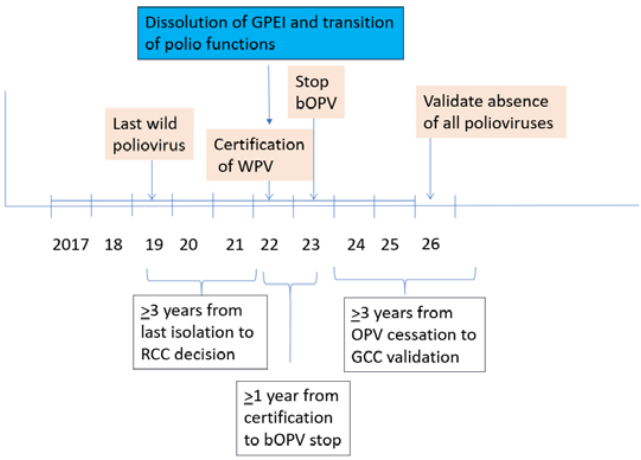
Objective 1: Complete the interruption of WPV transmission globally and more rapidly detect and interrupt any new outbreaks due to cVDPV within 120 days
Objective 2: Strengthen immunization services, introduce IPV, and withdraw OPV2 globally
Objective 3: Certify the eradication and containment of all WPV by end-2018.
Objective 4: Develop a plan to ensure polio investments contribute to future health goals.

As part of Objective 4 ("Transition Planning") the GPEI has drafted a *Polio Post-Certification Strategy (PCS)* which acknowledges the critical importance of stopping all poliovirus transmission but lays out the strategies for transitioning responsibility for polio eradication functions from GPEI to other stakeholders based on achieving certification of WPV eradication. The PCS also lays out the parameters for extending Objective 2 to include withdrawal of all OPV after this certification.

Figure 1 provides the currently anticipated timelines to reach the PEESP and initial PCS objectives. While meeting the projected timeframes remains problematic, the scope of these objectives (including certification of eradication defined as stopping WPV) continue to drive program operations and serve as the basis for determining financial resource requirements.

Options 1A and 1B are therefore clearly within the scope of certification as envisioned in the current strategic plan, although option 1B could delay certification of WPV eradication based on the context of cVDPV. Option 2 however goes beyond the scope of the PEESP and would require a new or renegotiated strategic plan and a process put in place to engage donors and partners in the extended scope. The separate certification of cVDPV could require another four to six years after WPV certification and would most likely exclude consideration of iVDPV (see below).

Figure 1. Anticipated timeline of GPEI, as of July 2018



2. GPEI Partnership

To date, all core global partners of the GPEI have endorsed the concept of certification as applying to WPV eradication and have framed donor communication accordingly. In particular, Rotary International has noted this specific focus as the stated goal of their Polio Plus program since they launched the global effort in 1985 prior to formation of the GPEI.

As an additional component of transition planning, the GPEI has determined that it will dissolve as a management structure at the time of certification of WPV eradication. Any changes to the scope or definitions of certification will required concomitant modifications to these plans and potentially impact engagement of both current and future partners. Future stakeholders who will continue to implement the functions required to sustain WPV-free status and eventually all poliovirus eradication have not yet been officially identified.

3. Epidemiology (as at 26 July 2018)

WPV:

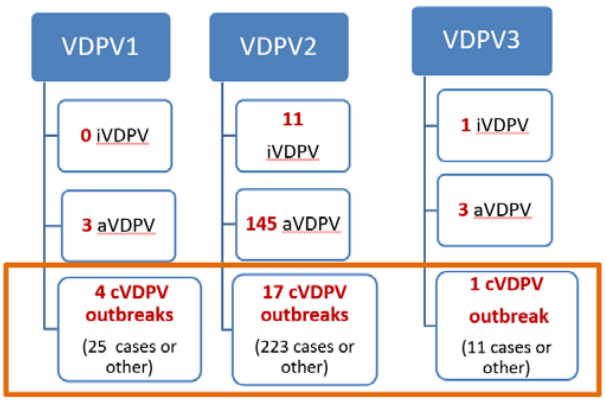
- *type 1*—three countries still considered endemic: Nigeria (onset of last case August 2016), Pakistan (last case- May 2018), Afghanistan (last case-June 2018);
- *type 3*- last case: November 2012 (Nigeria)

VDPV:

The appraisal is based on an analysis of VDPV and cVDPV for the period 2014 – July 2018. This period was chosen as it reflects relevant epidemiology and programmatic responses starting when the GPEI developed standardized classifications and response protocols for VDPVs in the lead-up to the global OPV2 withdrawal in April 2016.

As shown in **Figure 2** the majority of VDPVs detected have been classified as cVDPV (which have the most direct ramifications for future certification of eradication). Detection of aVDPV or iVDPVs (which are overwhelming type 2) will have longer term implications when considering how to eventually deal with VDPVs.

Figure 2. VDPV detections (AFP cases, contacts and environmental) and cVDPV outbreaks, 2014-2018 July 26



cVDPV: serotypes and location

There have been 22 cVDPV outbreaks from 2014-July 2018, affecting 13 countries in five regions (see **table 2**). cVDPV2 was by far the commonest serotype: 17 were type 2, four were type 1, and one was type 3.

Table 2. cVDPV outbreaks by type and region/country, 2014-July 2018

Region	cVDPV1	cVDPV2	cVDPV3
African	Madagascar	Nigeria (6), Kenya, South Sudan, DR Congo (3)	
Eastern Med.		Pakistan (3), Syria, Somalia	Somalia
European	Ukraine		
South East Asian		Myanmar	
Western Pacific	Lao PDR, PNG		

# of outbreaks = 1 unless otherwise indicated (_)

Most of the 17 cVDPV2 outbreaks are thought to have originated from poor coverage with tOPV before the switch or continued inappropriate use afterwards in a few areas. The risk for additional type 2 cVDPVs should decline rapidly over time. However, three cVDPV2 emergences were detected for the first time in 2018 (JIS1 in Jigawa, SOS3 in Sokoto, and DRC Mongala). The date of origin for the DRC Mongala virus remains unclear. Of concern, the new Jigawa and Sokoto detections provide evidence of the first episodes of 'second generation' cVDPV2 (i.e. those seeded after tOPV withdrawal), representing either illicit use/release of tOPV, or the end-result of low-coverage mOPV2 used for response to other VDPV2 events. So far, cVDPV2 outbreaks have all been in known high-risk areas (i.e. poor governance, inadequate health systems, low routine immunization rates, and access issues). Declining mucosal immunity could allow emergence/spread in areas typically considered low-risk.

While cVDPV1 and cVDPV3 outbreaks have been relatively rare to date, their future emergence and thus relevance for certification remains unclear. The recent emergences in Somalia (cVDPV3) and PNG (cVDPV1) underscore that the risk still exists as long as bOPV remains in use. The long-term risk may be highly dependent on population immunity at the time of bOPV cessation. However, based on expected Sabin strain transmissibility and empirical ranking of past cVDPV detections, the risk of cVDPV1 or cVDPV3 outbreaks post-bOPV cessation should be smaller than the risk for type 2 after tOPV withdrawal.

The geographic distribution of all serotype outbreaks demonstrates the continued vulnerability of populations in insecure or inaccessible areas which are susceptible to gaps in both surveillance and population immunity.

cVDPV: temporal analysis

*Please refer to the chart of the timelines for each of the 22 outbreaks in **Annex 1, Figure 3**.*

Globally, cVDPV2s have been found regularly from 2014-July 2018 through AFP and environmental surveillance in multiple countries. Detections of cVDPV1 and cVDPV3 have been fewer, more sporadic, and more widely distributed.

During the period 2014 to June 2018, cVDPV has been consistently detected, and there has been a median of three ongoing cVDPV outbreaks per month globally, with the range from zero (Sept 2016, Jan

2017) to seven outbreaks (Sept 2014, April and May 2017) **(See Annex 1, Figure 4,).** Over these 54 months, there have been only six months (February, April, May, June, and September 2016; and January 2017), when no cVDPVs of any type were detected either in a human case or the environment; and only in two of these months (September 2016 and January 2017) was there no evidence of circulation (i.e. cVDPV neither detected nor presumed).

Due to gaps in surveillance, population movement, and delays or poor-quality vaccination responses, only six [9] of the 17 possibly concluded outbreaks were controlled within 120 days of detection. Ten of 22 outbreaks have continued for longer than six months (i.e. defined as 'persistent')[10]. The three persistent outbreaks, all cVDPV2, detected post-switch have all occurred in areas of insecurity and/or inaccessibility (e.g. DRC, Syria, Somalia).

Nine of the 17 cVDPV2 outbreaks have persisted for longer than 6 months. The longest gap without a persistent cVDPV2 outbreak detected globally has been five months (September 2016 – January 2017), although the designation of persistence could only be determined retrospectively. The longest time between the end of a persistent cVDPV2 outbreak and determination of the next persistent cVDPV2 outbreak has been 20 months (i.e. period between the last detection in Borno, Nigeria in August 2016 and the determination in September 2017 that both the outbreaks in DRC and Syria had passed the persistent threshold.)

Co-circulation of cVDPV and WPV

Low population immunity is a risk factor for both WPV and cVDPV transmission but co-circulation of these polioviruses in the same country has been uncommon during the period under review. Since 2014, nine countries have detected WPV and 13 countries have detected at least one cVDPV. Only two endemic countries, Nigeria and Pakistan, have demonstrated co-circulation of cVDPV and WPV. In non-endemic countries, circulation of VDPV has not preceded an importation of WPV during the analysis period (i.e. cVDPV has not been predictive of WPV risk).

4. Surveillance analysis (2014 – July 2018)

Timeliness of detection

There has been wide variability in timeliness of detection for all types of VDPV outbreaks. For outbreaks initially identified after 1 January 2014, the number of nucleotide (nt) changes from Sabin of the initially detected VDPV ranged from 14-32nt for cVDPV1 (n=4) and from 7 to 38nt (median: 13nt) for cVPDV2 (n=13) (**See Table 3**). Of concern have been the recent outbreaks in Syria and Horn of Africa with extensive nt changes which demonstrate that transmission can persist without detection for prolonged periods, particularly in inaccessible and/or security compromised areas.

[9] Lao PDR, Ukraine, DRC Maniema, South Sudan, Nigeria SOS, Pakistan Quetta. Four outbreaks are still considered ongoing.

[10] *These time intervals are calculated on either the onset date of the index case or collection date of the environmental sample. However, due to inherent steps in the verification process, including transport and lab testing, reporting date can be significantly later, especially in areas where there are security or transport challenges which can result in delay of outbreak determination. For example, the index case in the Syrian outbreak was identified in March 2017 but outbreak notification was not until May 2017.*

Sensitivity of surveillance during outbreaks

Since 2014, after an outbreak has been initially identified, the gap between detections of linked cVDPVs has been less than four months-- with two exceptions which both occurred pre-switch: in security constrained areas of Borno there was a gap of 16 months, and in Guinea there was a gap of 10 months contemporaneous with the Ebola virus outbreak when poliovirus surveillance collapsed.

Sensitivity of surveillance after initial detection appears to have improved since the switch. In the 11 outbreaks first detected post-switch, there has been no surveillance gap of greater than one month between isolates. The overall detection rate (i.e. cumulative monthly detections compared to total number of months of circulation) for these outbreaks is 81% compared to 39% before the switch (**Table 3**). This improvement is likely due to greater focus on VDPV surveillance and response, including increased contact sampling, expanded environmental surveillance (ES), and other intensified surveillance strategies.

Table 3: Indicators of timeliness and sensitivity of global cVDPV surveillance

Country / 'Outbreak name'	**Duration (months) as at July 2018**	**# of months there was at least one detection**	**nt changes of the earliest virus detected**
PRE-SWITCH			
Type 1			
Lao	5	5	32
Madagascar	12	6	20
Ukraine	2	2	20
Type 2			
Nigeria '2005 emergence'	16	4	n/a*
Nigeria 'CHAD emergence'	32	11	n/a
Nigeria 'KDS'	9	4	13
Pakistan 'KAB'	5	4	n/a
Pakistan 'NWZ'	15	3	n/a
South Sudan	1	1	9
Myanmar	6	2	13
Guinea	18	5	12
TOTAL	***121***	***47 (39%)***	
POST SWITCH			
Type 1			
PNG	2 (on going)	2	14
Type 2			
DRC 'Haut Lomami'	16 (ongoing)	13	16
DRC 'Maniema'	3	3	7
DRC 'Mongala'	2 (ongoing)	2	19
Syria	7	7	22
Horn of Africa PV2	8 (ongoing)	1	38

Nigeria 'SOS2'	2	2	12
Nigeria 'JIS'	5 (ongoing)	5	13
Nigeria 'SOS3'	5 (ongoing)	4	8
Pakistan QT	3	3	19
Type 3			
Somalia PV3	4 (ongoing)	4	15
TOTAL	***57***	***46 (81%)***	

*n/a – not applicable as emerged prior to 2014

ES in particular has been key to detection and monitoring duration of circulation of the VDPVs. The recent cVDPV2 and cVDPV3 outbreaks in Somalia were both detected through ES. Nine of the 11 outbreaks detected in locations with pre-existing ES had positive environmental samples at some point during the outbreak, adding confidence to the sensitivity of this surveillance. Conversely, three of the four countries which had detection gaps of >3 months did not have ES at the time of the outbreak. (All three-- Guinea, Madagascar, and Myanmar-- have established ES now.) The current expansion of ES is likely to further increase the sensitivity of global surveillance to detect cVDPV. Of the 27 countries that have had cVDPV since 2000, 23 have already established ES, and in the remaining four (i.e. PNG, Lao PDR, Cambodia and Yemen) plan to do so by 2019.

iVDPV and aVDPV: certification implications

Detection of iVDPV and aVDPV may also have implications for certification under certain circumstances. For example, a single VDPV with a high number of nucleotide (nt) changes may lead to conducting an SIA in a high-risk situation and thus re-introducing OPV vaccine.

iVDPV. Since the GPEI intensified its search for asymptomatic long -term iVDPV excretors in 2006, there has been a marked increase in cases, identified primarily in middle-income countries. Between 1962-2016, WHO registered 101 iVDPV cases; 72% associated with type 2, 17% with type 1, and 16% with type 3.[11] Since the switch in 2016 there have been six iVDPV2s identified in five countries. Evidence of iVDPV among family contacts or into the community is very rare and no poliomyelitis outbreaks have been attributed to iVDPV. However, the risks of transmissibility from asymptomatic long-term iVDPV excretors, especially in the future environment of lowered mucosal immunity, are not fully known. These uncertainties coupled with the limited current surveillance among patients with primary immunodeficiency diseases make long term declarations on the potential for iVDPV emergence problematic, but it is a non-zero risk.

aVDPV. From 2014-2018, WHO documented 42 aVDPV cases: 3 aVDPV1, 35 aVDPV2, and 4 aVDPV3. Since the switch, there have been 44 aVDPV2 events (i.e. from AFP, contact or healthy humans, or ES). A significant number are related to mOPV2 use and clustered in specific countries. The clear majority have $\leq$10 NT changes and have not resulted in further circulation. However, some initially classified aVDPVs with many nt changes (e.g. Somalia 38nt and Syria 22nt) have later been linked to community transmission. While these long chain detections could be expected in high-risk areas, environmental surveillance in Australia picked up a VDPV with 76nt changes. Option 1B specifically refers only to the

[11] Macklin G et al. Prolonged excretion of poliovirus among individuals with primary immunodeficiency disorder: an analysis of the WHO registry. Front. Immunol. 8:1103. Doi:10.3389/fimmu.2017.01103

context of cVDPV but may need to assess how/if to consider long chain aVDPV events in the context of WPV certification.

Key implications of epidemiologic and surveillance analysis for certification options:

- Detection of cVPDVs and even persistent outbreaks have been almost constant since 2014. As the clear majority of detections have been type 2, the overall incidence of cVDPV detections should decline with time since the switch. However, the most recent "second generation" detections possibly linked to mOPV2 use could markedly extend the timeframe in which cVDPV2 may be expected. cVPDV1 and cVPDV3 have been infrequent and historically easier to contain then cVDPV2. Still, recent outbreaks of cVDPV1 and cVDPV3 after a prolonged absence of these types make the future context of all VDPVs highly problematic to predict.
- Outbreaks have occurred predominantly in known high-risk areas and confined to the initial area of detection, allowing future surveillance and context considerations to focus on these areas. However, declining mucosal immunity could allow emergence/spread in areas typically considered low risk.
- Once an outbreak is detected, surveillance gaps of >4 months are rare. ES should increase the overall sensitivity of poliovirus surveillance; however, as recent detections of long-chain VDPVs attest, gaps persist, especially among inaccessible or conflict-affected populations, which can also substantially delay initial discovery of circulation.

5. Communication Considerations

Coordination and alignment of clear, cogent messages defining the scope and program implications of certification will be critical for gaining understanding and support from multiple audiences, including the general public, government officials, donors, public health workers, and the media. All options can present communication challenges. Since paralysis from natural or vaccine poliovirus is indistinguishable, explaining ongoing cVDPV cases in spite of declaring eradication of WPV can be difficult. Even explaining the origins of VDPVs and the necessity to further respond with additional polio vaccine can complicate messaging around eradication strategies and long-term certification issues. And, after multiple claims that eradication is 'this close', any option which further extends the time required to reach certification, especially Option 2, will require careful messaging and advocacy. In all scenarios inadequate or confusing communication can have a negative impact on GPEI credibility and support.

Other components of certification

Containment

The GCC has set safe and secure containment of WPV as a key criterion for certification of WPV eradication. However, for multiple reasons there have been challenges to aligning containment certification timelines (as initially specified in GAPIII) with stopping poliovirus transmission.

Due to delays in implementation of GAPIII, the GCC has recognized that full implementation of the original containment benchmarks by the time poliovirus transmission is stopped may prove difficult. Containment requirements apply to all poliovirus categories (i.e. WPV, VDPV, Sabin) alike but

implementation differentiates by type, starting with type 2. Completing surveys and destroying type 2 viruses that are not kept in poliovirus essential facilities (PEFs) has taken longer than anticipated. The timeframe for eventually completing these tasks for types 1 and 3 as well could be many more years (see **Annex 2, Figure 5**). Ensuring that all PEF's obtain a final certification of containment (CC) has likewise turned out to be a prolonged process (see **Annex 2, Figure 6**) further complicating establishing containment parameters as criteria for certification.

In any case, implementation of containment procedures will need to continue indefinitely. The responsibility for future oversight, including monitoring GAPIII benchmarks for Phase III remains to be determined.

Sequential consideration of type 3 and type 1

All the options propose to concurrently address the certification of eradication of type 3 and type 1. However, all options could be modified to sequentially address type 3 and then type 1. The last WPV3 was detected in 2012. The six years since the last detection of WPV3 provides high confidence that this poliovirus is no longer circulating. From an epidemiologic perspective, it is feasible to consider certifying the global eradication of WPV3 as a 'test run' for certification of all WPV. However, if the parameters for certification conflate both WPV and cVDPV, the expected timeframes to reach certification could be affected by the recent discovery in Somalia which reaffirms that, although rare, the risk for cVDPV3 remains as long as type 3 containing vaccine is in use.

Current plans are to initiate a globally synchronized withdrawal of bOPV within 12 months of the certification of eradication of both WPV1 and WPV3. Sequential certification could potentiate another global switch from bOPV to mOPV1 for routine immunization use to reduce the already small risk for cVPDV3 and VAPP. [12] However, due to supply challenges and other considerations (e.g. logistics, cost, communication) this option is not currently being considered.

Addressing long-term status of VDPVs

Under options 1A and 1B there would still need to be a subsequent process to validate the absence of VDPVs after certification of WPV eradication. The details for this validation process would need to be determined by the time of bOPV cessation, but given their differential risks for emergence, cVDPV and iVDPVs would most likely be considered separately. Option 2 would explicitly require certification of VDPV eradication. Although the process has not yet been defined, this certification could prove problematic, especially for iVDPV, given the uncertainties about the risks for persistent low-level transmission.

[12] While data on incidence is difficult to obtain, VAPP of all types is thought to be a relatively rare occurrence. A 2014 global review found that Sabin 3 was isolated from 42% of recipient VAPP cases and 37% of contact VAPP cases. See L Platt et al. Vaccine-Associated Paralytic Poliomyelitis: A Review of the Epidemiology and Estimation of the Global Burden. JID 2014:210 (Suppl 1), S380-89. https://doi.org/10.1093/infdis/jiu184.

Option Appraisal

Option 1A. Considerations for certification of eradication based on the interruption of transmission of WPV alone, followed later by separate "validation of absence" determination for VDPVs

	Program	Epidemiology and Surveillance	Partnership	Communication
Pro's	• Reflects historical program priorities and measure of program success; consistent with WHA resolutions, GCC 2004 criteria, PEESP, and PCS. • Consistent with declaration of WPV2 global eradication and certifications of regional certification in AMR, WPR, EUR, and SEAR. • Most likely option to meet current GPEI timeline-- thereby keeping within estimated financial resource requirements & program capacity. • Facilitates w/drawal of bOPV as scheduled (& thus potentially lowering risk of future VDPVs) • By limiting criteria, provides the most straightforward eradication process	• Only 12 WPV cases through July 2018 • Sensitive surveillance for WPV and VDPV operational in most countries-- giving confidence to proposed 3-year requirement for certifying polio-free status	• Most aligned with all GPEI partners' initial global commitment • Facilitates implementation of GPEI sunset as planned and transition of functions to other stakeholders	• Widely understood and accepted; simple and straightforward
Risks	• Stopping cVDPV transmission could be seen as a lower priority	• Decline of attention to poliovirus surveillance once WPV certification is attained	• Loss of GPEI credibility if/when cases of cVDPV are detected at or post WPV certification	• Potential confusion and challenges for messaging if/when cases of cVDPV are detected at or post WPV certification

Option 1B. Certification of eradication based on the interruption of WPV transmission, with consideration of the context of ongoing or recent cVDPV outbreaks followed later by separate "validation of absence" determination for VDPVs. Proposed contextual considerations:

- **No detection of a persistent cVDPV2 outbreak from any population source in the previous 18* months; and No detection of a cVDPV1or 3 outbreak from any population source in the previous six* months; OR**
- **No detection of a cVDPV 1or 3 outbreak from any population source in the previous six* months;**

*NOTE: Time parameters could be further discussed

	Program	Epidemiology and Surveillance	Partnership	Communication
Pro's	• Continues attention on achieving PEESP objective to stop all cVDPV outbreaks within 120 days	• See 1A • If limited only to cVDPV1 and 3, recognizes lack of epidemiologic connection among different serotypes and avoids tying WPV1/3 certification to type 2	• May further credibility of GPEI by acknowledging role of VDPV in eradication	• Removes the risk of declaring WPV eradication in the face of a cVDPV outbreak.
Risks	• Depending on the actual cVDPV conditions set and global epidemiology, could lead to delay in WPV certification thereby risk further pushback of the GPEI timeline w/ resulting increased costs, possible diminished program capacity, and postponement of bOPV cessation. • Adds further considerations to certification process—e.g. VDPV detection just before 3-year window could complicate certification process for both global level and remaining regions.	• Multiple post-switch examples of cVDPV2 outbreaks of long duration—may still be circulating when WPV1/3 certification could occur • Recent detections of cVDPV1 and 3 after long absence periods • Insecure or inaccessible areas which are common globally remain at high risk for delayed detection and/or persistent circulation.	• Possible delay could negatively affect donor and partner support; modification of certification concept may be contrary to stated goal of Polio Plus program • Political and media pressure to certify eradication according to historical criteria	• Requires consistent and careful messaging regarding the concept and role of VDPVs. • May require significant shift in communication messaging that certification will occur 3 years after the last WPV case.

Option 2. Considerations for Certification of eradication in two stages: Stage 1 based on interruption of WPV transmission (with or without consideration of context of cVDPVs); Stage 2 based on evidence of no new VDPV emergence and circulation post WPV eradication

	Program	Epidemiology and Surveillance	Partnership	Communication
Pro's	•	• Provides clearest and most explicit framework for the current situation of ongoing emergence and circulation of VDPVs. • Logical progression of WPV to OPV w/drawal to VDPV	• Global commitment to eradicating all poliovirus transmission could increase credibility	• Directly acknowledges risk of paralysis from all polioviruses • Manages the risk of declaring WPV eradication in the face of a cVDPV outbreak.
Risks	• May require a new WHA resolution, revised GPEI strategic plans and PCS • Requires new certification process at global, regional, national levels; including revised mandates for GCC/RCC/NCC • In addition to disadvantages from possible delays noted if Stage 1 uses cVDPV criteria (e.g. Option 1B), could commit GPEI to extended timeframe w/ resulting increased costs and challenges to sustaining program capacity. • Given uncertainty of risks from VDPVs (especially iVDPVs) defining end-point and parameters for VDVP certification could be highly problematic or even unobtainable. • Achieving Stage 2 could be jeopardized by uncertain future availability of nOPV and antivirals which could be required to fully eliminate risk of VDPV emergence and circulation.	• Risks noted in 1B • Capacity for widespread iVDPV surveillance not yet established; potential for long delays or inability to finally classify VDPVs from ES because immune-deficiency can only be determined conclusively from a case. • Infrastructure to maintain "certification standard" surveillance will need to continue globally and raise costs compared with transition to risk-based surveillance envisioned in PCS.	• Disadvantages listed in 1B could be magnified by changing definition & timeframe of certification (especially new funding negotiation) • Requires revision of plans for GPEI sunset and implementing partner commitments • Risks current consensus around certification – some partners may opt out.	• In addition to risks in 1B, further challenge to justify changing 'goalposts'.

	• Adds further considerations to certification process—e.g. VDPV detection just before 3-year window could complicate certification process for both global level and remaining regions. .			

Conclusions

Establishing clear parameters for certification of global poliovirus eradication is critical to setting strategies and priorities for the GPEI and future stakeholders committed to this goal. Although prior definitions of certification have been focused primarily on stopping WPV transmission, the persistence of VDPV circulation has raised questions about whether this scope needs to be expanded. Three primary options (along with possible permutations) for defining certification can be evaluated based on five key considerations: strategic and operational program perspectives, GPEI partnership, epidemiology, surveillance, and communication.

Option 1A limits certification only to consideration of WPV transmission. This option is consistent with prior global and regional certification processes and is the most closely aligned with current GPEI commitments and strategies. Since WPV2 has already been declared eradicated based on this approach, the option deals only with WPV1 and WPV3. While challenges remain to reach the goal of WPV eradication, this option represents the best opportunity to meet proposed GPEI timelines and budget. The primary drawbacks are the communication challenges and potential loss of GPEI credibility associated with any ongoing poliovirus circulation from VDPV at the time of WPV certification. This option acknowledges the importance of eventually stopping all poliovirus transmission and proposes that parameters for validating the absence of VDPVs after certification will be addressed in a future process.

Option 1B also limits certification to WPV but attempts to reduce the risk of declaring eradication in the face of ongoing poliovirus transmission by explicitly taking VDPV circulation into consideration. Although this expanded scope may limit some communication challenges, the uncertainties surrounding persistence of cVDPVs, especially of cVPDV2, may further delay certification--- leading to added costs, challenges to sustaining program quality, and postponement of bOPV withdrawal (which could foster additional cVDPV). The risks for delay could be mitigated by limiting the consideration of cVDPV outbreaks to only cVDPV1 and cVDPV3, thereby delinking any future problems with ongoing type 2 outbreaks from the issue at hand, i.e. certification of WPV1 and WPV3. Option 1B adopts a similar approach as 1A for dealing with VDPVs after certification.

Option 2 widens the scope of certification to include all poliovirus transmission in two sequential stages: WPVs followed by VDPVs. This approach required the most rigorous standards to confirm eradication of all polioviruses regardless of origin. Stage 1 focusing on WPV eradication may or may not include the context of VPDVs with the same advantages/risks of each approach as noted under Options 1A and 1B. Stage 2 would go beyond the validation of absence for VDVPs proposed by these options and require strict parameters (e.g. documentation process by every country, oversight and vetting by regions, and then oversight and vetting globally) which could provide high confidence that VDPV transmission has stopped. Given the uncertainties of future risks from VDPV, this approach could, at a minimum, significantly extend the time frame for achieving overall polio eradication with all the disadvantages inherent to such a delay. Certifying the eradication of iVDPV may not be feasible. Option 2 would also require revising certification strategies, processes, and partner/donor commitments.

While satisfactory implementation of containment phases identified in GAPIII will be a criterion for certification of WPV or WPV + VDPV eradication, certification of containment will need to follow a separate but coordinated time line under all proposed options.

Annex 1.

Figure 3. Monthly global detection of WPV and cVDPV, 2014-2018 July (best viewed in color)

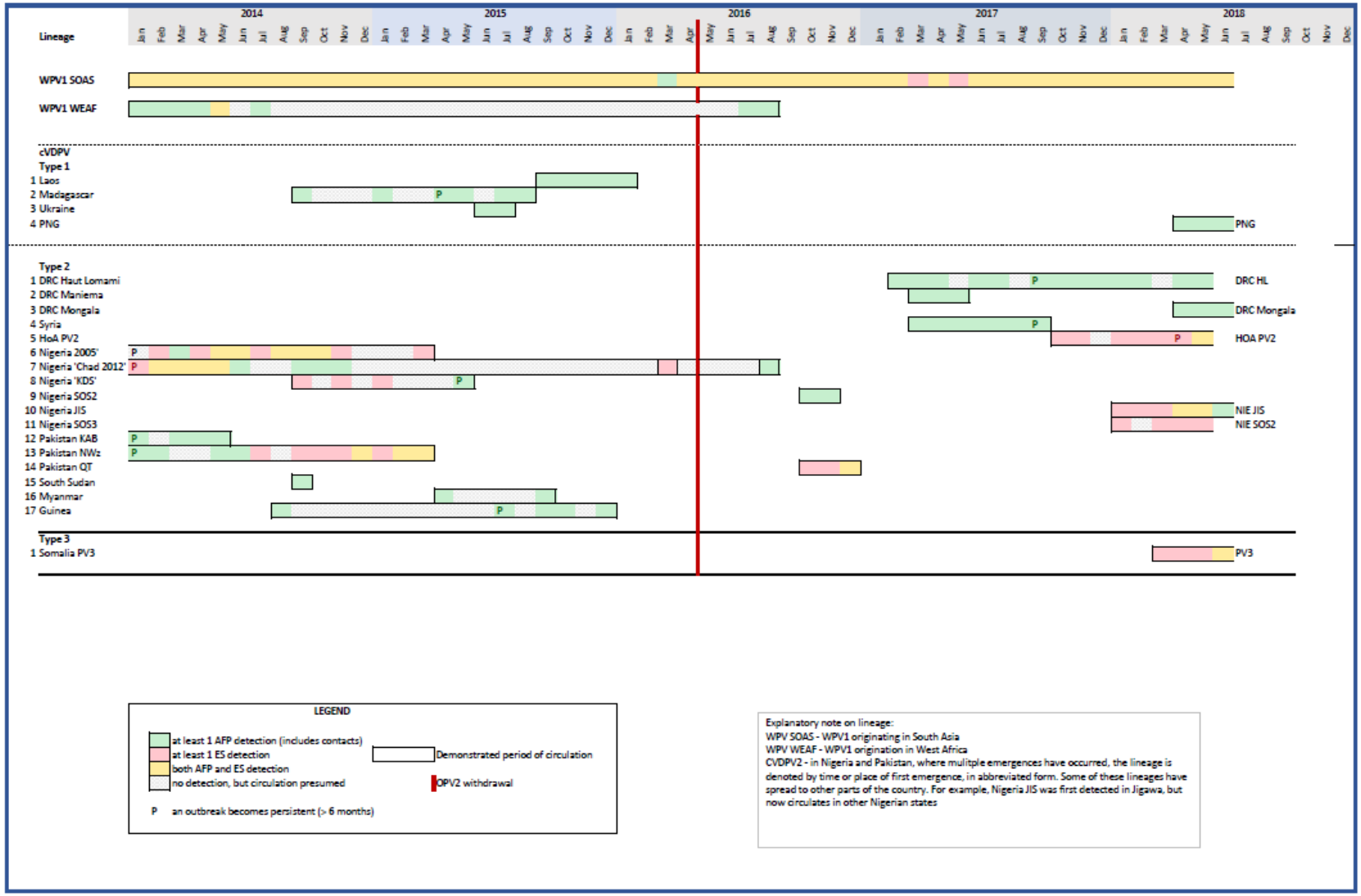
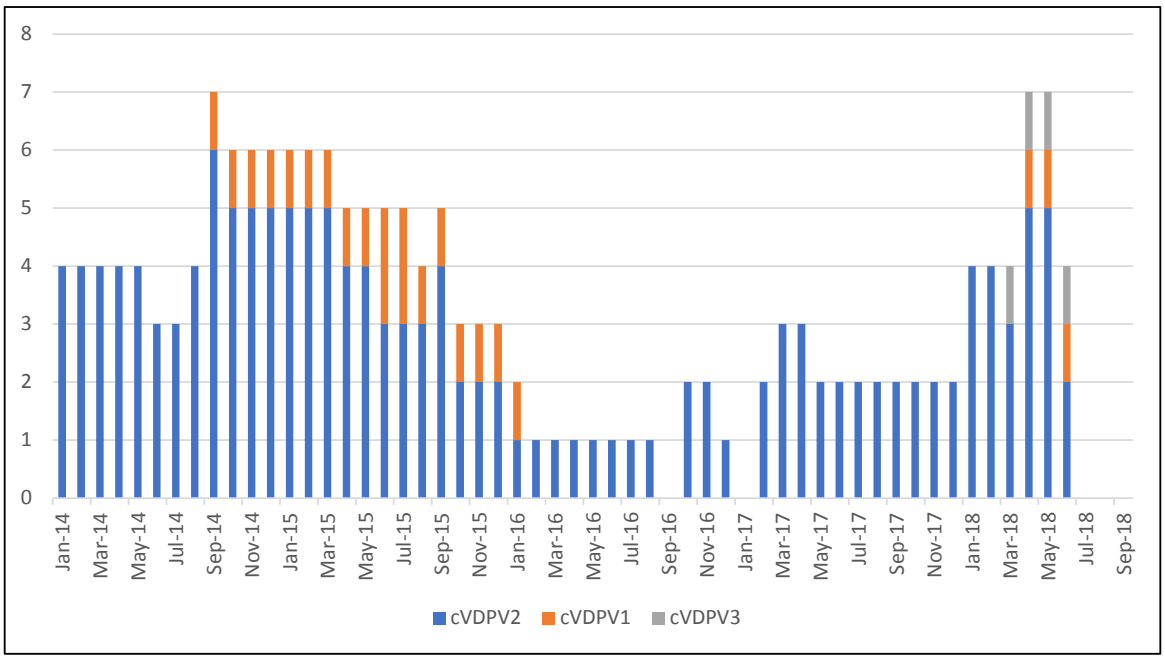


Figure 4. Number of circulating VDPV lineages, by type, 2014-2018 July



Annex 2. Containment

Figure 5. Containment timeline

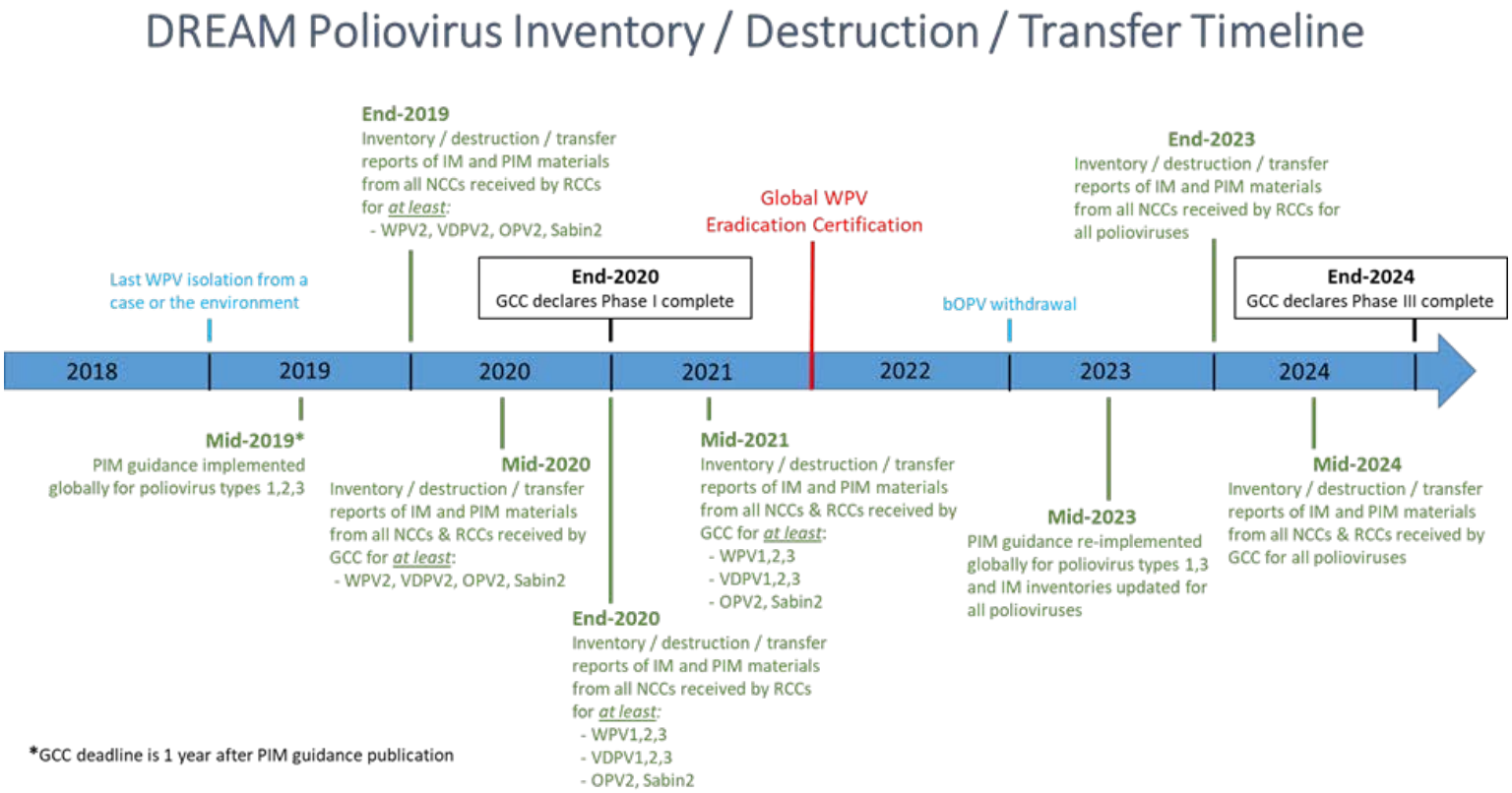
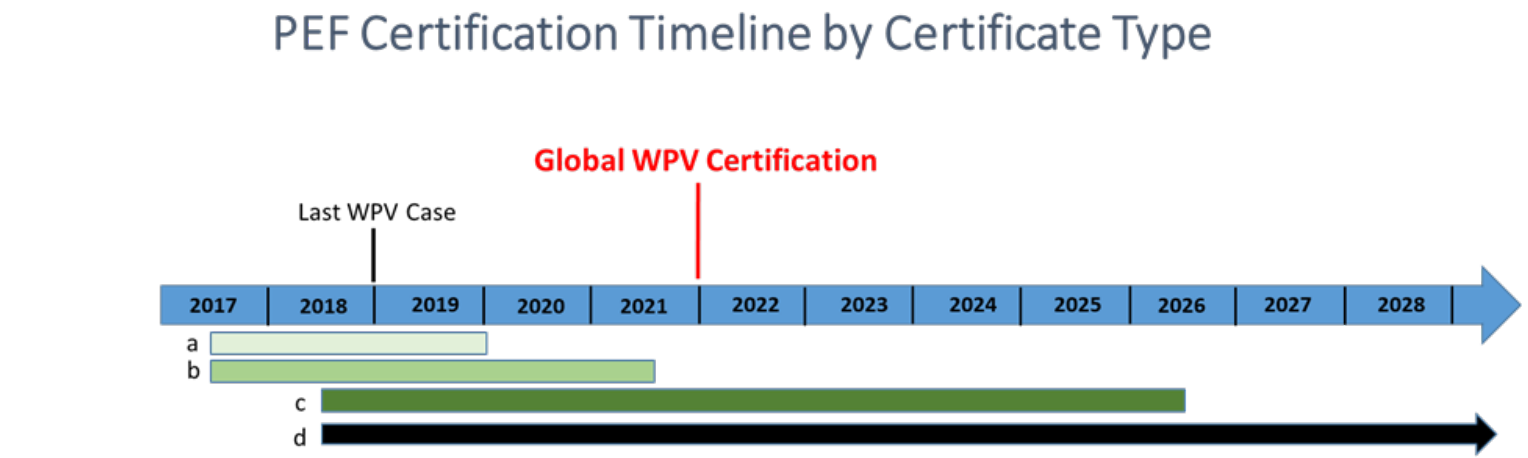


Figure 6. PEF Certification Timeline



a = Certificate of Participation (CP) issuance period*

b = Max CP validity interval**

c = Max Interim Certificate of Containment (ICC) issuance and validity interval***

d = CC issuance interval****

*Latest date possible for CP issuance = 31 December 2019 as per WHA Resolution
**Latest date possible for CP validity is 30 June 2021, i.e. 1.5 years after latest date possible for CP issuance
***Latest date possible for ICC validity is 30 June 2026, i.e. 5 years after latest date possible for CP validity
****Latest date possible for CC issuance is 30 June 2031, i.e. 5 year after latest date possible for ICC validity

Measles and Rubella- Session 6

This session is divided into four separate areas as follows:

1. **Global and regional update**:

This short session is intended to update the SAGE on the progress towards measles and rubella regional and global goals and highlights the key challenges. This session is for information only.

The measles and rubella chapters of the GVAP report (available in the SAGE web under the GVAP session) provide a summary of the global status for both diseases.

2. Feasibility of MR eradication:

At 2017 WHA, DG was requested to report through the EB to the 2020 WHA "on the epidemiological aspects and feasibility of, and potential resource requirements for, measles and rubella eradication, taking into account the assessment of the SAGE."

This session is intended to brief the SAGE on the ongoing work to address the request and obtain their feedback and guidance. The session is focused on the process, the structure and broadly, the content of the report. The SAGE is reminded that the feasibility of measles eradication has been assessed and a report of the previous assessment has been shared in the web. Further, the SAGE, at its November 2010 meeting, have indicated that measles eradication is indeed feasible "…..*SAGE concluded that 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. The eradication of measles represents unique disease control and developmental opportunities, and should be carried out in the context of strengthening routine immunization programmes*". The request from the 2017 WHA is on the feasibility of eradication of measles and rubella as well as the costs. The document in the yellow book provides broad headings for topics and areas that will be covered in the report. In addition the following documents are provided in the SAGE web:

- The published report ITFDE 2015 meeting on measles eradication in 2015
- Proceedings of the meeting to assess the feasibility of measles eradication held in 2010

3. Co-administration of YF vaccine with measles containing vaccine:

Current guidance in the rubella position paper (2011) states that:

"RCVs can be administered concurrently with inactivated vaccines. As a general rule, live vaccines should be given either simultaneously or at least 4 weeks apart…… [Interference may occur between MMR and yellow fever vaccines if they are simultaneously administered to young children. In a study published in 2011,57 seroconversion rates were lower when yellow fever and MMR vaccines were co-

administered to infants aged 12 months than when yellow fever vaccine was administered 30 days after MMR (rubella, 90% versus 97%; yellow fever, 70% versus 87%; mumps, 61% versus 71%). Seroconversion rates for measles were >98% in both groups. Difference in the timing of the blood draw for MMR recipients (30 days versus 60 days), but not for yellow fever vaccine recipients, may have effected MMR seroconversion rates. Therefore, *it may be prudent for routine immunization programmes to avoid simultaneously administering yellow fever vaccine and MMR to children aged <2 years.*"

In light of studies conducted since the 2011 WHO rubella position paper, a review was conducted to review evidence on the immunologic response to measles-containing vaccines (MCVs) and yellow fever (YF) vaccines when co-administered. The yellow book document summarizes the findings and conclusions of this review. For readers interested in the details of the published studies discussed, the following can be found at the SAGE website:

- Brazil study: Mutual Interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps and rubella."
- Gambia study: "Safety and Immunogenicity of inactivated poliovirus vaccine when given with measles-rubella combined vaccine and yellow fever vaccine and when given via different administration routes: a phase 4, randomized, non-inferiority trial in The Gambia."
- Appendix for the Gambia study
- The France study "CHRONOVAC VOYAGEUR: A study of the immune response to yellow fever vaccine among infants previously immunized against measles."

3. **Country classification and guidance to increasing population immunity:**

During the October 2017 SAGE, The SAGE reviewed and endorsed four categories that were proposed for classifying countries, based on their level of disease control and likelihood of achieving and sustaining measles and rubella elimination. However, 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. This work was conducted and presented for feedback at the April 2018 SAGE. This session and proposed recommendations are submitted for a decision form the SAGE. The document in the yellow book provides guidance to identify and address measles and rubella immunity gaps in order to raise population immunity. Countries' epidemiologic profiles as well as their program capacities are used to help prioritize interventions to increase population immunity. In addition, data sources for estimating immunity gaps and strategies to address specific immunity gaps are provided. Of note, this guidance document does not address surveillance or other components of the measles and rubella control/elimination strategies. The focus is on increasing population immunity through identifying and addressing immunity gaps.

Feasibility of Measles and Rubella Eradication

In Preparation for a Report to the
73rd World Health Assembly 2020

Draft Outline of Report to the World Health Assembly

Introduction

World Health Assembly request for report
Measles and Rubella Mid-Term Review assessment
Regional elimination goals
Measles and rubella eradication and broader development and immunization goals

- Sustainable Development Goal 3 and GPW 13
- Global Immunization beyond 2020

Objectives and scope of the report
Timelines for intermediate targets and possible eradication goal

Historical Context

Summary of Recent Assessments of Measles Eradication

- Global Technical Consultation to Assess the Feasibility of Measles Eradication (2010)[1]
- International Task Force for Disease Eradication (2015)[2]

Lessons from Prior Eradication Efforts

- Lessons learned from smallpox eradication
  Need research and program flexibility
- Lessons learned from the Global Polio Eradication Initiative (Steve Cochi)
  Use of targeted diseases initiative for broader health communication
  Global lab network and disease surveillance
  Experience with reaching every child
  Program monitoring and accountability frameworks
  Partner coordination, advocacy and resource mobilization

Status of Polio Eradication and the Polio Transition

- Brief status report on polio eradication and implications for measles and rubella eradication

[1]Proceedings of the Global Technical Consultation to Assess the Feasibility of Measles Eradication, 28–30 July 2010. JID 2011:203 (Suppl 1).

[2]Meeting of the International Task Force for Disease Eradication, November 2015. Weekly epidemiological record. No 6, 2016, 91, 61–72.

- Polio transition

Measles and Rubella Mid-Term Review

- Overview of the Measles and Rubella Mid-Term Review

Progress toward Elimination

Strategies and Tactics for Measles and Rubella Eradication

- Current strategies for achieving measles and rubella elimination
- Recommended strategies and tactics based on country categorization
- Regional and global strategies to coordinate and synergize eradication efforts

Update on global and regional progress toward measles and rubella elimination goals

- Region of the Americas
- European Region
- Western Pacific Region
- Eastern Mediterranean Region
- African Region
- South East Asia Region
    South East Asia Region mid-term review

Country case studies: successful elimination and failed elimination

Update on regional verification of measles and rubella elimination

Issues Raised by the Mid-Term Review

- Shift from primary reliance on supplementary immunization activities to primary reliance on routine immunization services (through strengthening the immunization delivery system) to assure high coverage with two doses of MCV
- Consideration of coverage targets needed to achieve and sustain elimination
- Acceleration of the introduction of rubella vaccine
- Shift from primary reliance on coverage to measure progress to incorporating disease incidence as a major indicator.
- Develop and maintain outbreak preparedness, respond rapidly to outbreaks and manage cases
- Classify cases to determine the proportion due to failure to implement existing strategies (i.e. directly programmatically preventable) versus cases that might require a change in strategy (e.g., change in

recommended age for dose 2) to induce immunity and directly prevent them
- Governance and resource mobilization

Operational Challenges

Operational Challenges to Measles and Rubella Eradication and Proposed Solutions

- Vaccine coverage required to achieve and sustain high levels of population immunity to measles
- Efficiency of current immunization programs
- Need for high quality and precise data on vaccine coverage and measles surveillance
- Methods to identify immunity gaps
- Susceptible adults and potential waning immunity
- Risk of measles and rubella virus re-introduction after eradication
- Region and country-specific challenges
    - Vaccine hesitancy
    - Conflict and insecurity
    - Weak health infrastructure and immunization programs
    - Subnational equity gaps
    - Need for regional coordination and synchronization of campaigns
    - Political support

Surveillance for Measles, Rubella and Congenital Rubella Syndrome

- Need for elimination quality surveillance
- Need for surveillance systems different from those used for polio eradication
- Best indicators to measure the sensitivity of surveillance
- Challenge of CRS surveillance

Challenges of sustaining elimination with delayed eradication

- Demographic changes, including population growth and urbanization
- Cost of outbreaks
- Waning immunity and secondary vaccine failure (susceptible adults)
- Fragility of control and the speed with which measles can return if immunization programs are eroded or interrupted (e.g. Venezuela)
- Potential loss of community confidence and political will

Innovative Strategies and Tools to Achieve Measles and Rubella Eradication

- Key research priorities and plans to establish mechanisms to fund and track research progress critical to eradication efforts
- New diagnostic and vaccination technologies, the timeline for their introduction, and a strategic plan for their implementation

- Strategies to achieve measles eradication without sustaining high levels of population immunity in all communities or through focusing on specific age-groups

Impact on the Health Sector

Impact of Measles and Rubella Eradication on Immunization and Health Systems

- Key published studies
- Diagonal rather than vertical approach
- GVAP goals on health system strengthening and WHO goals on immunization coverage and equity
- Case studies

Measles and Rubella Vaccine Supply

- Plans to engage vaccine manufacturers for the measles and rubella end game
- Use of measles and rubella vaccine after eradication

Financing

Expected Cost and Return on Investment

- Investment case analyses

Donor Support

- Strategies for engagement with potential donors
- Post-2020 GVAP stakeholder meeting

Cost of delaying eradication

Political and Public Support

Public Support for Measles and Rubella Eradication

- Social mobilization, media engagement and public relations
- Vaccine hesitancy and demand generation
- Role of professional societies
- Role of health sector confidence and engagement

Political Support for Measles and Rubella Eradication

- Engaging key stakeholders
- Country support at national, provincial and district levels
- Legislation in support of vaccination
- Donor support
- Cost of sustaining elimination

Ethical Imperative

Need for Measles and Rubella Eradication Champions

Case studies

Management and Accountability Framework

Measles and Rubella Midterm Review

- Integrated with the general immunization system and should be used to build and enhance the overall immunization system.
- RVCs should be established in all regions and serve as independent reviewers of progress toward measles and rubella elimination, and make region and country-specific recommendations
- M&RI and Gavi have complementary roles and should coordinate their support to countries based on the principles of
  - Governments have primary responsibility
  - Coordination of financial, technical, communication and advocacy support
  - Collaboration on program evaluation
  - Accountability for achieving results
  - Leveraging existing initiatives, networks, working groups and agency capacity
- Gavi and M&RI should work together to optimize use of available resources and to bring to bear the different strengths of each organization.

Global Polio Eradication Initiative governance and structure

- Governance
- Advisory and Monitoring
- Technical Advisory Groups
- Oversight
- Management

Timelines for Intermediate Targets and Possible Eradication Goal

Timeline for intermediate targets

- Realistic yet aspirational timelines for measles and rubella eradication
- Short, medium and long-term milestone and objectives
- Urgency
  - Preventable deaths, primarily in young children
  - More rapid loss of maternal antibodies in children of women with vaccine-induced immunity

- Potential waning immunity in adults not exposed to wild-type virus
- Impact of delay on measles epidemiology and the challenge of closing immunity gaps in older cohorts

Potential target date for measles and rubella eradication

Potential date to reconsider measles and rubella eradication

Risks of continued measles and rubella virus transmission

Conclusions and Recommendations

What will it take to achieve measles and rubella eradication?

What are the risks of setting an aspirational goal for measles and rubella eradication?

What is the new vision for measles and rubella eradication that integrates with a vision of a world in which all children have access to immunization and will mobilize the public, stakeholders and potential donors?

Recommendations to the World Health Assembly

Background Paper on Immunologic Response to Measles-Containing Vaccines (MCVs) and Yellow Fever (YF) Vaccines when Co-administered

Key Findings

1- There is inconsistent evidence that co-administration of MR/MMR and YF vaccines interferes with rubella, mumps and YF seroconversion. There is no evidence from any studies that co-administration of MR/MMR and YF vaccines interfere with measles seroconversion.
2- There is evidence of interference with the magnitude of antibody response against rubella, mumps, and YF when MR/MMR and YF vaccines are co-administered; however, titers were robust (well above the cut-off points for seroconversion) in all groups. The clinical implications of this and whether it has any effect on long-term immunity are not known. There is no evidence of interference with the magnitude of antibody response against measles when MR/MMR and YF vaccines are co-administered.
3- The programmatic implications of delaying one of these vaccines to a later vaccination visit instead of co-administering them would likely have a far greater impact on population immunity than any potential reduction in the immune response due to co-administration.
4- Additional research is needed in several areas.

Introduction

In line with regional measles elimination goals, all countries administer MCVs through their childhood vaccination programs. Most countries (167/194 countries and territories) also provide rubella vaccine, administered in a combination vaccine with measles vaccine (MR) or with measles and mumps vaccines (MMR). Of the 40 countries worldwide that are categorized as high risk for YF, either nationwide or within subnational areas, 13/13 in South America and 22/27 in Africa administer YF vaccine through their national immunization programs. The remaining 5 countries in Africa are expected to introduce YF vaccine in the next few years; in addition, YF vaccination is also used for outbreak control through campaigns. Countries in the World Health Organization (WHO) African region (AFR) typically administer YF vaccine along with measles or MR vaccine to children at 9 months of age; all countries that currently administer measles vaccine will eventually transition to MR vaccine. In countries in the region of the Pan American Health Organization (PAHO), YF vaccine has traditionally been co-administered at 12 months of age with MMR vaccine, though there are a few exceptions.

MCVs and YF vaccines are live attenuated vaccines and the WHO position papers on rubella and measles vaccines both state that live vaccines should be administered at the same time or at least 4 weeks apart.[1, 2] However, the rubella position paper from 2011 also states that “interference may occur between MMR and YF vaccines if they are simultaneously administered to young children.” This

was based on the findings of one study that found lower seroconversion rates against rubella, mumps, and YF (but not measles) when MMR and YF vaccines were co-administered compared to being administered 30 days apart to children aged 12-23 months in Brazil [3]. Because of this, the rubella position paper also states that "it may be prudent for routine immunization programmes to avoid simultaneously administering YF vaccine and MMR to children aged < 2 years." In 2013, the SAGE YF working group conducted a literature review on co-administration of YF and other vaccines, including eight studies that evaluated co-administration of YF and MCVs. None of the seven studies that evaluated co-administration with measles-only and YF vaccines showed evidence of interference. The previously-mentioned study from Brazil was the only study evaluating co-administration of YF vaccine and a combination measles vaccine.[4] They concluded in in the 2013 YF position paper that "Immunogenicity is usually unaffected when YF vaccine is co-administered with other vaccines" but then reference the study in Brazil as a "notable exception". Based on the available data, they further stated "there is insufficient evidence to change current recommendations and SAGE recommended that additional studies should be undertaken…"[5] Since the publication of the Brazil study in 2011, there have been three additional studies that evaluated potential interference between MCVs and YF vaccine when they are co-administered as compared to sequential administration (MCV and YF vaccines separated by ≥28 days with follow-up serum samples taken ≥28 days after the 2nd vaccine was received) or individually (receipt of one vaccine with follow-up sample collected ≥28 days later, prior to receiving the second vaccine). In this background paper, we review the evidence from the previously-mentioned Brazil study and these three additional studies.

From a programmatic perspective, co-administration of vaccines provides protection at the earliest possible age, maximizes efficient use of healthcare resources, and prevents children from potentially missing the vaccine dose should they not return for a later vaccination visit.[6] Hence the risk of interference needs to be weighed against the risk of non-vaccination should administration of one of the vaccines be delayed to a later, scheduled vaccination visit (e.g. 15 or 18-month visits). In this paper, we present programmatic data to show the potential impact on vaccination coverage if MR/MMR or YF vaccine were to be provided at a 15 or 18-month vaccination visit instead of the 9 or 12-month visit.

Methodology

We reviewed four studies evaluating co-administration of MCVs and YF vaccines. Three studies are published in peer-reviewed journals [3, 7, 8] and one is unpublished. The unpublished data was shared with the SAGE Measles-Rubella (MR) working group in September, 2018 and will be submitted for publication later this year. We also used data from the WHO-UNICEF Joint Reporting Form (JRF) and WHO-UNICEF estimates of immunization coverage (WUENIC) to look at programmatic implications.

When evaluating potential interference, we considered two aspects of interference:

> (1) Decreased seroconversion or response rates, as evidence by developing a detectable titer or having a titer increase by a defined amount.

(2) Decreased magnitude of antibody response, as evidence by lower antibody concentrations/titers

All four study designs were reviewed by the SAGE MR working group in July 2018 and results were further reviewed in September. At the September meeting, programmatic data were also reviewed and proposed recommendations were discussed with the MR working group members and invited YF subject matter experts. All working group members and several YF subject matter experts have had the opportunity to provide critical feedback to draft versions of this document, including the recommendations.

Existing Evidence

Study Findings

The methodologies of the four studies that evaluated the immune response of MCVs and YF vaccines when given together, individually, or separated by approximately one month are outlined in Table 1. The studies varied some in the specific vaccines administered and laboratory procedures used to assess immune response (Table 2). Three of these studies were randomized clinical trials (RCTs) and one was an observational study. Of note, the RCT from Brazil had differing time gaps between MMR vaccination and follow-up sample collection for their sequential and co-administration groups; samples were collected 30 days post-vaccination for the co-administration group and 60 days post-vaccination for the sequential group. Additionally, the results from the observational study in France were given much less weight by the working group when formulating recommendations due to the study's observational design and power limitations.

None of the studies showed decreased seroconversion against measles when the vaccines were co-administered compared to when the vaccines are administered individually or sequentially. The studies in The Gambia and Argentina did not find decreased seroconversion for any of the other antigens (mumps, rubella, YF) (Table 3). However, the study from Brazil did find interference in seroconversion to mumps, rubella and YF when MMR and YF vaccines were co-administered compared to being administered 30 days apart. The study from France also observed interference for YF, however their sample size calculations show that they were significantly underpowered to do the non-inferiority test that they performed making the findings difficult to interpret.

All of the studies, except the study from France which had limited power, show interference in the magnitude of antibody response with lower antibody concentrations/titers against all antigens except measles in the co-administration group compared to the individual or sequential groups (Table 4). However, it should be noted that the geometric mean titers (GMTs) for both the co-administration and individual/sequential groups are robust in all studies. Furthermore, while significantly lower titers were observed in the children that had the vaccines co-administered, the clinical implications of these differences and their impact on long-term immunity, in particular secondary vaccine failures, is

unknown. More research is needed to better understand whether lower antibodies concentrations/titers following vaccination are associated with different kinetics or rates of antibody decline.

Discussion of study findings

The results of the three RCTs were concordant for demonstrating interference as measured by a decrease in antibody concentrations/titers when the vaccines are co-administered. For interference measured by a decrease in seroconversion, the RCTs from Argentina and The Gambia showed no interference, while the Brazilian results showed interference for mumps, rubella and YF. The results from the French study were more difficult to interpret and were given much less weight by the working group due to the study's limitations.

Several hypotheses were discussed to explain the differing results for interference with seroconversion observed between the study from Brazil and the studies from Gambia and Argentina. The differing time gap between vaccination and sample collection may have contributed to the lower seroconversion for mumps and rubella observed in the Brazilian study, but this time gap did not exist for the YF results, yet differing titers were observed. Other hypotheses for the apparent difference is use of different vaccines; the Brazil study used 17DD and 17D-213 YF vaccines while the studies from The Gambia and Argentina used 17D-204 YF vaccine (manufactured in Senegal or France, respectively). This difference in children's immunologic response to different strains of YF vaccines has been noted by others.[9] The 17DD vaccine has on average a higher potency than other prequalified 17D vaccines [10] and its higher potency might have resulted in greater interference. Another possibility is the difference in laboratory tests and cut-off points used to classify people as seropositive or seronegative. While the studies in Brazil, The Gambia, and Argentina used the same testing procedure for YF (plaque reduction neutralization test with a cut-off of 50%, PRNT50), they used different criteria for classifying seropositive results (Table 2). For rubella testing, all RCTs used Siemens ELISA kits, but it is unclear how the Brazil study classified indeterminate results. Furthermore, during the working group discussions, laboratory experts commented that it would not be unusual to have slightly varying results from different laboratories, even when using the same test kits. Finally, it is possible that there were different background rates of exposure to related viruses (e.g., flaviviruses) in the different study populations and this affected the children's immunologic response to the vaccines.

Programmatic Considerations

To avoid any potential interference on the immunologic response to MCVs and YF vaccine, the two vaccines would need to be administered at different vaccination visits, typically with one of them delayed to a visit after the standard visit for MR/MMR and YF vaccines at 9- or 12-months of age. To assess the potential programmatic impact of delaying one dose, we examined vaccine coverage rates for MMR and YF in the 4 countries in the PAHO region that have moved YF vaccination from the 12-month vaccination visit (where it was co-administered with MMR) to either the 15 or 18-month visit. In each case, there was a substantial drop in coverage in the year the change was implemented (Figure

1). In Panama and Colombia, following the initial decrease in YF vaccine coverage, there has been a steady increase so the gap is almost closed. In Argentina and Peru, a coverage gap of approximately 20% has persisted after the change in the schedule that moved YF vaccine to a separate visit from MMR. In the AFRO region, all countries that provide YF through their national immunization program co-administer YF with M/MR at the 9-month vaccination visit and no changes have been made, hence similar case examples do not exist. However, coverage for YF, even when co-administered with MCV1 at the 9-month visit, is often lower than MCV1 (Figure 2). More significantly, second year of life vaccination programs are much less developed in the AFRO region than in the PAHO region. A few countries with stronger immunization programs (and without significant gaps between MCV1 and YF coverage) have introduced MCV2 during the second year of life, typically at a 15 or 18-month visit. In these countries, a significant coverage gap between MCV1 and MCV2 still exists several years after MCV2 introduction (Figure 2). These data suggest that delaying one of these vaccines to a visit during the second year of life may have an even stronger negative impact on coverage in the AFRO region than it did in the PAHO region.

Additional programmatic issues to consider are that there are measles and rubella elimination goals. Hence there is rationale not to delay MCV1 administration. However, WHO recommends two doses of MCV and thus most children receive a second dose either through MCV2 in routine immunization or through supplemental immunization activities. WHO recommends only one dose of YF vaccine; hence decreased coverage with YF vaccine could have significant impacts on population-level immunity to YF.

Conclusions and Recommendations:

Given the evidence just discussed, the working group concluded that:

1- There is inconsistent evidence that co-administration of MR/MMR and YF vaccines interferes with rubella, mumps and YF seroconversion. Two of three RCTs did not show a decrease (i.e., non-inferior) in seroconversion when MMR and YF vaccines were co-administered while one showed decreased seroconversion against rubella, mumps and YF when these vaccines were co-administered. There is no evidence from any studies that co-administration of MR/MMR and YF vaccines interferes with measles seroconversion.

2- There is evidence of interference with the magnitude of antibody response against rubella, mumps, and YF when MR/MMR and YF vaccines are co-administered; however, titers were robust in all groups. This was demonstrated in all three RCTs that examined this. The clinical implications of this and whether it has any effect on long-term immunity are not known. There is no evidence of interference with the magnitude of antibody response against measles when MR/MMR are and YF vaccines are co-administered.

3- The programmatic implications of delaying one of these vaccines to a later vaccination visit instead of co-administering them are substantial and would likely have a far greater impact on population immunity than any potential reduction in the immune response due to co-administration.

4- Additional research is needed in several areas: 1) better understand whether there are any clinical implications from the reduction in the magnitude of the antibody response for rubella, mumps and YF immunity; 2) determine if the lower titers or antibody concentrations observed following co-administration of MR/MMR and YF vaccine will impact long-term immunity; and 3) further examine the potential interference when different combinations of available YF and measles-containing vaccines (e.g., 17DD, 17D-204, MMR, and MR from different manufacturers) are co-administered.

Given these conclusions, the working group recommends the following:

WHO maintains its current guidance stating that MR/MMR and YF vaccines should be administered at the same visit or at least 4 weeks apart, according to the schedule that will maximize coverage for all antigens in the national immunization schedule [*removing all qualifications/precautions about co-administration].* Additional research is needed to determine if the lower titers or antibody concentrations observed following co-administration of MR/MMR and YF vaccine will impact long-term immunity and cause secondary vaccine failures.

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[9] Roy Chowdhury P, Meier C, Laraway H, Tang Y, Hodgson A, Sow SO, et al. Immunogenicity of Yellow Fever Vaccine Coadministered With MenAfriVac in Healthy Infants in Ghana and Mali. Clin Infect Dis. 2015;61 Suppl 5:S586-93.
[10] Barrett ADT. SAGE Presentation: Fractional dosing of Yellow fever vaccines: review of vaccine potency & stability information, available evidence, and evidence gaps. 2016.

Table 1: Study Design and Statistical Comparison

Study Reference [Location]	Target population	Study Design*	Sample size*	Statistical Comparison - Seroconversion	Statistical Comparison – Antibody titers /concentrations	Comments
Nascimento Silva et al., 2011 [3] [Brazil]	12-23-month old children	RCT: Children randomized to receive MMR & YF at same visit (co-administration) or MMR followed by YF 30 days later (sequential). Samples collected at baseline and 30 days after the last vaccination.	906 in co-administration group; 922 in sequential group	Difference in proportions seroconverting	Non-parametric test of difference in antibody concentrations / titers	Time gap between MMR vaccination and sample collection differed between groups: in sequential group, sample collection was 60 days post-vaccination; in co-administration group it was 30 days post vaccination
Clarke et al., 2016 [7] [The Gambia]	9-10 month old children	RCT: Children randomized to receive MR (individual), YF (individual), or MR & YF (co-administration) Samples collected at baseline and 30 days post-vaccination.	189 in individual MR group; 187 in individual YF group; 188 in co-administration group	Non-inferiority test with 10% margin	Non-inferiority test with 1/3 $\log_2$ titer / concentration	
Unpublished, 2018 [Argentina]	12-month old children	RCT: Children randomized to receive MMR (individual), YF (individual), or MMR & YF (co-administration) Samples collected at baseline and 30 days post-vaccination	248 in individual MMR group; 245 in individual YF group; 244 in co-administration group	Non-inferiority tests with 5% margin	Non-parametric test of difference in antibody concentrations / titers	
Goujon et al., 2017 [8] [France]	Children aged 6-24 months at time of YF vaccination	Observational: Children identified through YF vaccination record; grouped according to timing of prior M/MMR vaccine: Control 1: M/MMR & YF less than 24 hours apart (co-administration) Control 2: M/MMR & YF ≥ 28 days apart (sequential). Follow-up samples collected 6-12 months post YF vaccination	50 in co-administration group; 19 in sequential group	Non-inferiority test with 10% margin		Observational design; no baseline samples; did not reach sample size needed, hence they were underpowered for the planned statistical testing

*Definitions of selected terminology:
Co-administration: Received MR/MMR and YF at the same vaccination visit (or within 24 hours in Goujon et a. study)
Sequential: Received MMR and YF sequentially (MMR followed by YF at least 28 days later) with sample collected after both vaccinations received
Individual: Received either MR/MMR or YF individually with follow-up sample collected prior to receipt of the second vaccine

Table 2: Vaccine Strains and Laboratory procedures

Study Reference [Locations]	Vaccine strains				Laboratory methodology and cut-off criteria							
	Measles	Mumps	Rubella	Yellow fever	Measles test	Measles cut-off	Mumps test	Mumps cut-off	Rubella test	Rubella cut-off	Yellow fever test	Yellow fever cut-off
Nascimento Silva et al., 2011 [3] [Brazil]	-Moraten, -Schwartz	Jeryl Lynn -RIT 4385*	RA 27/3	-17D-213 (Brazil) -17DD (Brazil)	PRNT50	Not stated	ELISA (Siemens)	≥231 U/mL	ELISA (Siemens)	Non-reactive: <4.0; Inconclusive: 4.0 – 6.5; Reactive: >6.5 IU/mL	PRNT50	>2.7 log_{10} mIU/mL
Clarke et al., 2016 [7] [The Gambia]	Edmonston-Zagreb	N/A	RA 27/3	17D-204 (Senegal)	ELISA (Siemens)	≥150 IU/mL	N/A		ELISA (Siemens)	≥4 IU/mL	PRNT50	Positive ≥ 8
Unpublished, 2018 [Argentina]	-Schwartz, -Edmonston	-Urabe AM-9 -Jeryl Lynn	RA 27/3	-17D-204 (France)† -17DD (Brazil)	ELISA (Siemens)	Per manufacturer	ELISA (Siemens)	≥231 U/mL	ELISA (Siemens)	≥4 IU/mL	PRNT50	Positive ≥ 10
Goujon et al., 2017 [8] [France]	-Enders' Edmonston, -Schwartz	-RIT 4385* -Jeryl Lynn	RA 27/3	-17D-204 (France)	ELISA (Siemens)	≥150 mIU/mL	ELISA (Siemens)	≥231 U/mL	ELISA (Siemens)	Non-reactive: <8; Inconclusive: 8 – 11; Reactive: >11 IU/mL	PRNT80	Positive ≥ 10

* Derived from Jeryl Lynn strain

† ~98% of participants received 17D-204

Table 3: Seroconversion: Co-administration compared to individual or sequential administration of measles-containing vaccines and yellow fever vaccine

Study Reference [Location]	Measles (%)	Mumps (%)	Rubella (%)	Yellow Fever (%)
Nascimento Silva et al., 2011 [3] [Brazil]	Co-admin: 98.2* Sequen: 99.2 p=0.090	Co-admin: 61.1* Sequen: 70.8 P<0.001	Per protocol cohort Co-admin: 90.2 (88.0-92.2) Sequen: 97.2 (95.8 – 98.2) P<0.001 Intent to Treat Cohort Co-admin: 86.2 (83.8-89.0) Sequen: 94.4 (92.6 – 95.6) P<0.001	Per protocol cohort Co-admin: 69.7 66.4-72.8) Sequen: 87.7 (85.3 – 89.8) P<0.001 Intent to Treat Cohort Co-admin: 66.5 (63.3-69.6) Sequen: 82.8 (80.2 – 85.2) P<0.001
Clarke et al., 2016 [7] [The Gambia]	Co-admin: 78.9 (72.4 – 84.2) Individ: 76.9 (70.3 – 82.4) Co-admin was non-inferior	N/A	Co-admin: 96.8 (92.8 – 98.6) Individ: 98.2 (94.9 – 99.4) Co-admin was non-inferior	Co-admin: 94.9 (90.6 – 97.3) Individ: 96.0 (92.0 – 98.1) Co-admin was non-inferior
Unpublished, 2018 [Argentina]	Per protocol cohort Co-admin: 98.0 (95.0 – 99.2) Individ: 96.4 (93.0 – 98.1) Co-admin was non-inferior Intent to Treat Cohort Co-admin: 97.9 (95.3 – 99.1) Individ: 96.3 (93.1 – 98.1) Co-admin was non-inferior	Per protocol cohort Co-admin: 96.6 (93.1 – 98.3) Individ: 98.2 (95.4 – 99.3) Co-admin was non-inferior Intent to Treat Cohort Co-admin: 96.7 (93.6 – 98.3) Individ: 97.9 (95.3 – 99.1) Co-admin was non-inferior	Per protocol cohort Co-admin: 97.5 (94.3 – 98.9) Individ: 94.5 (90.6 – 96.8) Co-admin was non-inferior Intent to Treat Cohort Co-admin: 97.9 (95.2 – 99.1) Individ: 94.6 (91.0 – 96.8) Co-admin was non-inferior	Per protocol cohort Co-admin: 96.1 (92.5 – 98.0) Individ: 98.1 (95.1 – 99.2) Inconclusive result# Intent to Treat Cohort Co-admin: 96.3 (93.1 – 98.1) Individ: 97.5 (94.7 – 98.9) Co-admin was non-inferior
Goujon et al., 2017 [8] [France]	Co-admin: 92& Sequential: 95 P-value not stated	Co-admin: 86 Sequential: 95 P-value not stated	Co-admin: 94 Sequential: 100 P-value not stated	Co-admin: 92 Sequential: 100 Non-inferiority not shown

Co-admin: Received MR/MMR and YF co-administered

Sequen: Received MMR an YF sequentially (MMR followed by YF at least 28 days later) with sample collected after both vaccinations received

Individ: Received either MR/MMR or YF individually with follow-up sample collected prior to receipt of the second vaccine

*Paper focused on rubella and yellow fever results; less data presented for measles and mumps

#Per protocol cohort had 20-30 children per group fewer than the intent to treat cohort and was underpowered for a non-inferiority analysis with 5% margin

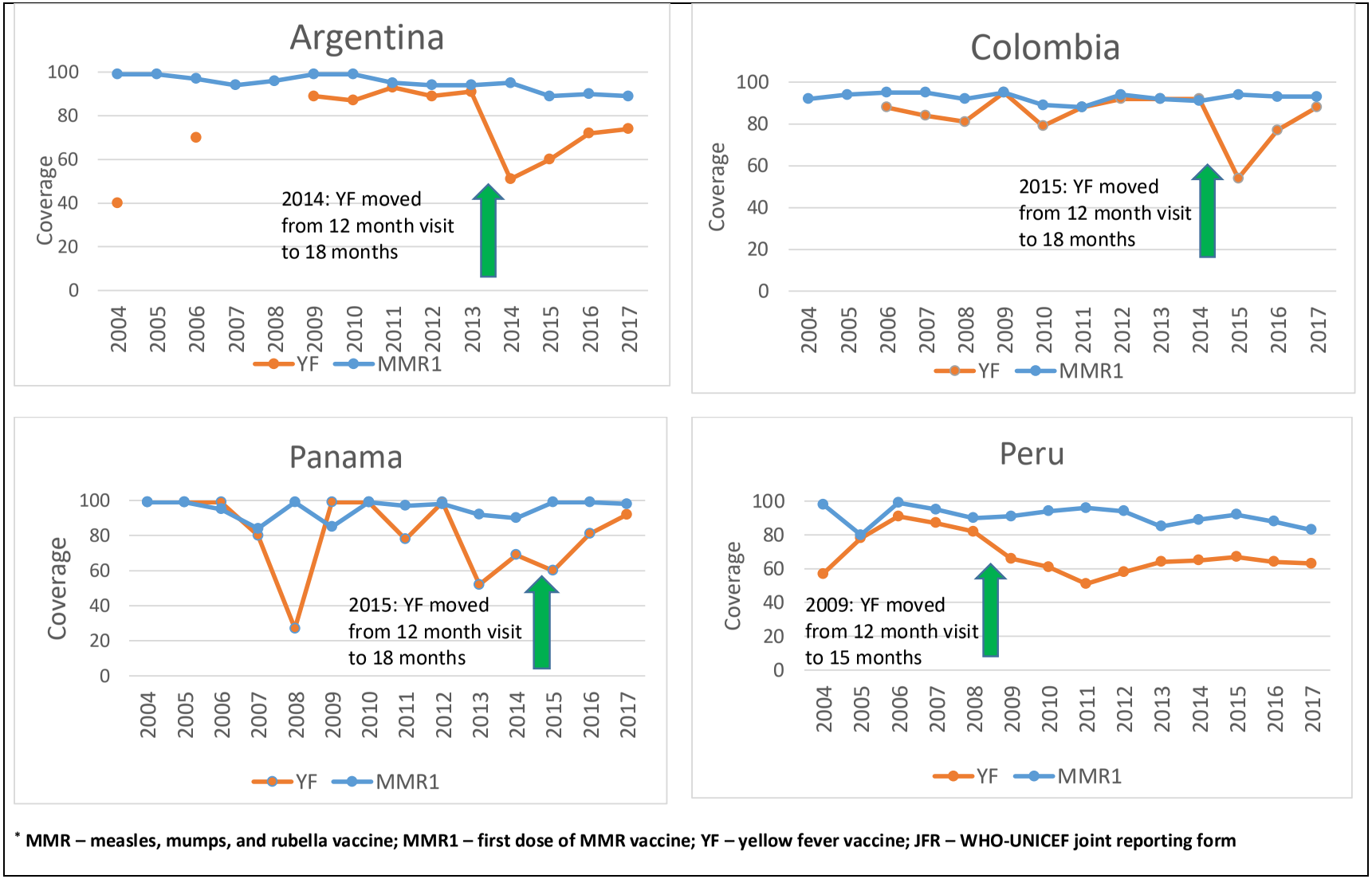
&Results from the Goujon et al. study are seropositivity rather than seroconversion as there were no baseline samples

Table 4: Antibody titers / concentrations: Co-administration compared to individual or sequential administration of measles-containing vaccines and yellow fever vaccine

Study Reference [Location]	Measles	Mumps	Rubella	Yellow Fever
Nascimento Silva et al., 2011 [3] [Brazil]	GMTs (95% CI) in IU/mL Co-admin: 3.44 (3.20 – 3.70)* Sequen: 3.19 (3.00 – 3.39) P-value not stated	GMTs (95% CI) in mIU/mL Co-admin: 335.5 (314.4 – 358.0)* Sequen: 414.1 (388.0 – 442.1) P-value not stated	GMTs (95% CI) in IU/mL Per protocol cohort Co-admin: 24.9 (23.3 – 26.6) Sequen: 59.9 (56.3 – 63.7) P<0.001 Intent to Treat Cohort Co-admin: 24.8 (23.2 – 26.5) Sequen: 60.1 (56.5 – 63.9) P<0.001	GMTs (95% CI) Per protocol cohort Co-admin: 1064.6 (976 – 1161.2) Sequen: 3385.2 (3105.2 – 3690.4) P<0.001 Intent to Treat Cohort Co-admin: 1060.2 (1015.1 – 114.6) Sequen: 3381.3 (3236.8- 3683.7) P<0.001
Clarke et al., 2016 [7] [The Gambia]	Median (95% CI) in IU/mL Co-admin: 270 (243 – 310) Individ: 250 (230 – 280) Co-admin was non-inferior	N/A	Median (95% CI) in IU/mL Co-admin: 27 (24 – 31) Individ: 31 (27- 36) Non-inferiority not shown / inconclusive	GMTs (95% CI) Co-admin: 64 (64 -491) Individ: 128 (91- 128) Non-inferiority not shown
Unpublished, 2018 [Argentina]	GMTs (95% CI) in mIU/mL Per protocol cohort Co-admin: 1956 (1629 – 2348) Individ: 1561 (124 – 1956) P=0.17 Intent to Treat Cohort Co-admin: 2024 (1705 – 2402) Individ: 1631 (1317 – 2021) p=0.16	GMTs (95% CI) in U/mL Per protocol cohort Co-admin: 1745 (1390 – 2192) Individ: 2320 (1925 – 2795) P=0.04 Intent to Treat Cohort Co-admin: 1806 (1470 – 2220) Individ: 2252 (1876 – 2703) P=0.08	GMTs (95% CI) in IU/mL Per protocol cohort Co-admin: 32.2 (28 – 37.1) Individ: 39.4 (33.5 – 46.4) P=0.0007 Intent to Treat Cohort Co-admin: 35.8 (31.5 – 40.7) Individ: 40.8 (34.9 – 47.5) P=0.005	GMTs (95% CI) Per protocol cohort Co-admin: 225 (181 – 279) Individ: 373 (308 – 452) P<0.001 Intent to Treat Cohort Co-admin: 219 (181 – 265) Individ: 340 (283 – 408) P<0.001
Goujon et al., 2017 [8] [France]	GMTs (95% CI) in mIU/mL Co-admin: 2872 (2013 – 4094) Sequential: 4076 (2377 – 6988) P> 0.05	Not reported	GMTs (95% CI) in IU/mL Co-admin: 97 (71 – 133) Sequential: 111 (79 – 156) P>0.05	N (%) with stated titer Co-admin: / Sequential: <5: 0 / <5: 4 (8) 10: 0 / 10: 1 (2) 20: 3 (16) / 20: 4 (8) 40: 4 (21) / 40: 15 (30) ≥80: 12 (63) / ≥80: 26 (52) P-value not reported

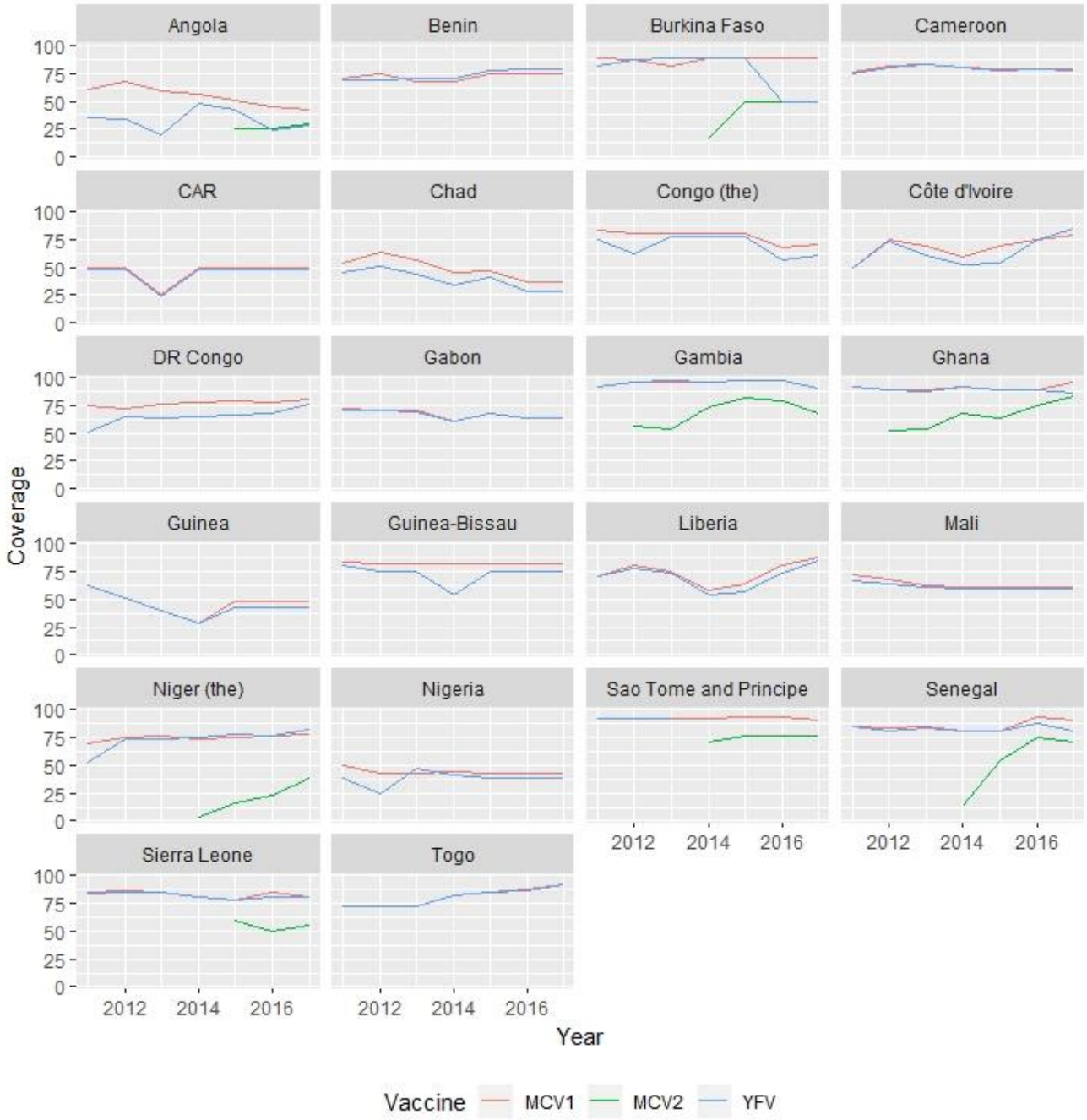
Co-admin: Received MR/MMR and YF co-administered
Sequen: Received MMR an YF sequentially (MMR followed by YF at least 28 days later) with sample collected after both vaccinations complete
Individ: Received either MR/MMR or YF individually (follow-up sample collection was prior to receipt of the second vaccine)
*Paper focused on rubella and yellow fever results; data presented for measles and mumps is minimal
#Per protocol cohort had 20-30 children per group fewer than the intent to treat cohort and was underpowered for a non-inferiority analysis with 5% margin

Figure 1: MMR1 and YF coverage in the 4 PAHO countries that initially co-administered YF with MMR at the 12 month vaccination visit and then moved YF to the 15 or 18 month vaccination visit (JRF data)*



* MMR – measles, mumps, and rubella vaccine; MMR1 – first dose of MMR vaccine; YF – yellow fever vaccine; JFR – WHO-UNICEF joint reporting form

Figure 2: MCV1, MCV2, and YF in YF-endemic countries* in the AFRO region: 2010 - 2017 (WUENIC data)



*Includes all countries in AFRO region that have ≥2 years of YF WUENIC estimates. All available MCV2 WUENIC data for these countries is included. Abbreviations: CAR=Central African Republic; DR Congo=Democratic Republic of Congo; MCV – measles-containing vaccines. Note: MCV1 – first dose of MCV; MCV2 – second dose of MCV.

Guidance to Increasing Population Immunity against Measles and Rubella

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Table of Contents

Opening Remarks

This document provides guidance to identify and address measles and rubella immunity gaps in order to raise population immunity. Countries' epidemiologic profiles are used to help prioritize interventions to increase population immunity. In addition, strategies to address specific immunity gaps (e.g. lower immunity in school-age children) are provided.

All guidance in this document should be considered in conjunction with any existing regional guidance as regional guidance may provide strategies better tailored to specific countries or sub-national areas. This guidance is intended mainly to support measles/rubella endemic countries although much of the guidance is applicable to countries that have achieved elimination, as they still need to maintain high population immunity. This framework may also be useful to countries as they prepare evidence for their national verification committees (NVCs) as demonstration of high population immunity is a key component to verification of measles and rubella elimination.

Note: This document focuses on strategies for increasing population immunity; it does not cover disease surveillance/surveillance systems nor provide detailed activities to improve the performance of routine immunization (RI) programs and campaigns. While these are all important areas to strengthen in order to increase population immunity, they are addressed in other documents.[1,2,3] and should be used in tandem with this document.

This guidance was developed with the following principles:

- Increasing population immunity should take a Continuous Quality Improvement (CQI) approach (explained below)
- Critical review of all available data sources is needed to identify immunity gaps
- Strengthening RI is the primary strategy for increasing population immunity
- Campaigns are needed (as rescue measures) where RI for two doses of measles and rubella-containing vaccines is sub-optimal and to address specific immunity gaps.
- During the time period following campaigns, activities must be quickly prioritized to strengthening RI systems.

[1] Sniadack DH, Crowcroft, N, Durrheim, DN, Rota PA**.** Roadmap to elimination standard measles and rubella surveillance. Weekly Epidemiological Record 2017; 92: Nos 9/10: 97-105.
[2] Global Routine Immunization Strategies and Practices (GRISP): a companion document to the Global Vaccine Action Plan (GVAP). Geneva, WHO Press, 2016.
[3] Planning and Implementing High-Quality Supplementary Immunization Activities for Injectable Vaccines using an example of measles and rubella vaccines: field guide. Geneva, WHO Press, 2016.

Background

Despite the existence of an effective vaccine, measles is still a leading driver of child mortality.[4] In 2016, nearly 90,000 children died from measles despite an 84% reduction in annual deaths since 2000. From 2000-2016, measles vaccination prevented roughly 20 million deaths, showing the importance of vaccination. For rubella, considerable burden remains as many countries have not yet introduced rubella-containing vaccine (RCV).[5] However, considerable progress towards rubella control and elimination has been achieved in the nations that have introduced RCVs. All six World Health Organization (WHO) regions have established a measles elimination goal for 2020 at the latest[6] and three WHO regions have a rubella elimination goal[7]. A standardized method to classify countries has been proposed for Regional Verification Commissions (RVCs) use to document countries' progress toward measles and rubella elimination[8].

Elimination will not be achieved and sustained without high population immunity in all administrative health areas and age groups. Table 1 shows core activities that all countries should implement as the foundation for achieving and sustaining high population immunity.

[4] http://www.who.int/news-room/fact-sheets/detail/measles, Accessed September 13, 2018.

[5] http://www.who.int/news-room/fact-sheets/detail/rubella, Accessed September 13, 2018.

[6] Dabbagh A, Patel MK, Dumolard L, Gacic-Dobo M, Mulders MN, Okwo-Bele JM, Kretsinger K, Papania MJ, Rota PA, Goodson JL. Progress Toward Regional Measles Elimination - Worldwide, 2000-2016. MMWR Morb Mortal Wkly Rep. 2017 Oct 27;66(42):1148-1153.

[7] Grant GB, Reef SE, Patel M, Knapp JK, Dabbagh A. Progress in Rubella and Congenital Rubella Syndrome Control and Elimination - Worldwide, 2000-2016. MMWR Morb Mortal Wkly Rep. 2017 Nov 17;66(45):1256-1260.

[8] Meeting of the Strategic Advisory Group of Experts on Immunization, October 2017 – conclusions and recommendations. Wkly Epidemiol Rec. 2017 Dec 1;92(48):729-747.

Table 1: Core Strategies for Achieving Elimination-Standard Immunity against Measles and Rubella

Program	**Target (as applicable)**
Provide 2 doses of MRCV through routine immunization services[9] [10] [11] [12] [13] [14] [15]	95% nationally and within each sub-national unit
Conduct high quality national follow-up campaigns at intervals determined by the country's epidemiology and vaccination coverage (typically every 2-4 years) and sub-national campaigns where appropriate [16]	Continue with nationwide campaigns* until routine coverage with both MCRV1 and MCRV2 is at least 90-95% for 3 consecutive years
Implement missed opportunities for vaccination (MOV) strategy e.g. use every contact with a health provider to check vaccination history and provide any missed vaccinations [17] [18] [19]	
Implement school entry checks with or without school-based vaccination program as appropriate in local context [20]	
Establish programs to vaccinate health workers[21]	
Establish programs to vaccinate immigrants/refugees/travelers and other high-risk groups	
Conduct high quality outbreak response immunization when outbreaks occur	
*Guidance on appropriate use of sub-national campaigns is under development	

It is recognized that countries have varying levels of financial and other resources to implement the above strategies in a consistent, high quality manner. Hence immunity gaps occur. This guidance provides a broad step-wise framework for Ministries of Health and WHO country/regional offices to think about a country's epidemiologic profile and identify specific

[9] Global Measles and Rubella Strategic Plan 2012-2020. Geneva, WHO Press, 2012.
[10] Measles vaccines: WHO position paper – April 2017. Wkly Epidemiol Rec. 2017 Apr 28;92(17):205-27.
[11] Rubella vaccines: WHO position paper. Wkly Epidemiol Rec. 2011 Jul 15;86(29):301-16.
[12] Global Routine Immunization Strategies and Practices (GRISP): a companion document to the Global Vaccine Action Plan (GVAP). Geneva, WHO Press, 2016.
[13] http://www.who.int/immunization/programmes_systems/service_delivery/red/en/, Accessed September 20, 2018.
[14] A Guide to Introducing a Second Dose of Measles Vaccine into Routine Immunization Schedules. Geneva, WHO Press, 2013.
[15] Introducing Rubella Vaccine into National Immunization Programmes. A step by step guide. Geneva, WHO Press, 2015.
[16] Planning and Implementing High-Quality Supplementary Immunization Activities for Injectable Vaccines using an example of measles and rubella vaccines: field guide. Geneva, WHO Press, 2016.
[17] Measles vaccines: WHO position paper – April 2017. Wkly Epidemiol Rec. 2017 Apr 28;92(17):205-27.
[18] Global Routine Immunization Strategies and Practices (GRISP): a companion document to the Global Vaccine Action Plan (GVAP). Geneva, WHO Press, 2016.
[19] http://www.who.int/immunization/programmes_systems/policies_strategies/MOV/en/, Accessed 20 September 2018.
[20] Measles vaccines: WHO position paper – April 2017. Wkly Epidemiol Rec. 2017 Apr 28;92(17):205-27.
[21] Measles vaccines: WHO position paper – April 2017. Wkly Epidemiol Rec. 2017 Apr 28;92(17):205-27.

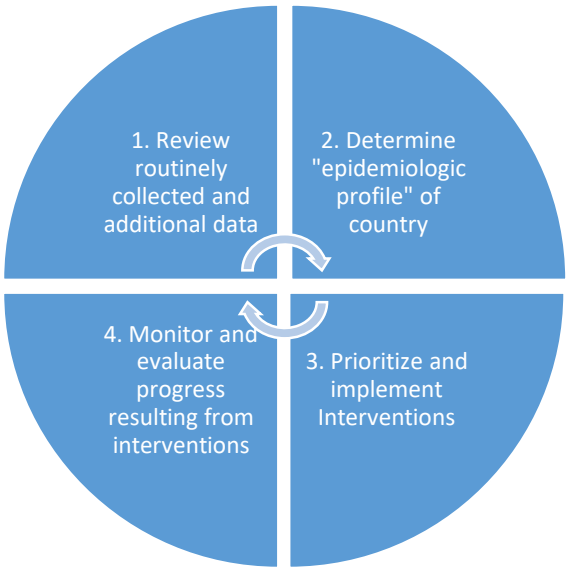
immunity gaps and then prioritize interventions to fill these gaps. As mentioned, all guidance should be used in conjunction with any regional guidance that may provide strategies specifically tailored to individual regions. In addition, measles and rubella interventions should be integrated together in approach, but their population immunity should be evaluated separately.

This guidance is organized in a step-wise approach:

- **Step 1**: Review all available data to understand measles and rubella/CRS epidemiology and potential immunity gaps
- **Step 2**: Assess general epidemiologic profile of country
- **Step 3**: Identify, prioritize and implement interventions
- **Step 4**: Assess outcomes resulting from interventions

The four steps above are meant to be implemented within a CQI framework (Figure 1). CQI is a cyclical framework in which problems are assessed, interventions are implemented, and then the impact of the interventions are evaluated.

Figure 1: Continuous Quality Improvement (CQI) Framework



Stepwise Framework

Step 1: Review available data sources to understand measles and rubella/CRS epidemiology and possible immunity gaps (including at sub-national levels)

In implementing Step 1, countries should gather ALL available data that may provide insight into levels of population immunity and gaps that may exist. Different sources of data (e.g. administrative coverage, campaign coverage, surveillance data) should be compared through a process called "triangulation." Triangulation is described more fully in Annex A, but the basic principle is to look at different sources of existing data to see where complementary and contradictory information exists. As all data sources have their limitations, this can provide a more complete understanding of a country's epidemiologic profile. Where data contradict each other, critical thinking is required to try to understand what is underlying the discrepancy. When interpreting data, the quality of the data must always be considered as well as the strengths, weaknesses and best usages for each type of data. Finally, if financial and human resources are available, a root cause analysis should be considered to better understand the underlying causes of the identified gaps.

Annex A provides more detailed information on various data sources and available tools/methodologies for assessing population immunity. Brief summaries of each data source and tool are provided here:

Routinely available data:

Surveillance

Case-Based Surveillance is the WHO-recommended surveillance standard for measles and rubella and is used to detect and investigate suspected measles and rubella cases. It involves the ongoing and rapid identification of suspected cases for the purpose of case investigation. Data from a case-based system may or may not be complete or representative, however it is critical for understanding which suspected cases are laboratory-confirmed, epidemiologically-linked or discarded. Furthermore, as countries approach elimination, their case-based surveillance should become a more accurate source of data from the true number of cases in a country. Finally, vaccination history should be collected in all of the suspected cases; this can be used as another source of information on vaccination coverage. With good data on vaccination history, *vaccine effectiveness analyses* can be conducted which can be very helpful in populations where effectiveness may vary from the global norms which can result in inaccurate immunity estimates. If *genotyping* of samples is conducted, this data can help to define the spatial and temporal transmission dynamics of measles, which can highlight underlying immunity gaps. Countries may choose to analyze the 5 previous years of surveillance data stratified by age, sex, birth cohort, sub-national level (2nd or 3rd administrative level depending on population size) and vaccination status

Aggregate surveillance data: The Integrated Disease Surveillance and Response (IDSR) and other aggregate surveillance data systems typically collect aggregate case counts for selected priority

diseases or conditions. Aggregate systems require fewer resources than case-based systems, however they typically do not distinguish between suspected and confirmed cases; hence it is difficult to understand the true burden of disease.

Historical Coverage Data

Routine (administrative) vaccination coverage data is a key measure of immunization system performance and can be used to assess population immunity when adjusted for vaccine effectiveness. Unfortunately, in many countries, administrative coverage estimates are inaccurate due to errors in the denominator (total target population), errors in recording vaccinations at health facilities, and errors in compiling the data to report to higher levels.[22] To address these challenges, WHO and UNICEF release WUENIC estimates each year which are estimates derived through triangulation of all data sources reflecting coverage in a country. These are typically considered to be more accurate that reported administrative data. National and sub-national coverage by birth cohort, and since the introduction of MRCVs should be reviewed.

Campaign administrative coverage data: Administrative coverage from campaigns is one source of information for assessing coverage. However, it must be interpreted cautiously because imprecision of both numerators and denominators can provide false reassurance that coverage objectives have been met.[23]

In addition to the routinely available data sources above, the following critical sources should be reviewed if a country has them:

Population Coverage Surveys:

Post-campaign coverage surveys should be nationally representative surveys using probability sampling to assess the coverage. They provide an independent, and more accurate, estimation of campaign coverage. However they may not provide estimates at lower sub-national levels[24].

Other Coverage Surveys (MICS, DHS, etc.): Household surveys include the Multiple Indicator Cluster Survey (MICS) from UNICEF and Demographic & Health Survey (DHS) from USAID. MICS and DHS are large-scale, nationally representative household surveys that typically include a component of vaccination coverage in young children (e.g. 12-23 months).[25] Coverage estimates from surveys are often trusted more than administrative estimates but, like administrative estimates, their accuracy depends in part on the quality of primary recording of vaccinations. In addition, surveys are subject to other types of information bias, selection bias and sampling error.[26] Finally, these surveys only provide data on one birth cohort of children and may only be administered every 3-10 years.

Outbreak Investigation Reports:

In general, the primary reason for an outbreak investigation and response is to control the outbreak and help prevent future outbreaks. High quality outbreak reports will describe the

[22] Cutts FT, Izurieta HS, Rhoda DA. Measuring coverage in MNCH: design, implementation, and interpretation challenges associated with tracking vaccination coverage using household surveys. PLoS Med. 2013;10(5):e1001404.
[23] Zuber PL, Yaméogo KR, Yaméogo A, Otten MW Jr. Use of Administrative Data to Estimate Mass Vaccination Campaign Coverage, Burkina Faso, 1999. J Infect Dis. 2003 May 15;187 Suppl 1:S86-90.

[24] World Health Organization Vaccination Coverage Cluster Surveys: Reference Manual. http://www.who.int/immunization/documents/who_ivb_18.09/en/
[25] http://www.publishwhatyoufund.org/wp-content/uploads/2016/11/Household-surveys-do-competing-standards-serve-country-needs.pdf, Accessed September 13, 2018.
[26] Cutts FT, Claquin P, Danovaro-Holliday MC, Rhoda DA. Monitoring vaccination coverage: Defining the role of surveys. Vaccine. 2016 Jul 29;34(35):4103-4109.

epidemiology of the outbreak, the causes contributing to the outbreak, and the outbreak response conducted. This information can be very helpful to see where immunity gaps developed in the past and how they resulted in an outbreak.[27] Reports from the last 5 years are the most relevant to current immunity gaps.

Serosurveys:

Data/reports from past serosurveys provide data on actual immunity to measles and rubella in a population. Serosurveys may be conducted through DHS/MICS surveys or other survey designs, including rubella serosurveys among women of childbearing age. While these provide high-quality data on immunity, they may be conducted in specific sub-populations or birth cohorts and this needs to be taken into consideration when interpreting the data. Furthermore, they may be based on convenience rather than representative sample populations. [28]

Modeling Studies (see Annex B)

Reports/publications from previously-conducted modeling studies: Modeling studies can be used to create estimates of immunity based on multiple sources of data. They can also be used to measure the impact of many scenarios on the progress and speed towards measles elimination and outbreak control. Scenarios may include demographic transitions, subclinical measles, investing resources for measles elimination, differing coverage rates, etc.

There are several tools/methodologies that can be used to analyze existing data. These are described briefly below and more thoroughly in Annex B. The quality of the source data used with these tools will strongly impact the accuracy of any estimates/results that they generate.

Data triangulation (concept presented above): 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.

Risk assessment tool: The World Health Organization (WHO) measles programmatic risk assessment tool was developed to help national programs to identify areas not meeting measles programmatic targets, and based on the findings, guide and strengthen measles elimination program activities and reduce the risk of outbreaks. It takes into consideration several areas of data that contribute to risk of measles outbreaks in sub-national geographic areas[29]

WHO MSP Tool (and other Excel based tools for birth cohort analyses): The WHO Measles Strategic Planning (MSP) Tool was developed in the mid-2000s to facilitate a combined analysis of national immunization and surveillance data and generate immunity estimates by birth cohort. It can also estimate the effectiveness and cost effectiveness of different vaccination strategies.

Mathematical Modeling: Mathematical modeling uses population-based disease transmission and susceptibility models to estimate gaps in immunity and susceptibility.

[27] Guidelines for measles and rubella outbreak investigation and response in the WHO European Region. Copenhagen, WHO Regional Office for Europe, 2013.
[28] Guidance on conducting serosurveys in support of measles and rubella elimination in the WHO European Region. Copenhagen, WHO Regional Office for Europe, 2013.
[29] http://www.who.int/immunization/monitoring_surveillance/routine/measles_assessment/en/. Accessed September 13, 2018.

Key questions to consider when analyzing the data are: where is immunity high (>95%)? Where are immunity gaps? To identify gaps, both low vaccination coverage and the occurrence of cases/outbreaks should be considered. Sub-national levels, age group/birth cohort analyses, and high risk populations should be evaluated.

Step 2: Determine the "epidemiologic profile" of the country

After reviewing and analyzing available data, countries should identify which row in Table 2 best describes their epidemiologic profile for measles and rubella which takes into account their disease burden, population immunity, immunization program capacity, and capacity to conduct outbreak investigations. When using Table 2, the first column is meant to summarize the overall epidemiologic profile of a country which takes into account the areas described in the following 4 columns. The last column presents overarching recommendations for countries who fit in that row. Countries may identify with characteristics in multiple rows, and if this is the case, they should determine which classification best fits their overall standing. *Table 2 is not meant to be a rigid classification system, but rather general guidance to help countries think about where they fit along a spectrum from high endemicity to elimination and then prioritize strategies to raise population immunity.*

Countries should also consider how their population size, density, and size of birth cohort nationwide and in sub-national areas may influence their capacity to interrupt transmission. For example, in small island countries or rural populations, sparsely populated areas' transmission may appear to be interrupted at lower levels of population immunity while large, populous countries or cities may continue to have endemic transmission despite relatively high 2 dose coverage.

Table 2: Country-level epidemiologic profiles

Overall Epidemiologic Profile (summary of general characteristics in the next four columns)	General Characteristics of Countries with this Epidemiologic Profile *(measles and rubella should evaluated separately; countries may fall into different rows for different characteristics)*				Recommendations for Immunization System Priorities
	Disease Burden	**Population Immunity**	**Immunization Programme Capacity**	**Capacity to Conduct Outbreak Investigations**	
Low disease incidence with infrequent outbreaks, high population immunity, strong program capacity and outbreak investigations. Can include countries that have eliminated measles/rubella as well as endemic countries. Note that incidence may be very low in the honeymoon period[30].	Low incidence of disease Infrequent outbreaks, temporally (<12 months duration) and geographically-limited Cases predominantly in children too young to be immunized and/or adolescents/adults	High population immunity, particularly among children; however, may have age, sub-population or geographic immunity gaps. During the honeymoon period, susceptible individuals will accumulate rapidly unless routine immunization is strengthened	Consistent high coverage (e.g. ≥90%) [31]with both doses of MRCV†. Highly sensitive case-based surveillance system. Demonstrated capacity to conduct high-quality campaigns and timely ORI.	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 and actions are taken to close gaps.	Increase or sustain coverage with two routine doses of MRCV to at least 95%. Actively look for age-specific, sub-population and/or geographic immunity gaps and address them so that outbreaks are averted. Conduct targeted interventions as needed to fill identified immunity gaps; may be sub-national or population-specific Rapidly investigate and contain outbreaks that occur. Immediately after a campaign, rapid strengthening of RI with high coverage needs to be implemented and maintained to avoid later outbreaks.

[30] When there are low amounts of cases following a campaign due to a spike in increased population immunity (especially following a wide-age range SIA)

[31] The 90% suggestion is not a prescriptive cut-off. It is rather an estimation signaling a strong coverage, although there may be fluctuation with this figure. As explained, countries may have various inconsistencies and may not fit directly into one of the categories.

Medium disease incidence with periodic outbreaks, inadequate immunity in some populations, and moderate program/outbreak investigation capacity. Note that incidence may be very low in the honeymoon period[32].	Medium incidence of disease Periodic outbreaks that are responded to and 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 MRCV doses through routine immunization and/or campaigns; most adults were either vaccinated or had prior infection.	Suboptimal MRCV1 coverage (e.g. 85 - 90%); MRCV2 may or may not be introduced. if introduced, coverage is likely suboptimal or lower. Sensitivity of case-based surveillance system may be sub-optimal and may vary across sub-national divisions. Campaigns may have sub-optimal quality, and/or may not have been conducted recently.	Outbreak investigations are conducted for the majority of outbreaks. Investigations provide additional information on immunity gaps which may or may not be addressed.	Increase quality of routine immunization services with aim to decrease reliance on campaigns. Conduct high quality campaigns with a focus on reaching those unreached through the RI system. Determine inter-campaign intervals and targeted age group by epidemiologic analysis and population susceptibility analyses. If high quality data are available to allow accurate subnational analysis, campaigns may be targeted based on the epidemiological profile of the sub-national areas concerned[33] Implement specific strategies to fill known immunity gaps (e.g. HCWs, migrants, subpopulations). Increase outbreak response preparedness so that outbreaks can be rapidly detected, investigated and contained. Immediately after a campaign, rapid strengthening of RI with high coverage needs to be implemented and maintained to avoid later outbreaks.

[32] When there are low amounts of cases following a campaign due to a spike in increased population immunity (especially following a wide-age range SIA)

[33] This requires epidemiologically distinct and heterogeneous geographical areas, and the subnational approach must be programmatically feasible. The MR SAGE WG is working on more precise guidance for countries when carrying out targeted sub-national approach which will be presented to the SAGE in 2019.

High disease incidence with frequent outbreaks, inadequate population immunity, and limited program/outbreak investigation capacity. Note that incidence may be very low in the honeymoon period[34].	High incidence of disease On-going, endemic transmission and regular large-scale, long duration outbreaks even shortly after campaigns. 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.	Long standing low MRCV1* coverage (e.g. < 85%) MRCV2# not introduced or very low coverage. Case-based surveillance not implemented or inadequately sensitive. Quality of campaigns is inadequate and/or they have not been conducted in a timely manner.	Due to large-scale and frequent outbreaks, outbreak investigations are typically inadequate. The beginning and end of outbreaks may not be determined consistently. ORI may not be implemented in a timely manner (or at all)	Assess existing routine immunization system; develop and implement comprehensive plan to address shortcomings. Identify and address issues with quality of campaigns to ensure zero dose and under vaccinated children are reached. Conduct high quality campaigns with inter-campaign intervals and targeted age group determined by epidemiologic analysis. Increase outbreak response preparedness so that outbreaks can be rapidly detected, investigated and contained. Immediatley after a campaign, rapid strengthening of RI with high coverage needs to be implemented and maintained to avoid later outbreaks
Applicable only for rubella in countries that have not yet introduced RCV[35]. Pre-vaccine epidemiology: high incidence with outbreaks typically among children	Endemic rubella virus transmission. Highest burden typically among children aged 5-9 years.	All immunity due to natural infection.	RCV not yet introduced. Case-based rubella surveillance may or may not exist as part of a joint measles-rubella surveillance system. CRS surveillance may or may not be implemented.	Rubella outbreaks may or may not be detected and investigated.	Set up basic structure for rubella elimination through wide-age range introductory campaign and introduction of two doses of RCV into routine immunization services.

[34] When there are low amounts of cases following a campaign due to a spike in increased population immunity (especially following a wide-age range SIA)
[35] Some countries may provide RCV through the private sector. This category concerns countries that have not introduced RCV nationally.

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; campaign = supplementary immunization activity; WUENIC = WHO-United Nations Children's Fund (UNICEF) coverage estimate

Step 3: Identify, prioritize, and Implement Interventions:

Using the last column of Table 2, countries can identify the overarching strategies that are most helpful to countries with their epidemiologic profile. This guidance provides several additional tools to plan more specific activities that are organized in three ways:

-Core activities that all countries should implement are shown in Table 1

-Activities most useful for countries within a specific epidemiologic profile (as described in Table 2). Some examples of activities prioritized in this way are discussed below.

-Activities to fill specific immunity gaps are shown in Table 3

When prioritizing interventions, the following need to be considered:

- Country context
- The effectiveness of interventions in addressing the identified issue/gaps
- The feasibility of conducting a high quality intervention, which includes the programmatic capacity in country as well as the availability of needed resources (human and financial)
- Size of the population, population movements, and migration

In addition, one good resource is the WHO'S GRISP guidance[36] which provides a more comprehensive overview of strategies to strengthen immunization programs. However, working within the context of epidemiologic profiles as presented in Table 2, the following are a few examples of interventions that should be prioritized for countries depending on their epidemiologic profile as described in Table 2:

For countries whose epidemiologic profile fits best in the **first** row of Table 2:

Long Term Strategies To Raise Population Immunity	**Short term and Immediate Approaches to Address Immunity Gaps**
Increase/sustain 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 and strengthen MR surveillance	Targeted activities may be needed if immunity gaps /susceptible populations are identified. If national coverage is very high but a gap is identified, interventions should be targeted to the identified gaps

For countries whose epidemiologic profile fits best in the **second** row of Table 2:

[36] World Health Organization. Global Routine Immunization Strategies and Practices. 2016.

Primary Long Term Strategies To Raise Population Immunity	Short term and Immediate Approaches to Address Immunity Gaps
Strengthen routine immunization services (logistics, cold chain, demand, coverage, etc.). Focus on strategies to increase coverage with both MRCV1* and MRCV2# to >95% so that regular campaigns will not be necessary. Consider PIRIs and more outreach sessions. 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 and strengthen MR surveillance	Conduct follow-up campaigns, focusing strategies on reaching those not reached through routine immunization services. Where epidemiologic data indicate immunity gaps in children >5 years old, national or subnational wide age range campaigns may be considered if effective strategies to reach the under- or un-vaccinated are in place.

For countries whose epidemiologic profile fits best in the **third** row of Table 2:

Primary Long Term Strategies To Raise Population Immunity	Short term and Immediate Approaches to Address Immunity Gaps
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 and strengthen MR surveillance	Address quality of campaigns. Determine why children are being missed and address the problems. Conduct follow-up campaigns at regular intervals. Focus strategies on reaching those not reached through routine immunization. Where epidemiologic data indicate immunity gaps in children >5 years old, national or subnational wide age range campaigns may be considered if effective strategies to reach the under- or un-vaccinated are in place.

For countries whose epidemiologic profile fits best in the **last** row of Table 2:

Primary Long Term Strategies To Raise Population Immunity	Short term and Immediate Approaches to Address Immunity Gaps
Strengthen routine immunization services to ensure high coverage with RCV. Strengthen MR case-based surveillance; consider establishment of CRS surveillance.	Conduct RCV introductory catch-up campaigns. Introduce two doses of RCV into the routine program as MR/MMR vaccine.

When immunity gaps are identified within specific sub-populations, interventions can be targeted to those specific sub-populations (Table 3). Again, this table is not an exhaustive list; activities should to be assessed and prioritized according to the country context and other issues listed above. Finally, root cause analyses are highly recommended to understand what is causing the gaps so that interventions can be tailored to address the true cause of the gap.

Table 3: Activities[1] to address specific immunity gaps.

Immunity Gap	Long Term Strategies to Avoid Accumulation of Susceptible Persons	Immediate Approaches to Address the Gap
Under 1	- Implement strategies to improve the coverage and timeliness of MRCV1* in countries where vaccine is administered at 9-11 months of age.	- Include infants from 6 months of age in preventive vaccination campaigns and in outbreak response campaigns. - Consider source of exposure and consider targeting that group (e.g., parents/adults, older siblings, HCW).
Age 1 to 5	- Identify and address the underlying reasons for the immunity gap. - Strengthen routine MRCV1 and MRCV2 programs and improve coverage. - Remove maximum age limits for MRCV1 and MRCV2 to ensure that they receive both doses, even if they present for vaccination after the recommended ages for vaccination. - 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. - Ensure that MRCV2 is included in Fully Immunized Child (FIC) estimates - Monitor the gap in coverage between MRCV1 and MRCV2; identify and address reasons for gap (ref GRISP).	- Conduct high quality campaigns (nationally or sub-nationally, depending on the extent of the identified gap; consider school-/daycare-based campaigns/strategies).
Children ≥5 and adolescents	- 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. - Eliminate any policies that discourage use of MRCV vaccines in this age group	- Conduct a high quality, wide-age range campaign (nationally or sub-nationally, depending on the extent of the identified gap; consider school-based campaigns/strategies).

Adults	- 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 care for women, and other interactions with health care services. - Offer vaccination before international travel.	- Consider conducting campaign targeting the affected groups. - Make MRCV available free of charge to affected age groups, with priority given to persons who are unvaccinated or vaccinated with only one dose, but available to all regardless of vaccination status.
Migrants	- 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.	- Conduct a high quality campaign targeting migrants as a priority, but with extension to local susceptible populations, under the same rights 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.
Refugees	- 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.	- Provide vaccination services in line with national regulations and with equal rights to refugees at entry and in camps. - Conduct campaigns in refugee camps starting from 6 months of age. - Offer vaccination services through the health system, regardless of the patients' residency status and legal/administrative regulations.
Populations not vaccinated due to lack of vaccination services (e.g., rural, indigenous populations)	- 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. -Consider activities such as Periodic Intensification of Routine Immunization as a periodic systematic intervention	- Conduct periodic intensification of routine immunizations (PIRIs) (or mop-up activities for populations missed during a campaign).
Populations not vaccinated	- Register new inhabitants with health services and include in target population for routine immunization.	- Conduct campaigns in low coverage areas; consider different strategies e.g. many vaccination sites/mobile

due to "invisibility" to vaccination services (e.g., urban, border populations)	- Increase social mobilization, advocacy and communication about vaccination services.	teams, vaccination at markets, transportation centers, work places, schools and universities, extended vaccination hours, - Increase social mobilization, advocacy and communication (targeting diverse age groups).
Populations not vaccinated due to vaccine hesitancy	- Identify and address the underlying reasons for vaccine hesitancy - Tailor social mobilization, advocacy and communication activities to increase uptake of immunization services, considering the unique local context	- Identify and address the underlying reasons for vaccine hesitancy - Tailor social mobilization, advocacy and communication activities to increase uptake of immunization services, considering the unique local context - Campaigns/ORI in surrounding communities to ensure high herd immunity in surrounding populations.
Populations not vaccinated due to stock-outs	- Address root cause that resulted in stock-out and prevent further episodes.	- Campaigns/PIRIs 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.
Any population identified due to an outbreak or serosurvey	- Identify and address root cause of immunity gap. - Consider periodic campaigns 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.	- Adjust ORI to population affected (including all ages affected), e.g., geographic area, work place, university, ethnicity, religion, etc.
[1]Activities presented are not a comprehensive list		

Note: When conducting interventions, campaigns should be used as a temporary measure to address immunity gaps and strengthening RI must be the primary focus. Countries should continually look for opportunities to incrementally improve routine immunization coverage. In addition, it is worth noting (as mentioned in Table 2) that countries often experience no/few cases shortly following a campaign, which is known as the "honeymoon period" by some experts. However, susceptible persons are still accumulating during this time period if routine immunization programs are not reaching full birth cohorts. This reiterates the need to strengthen RI so that countries can eventually stop depending on campaigns.

Step 4: Assess outcomes resulting from interventions

Re-enforced by the CQI Framework, this process is cyclical in nature. All interventions should be evaluated with the attempt to improve upon past successes as figure out how to improve things. As part of this process, countries should:

-Conduct on-going monitoring and evaluation of interventions implemented

-Evaluate progress of interventions several months after implementation

-Consider: Does sufficient data exist to evaluate the implementation effectively? Or is additional data needed? If so, what kind of data, and what is the best way to collect it?

-Review roadblocks to the success of the intervention and figure out how to overcome them

Conclusion

In conclusion, this guidance attempts to guide countries to assess their epidemiologic profile and then implement targeted and data driven interventions at the national and sub-national levels. A four-step process was introduced with in-depth tables for many of the elements. However, in order to provide effective and appropriate interventions, multiple sources of data must be analyzed both pre- and post-intervention with a continuous focus on monitoring and evaluation to improve interventions. Finally, this guidance should be used in conjunction with any existing regional advice, as well as other resources that provide more in-depth guidance for specific areas.

Draft Recommendations from the SAGE WG:

Guiding Principles:

These recommendations are to serve as guiding principles for the immunization program for all countries.

1) Increasing population immunity should take a Continuous Quality Improvement (CQI) approach
2) Critical review of all available data sources is needed to identify immunity gaps
3) Strengthening RI is the primary strategy for increasing population immunity
4) Campaigns are needed (as rescue measures) where RI for two doses of measles and rubella-containing vaccines is sub-optimal and to address specific immunity gaps.
5) During the time period following campaigns, activities must be quickly prioritized to strengthening RI systems.

For countries with the following epidemiological profiles:

1) Countries with Low disease incidence with infrequent outbreaks, high population immunity, strong program capacity (with consistently high coverage with both doses of MRCV) and outbreak

investigations. This also can include countries that have eliminated measles/rubella as well as endemic countries.

a. Recommendations for Immunization System Priorities include:
    i. Increase or sustain coverage with two routine doses of MRCV to at least 95%.
    ii. Actively look for age-specific, sub-population and/or geographic immunity gaps and address them so that outbreaks are averted.
    iii. Conduct targeted interventions as needed to fill identified immunity gaps; may be sub-national or population-specific
    iv. Rapidly investigate and contain outbreaks that occur.
    v. During the time period immediately following campaigns, activities must be quickly prioritized to strengthening RI systems.

2) Medium disease incidence with periodic outbreaks, inadequate immunity in some populations, and moderate program (with suboptimal coverage of MRCV) and outbreak investigation capacity.
    a. Recommendations for Immunization System Priorities include
        i. Increase quality of routine immunization services with aim to decrease reliance on campaigns.
        ii. Conduct high quality campaigns with a focus on reaching those unreached through the RI system. Determine inter-campaign intervals and targeted age group by epidemiologic analysis and population susceptibility analyses.
        iii. If high quality data are available to allow accurate subnational analysis, campaigns may be targeted based on the epidemiological profile of the sub-national areas concerned[37],.
        iv. Implement specific strategies to fill known immunity gaps (e.g. HCWs, migrants, subpopulations)
        v. Increase outbreak response preparedness so that outbreaks can be rapidly detected, investigated and contained.
        vi. During the time period immediately following campaigns, activities must be quickly prioritized to strengthening RI systems.

3) High disease incidence with frequent outbreaks, inadequate population immunity, and limited program (with low coverage of MRCV) and outbreak investigation capacity.
    a. Recommendations for Immunization System Priorities include
        i. Assess existing routine immunization system; develop and implement comprehensive plan to address shortcomings.
        ii. Identify and address issues with quality of campaigns to ensure zero dose and under vaccinated children are reached.
        iii. Conduct high quality campaigns with inter-campaign intervals and targeted age group determined by epidemiologic analysis.
        iv. Increase outbreak response preparedness so that outbreaks can be rapidly detected, investigated and contained.
        v. During the time period immediately following campaigns, activities must be quickly prioritized to strengthening RI systems.

[37] This requires epidemiologically distinct and heterogeneous geographical areas, and the subnational approach must be programmatically feasible The MR SAGE WG is working on more precise guidance for countries when carrying out targeted sub-national approach which will be presented to the SAGE in 2019.

4) **Applicable only for rubella in countries that have not yet introduced RCV[38].** Pre-vaccine epidemiology: high incidence with outbreaks typically among children
    a. Recommendations for Immunization System Priorities include
        i. Set up basic structure for rubella elimination through wide-age range introductory campaign and introduction of two doses of RCV into routine immunization services.

Annexes

Annex A: Data sources for estimating immunity gaps

Annex B: Analytic tools for estimated immunity gaps

Annex C: Classification based on Epidemiologic Profile and Priority Interventions in Algorithm format

[38] Some countries may provide RCV through the private sector. This category concerns countries that have not introduced RCV nationally.

Annex A: Data sources for estimating immunity gaps

	Surveillance Data	Historical Coverage Data (Administrative and WUENIC)	Population Coverage Surveys (Including Post-Campaign, MICS, DHS, etc.)	Outbreak Investigations	Serosurveys
Description	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. With good data on vaccination history, *vaccine effectiveness analyses* can be conducted which can be very helpful in populations where effectiveness may vary from the global norms which can result in inaccurate immunity estimates If genotyping is done, this data can help to define the spatial and	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. Administrative coverage from campaigns is another source of information for assessing coverage.	Population-based surveys are typically cluster surveys such as WHO Vaccination Coverage Cluster Surveys, Demographic and Health Surveys (DHS), and Multiple Indicator Cluster Surveys (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.	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.	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. Reports/publications from modeling studies: Modeling studies can be used to create estimates of immunity based on multiple sources of data

	temporal transmission dynamics of measles and rubella, which can highlight underlying immunity gaps. Aggregate surveillance data systems typically collect aggregate case counts for selected priority diseases or conditions, such as measles and rubella.				
Strengths	• Confirmed cases indicate actual susceptibility, and show where there are susceptible groups in the population • 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 • Aggregate systems require fewer resources than case-based systems	• Data readily available • Data is typically available for many years, at multiple levels, often since vaccine introduction • Countries have ownership of the data	• Obtain more accurate coverage estimates than administrative data since survey data do not depend on poor quality data on doses administered and population estimates • 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	• Shows where actual cases are occurring during an outbreak period • 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	• Serologic testing provides direct measurement of immunity • 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	• 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	• Does not account for protection from SIAs, catch-up vaccination, natural infection • Administrative coverage is often inaccurate due to inaccurate	• 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	• 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	• The sensitivity and specificity of the test used to detect measles or rubella IgG need to be taken into consideration • Waning antibodies may

	• 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 data, the quality of which (including sensitivity) may decline as the incidence of disease declines • 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 • Aggregate data typically do not distinguish between suspected and confirmed cases.	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 • 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 • Campaign administrative coverage data must be interpreted cautiously because imprecision of both numerators and denominators can provide false reassurance that coverage objectives have been met.	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 parents work away from home, places with older subjects that are typically away from home at school or work) • 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)	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 biasing estimates of the immunity profile • 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	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 costs of specimen collection, transport, storage and laboratory testing • 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
Best Use of Data Source to	Case-based surveillance is recommended to be ongoing in all	Historical coverage should be monitored during all	Most useful in countries that have difficulties obtaining accurate	In endemic countries, outbreak investigations are used to identify	Serosurveys are most helpful when coverage

Estimate Immunity Gaps	countries. It can be useful to estimate immunity gaps for all countries; utility increases as the system achieves and maintains elimination standard surveillance standards.	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.	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.	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 issues that led to susceptible persons in the population.	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

Annex B : Analytic methods for estimating immunity gaps

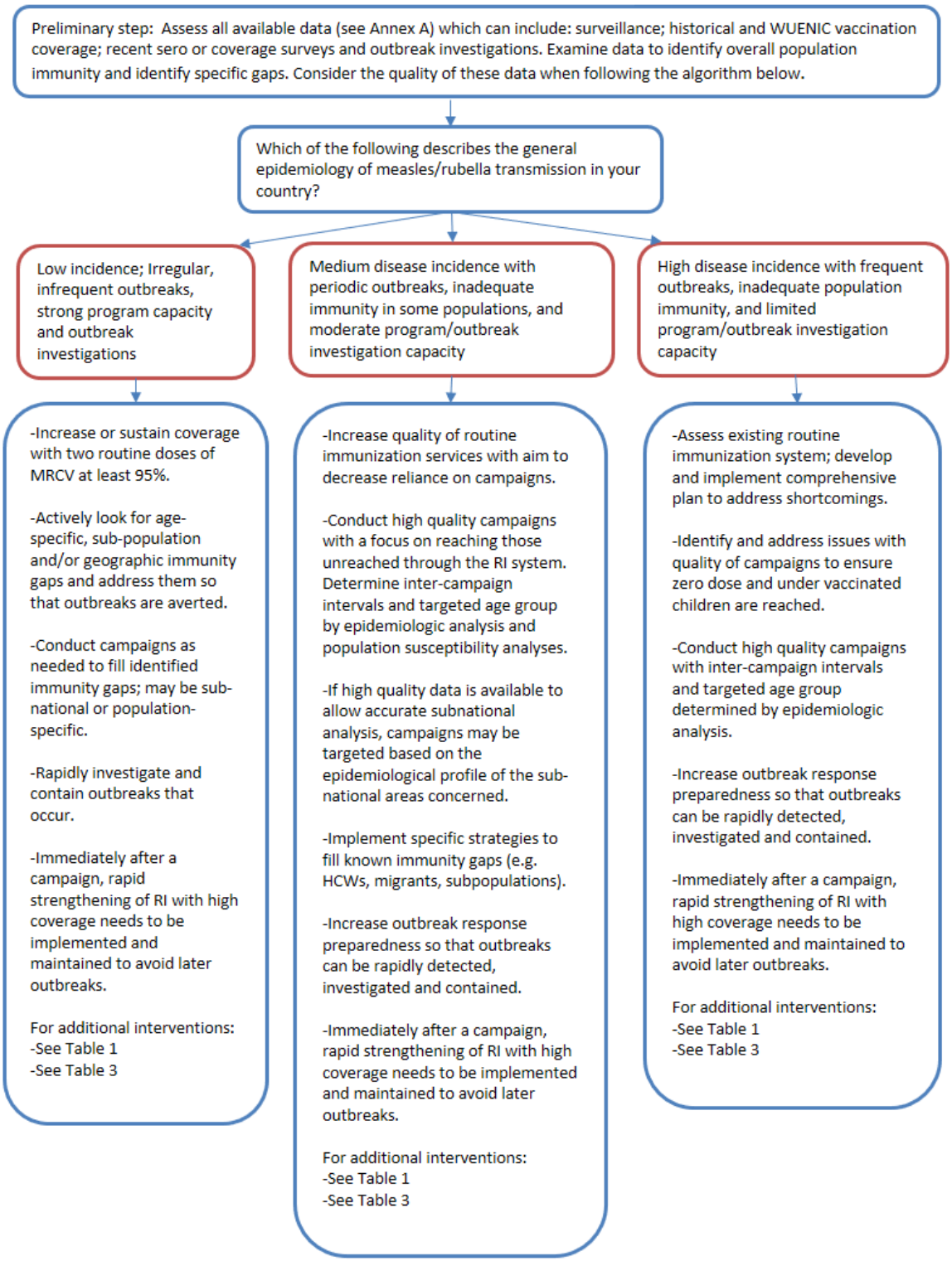
	Data Triangulation	Measles Risk Assessment Tool	WHO Measles Strategic Planning (MSP) Tool and Other Excel-Based Tools to evaluate immunity by birth cohort	Mathematical Modeling
Description	There are many types and methods of data triangulation. It often includes a process of reviewing existing data from 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., • 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? Data should also be compared for concordance across different types of data, e.g., • Do outbreak data show that cases are arising in geographic areas with low or high coverage? Does	• The Measles Risk Assessment Tool is meant to "help national programmes to identify areas not meeting measles programmatic targets, and based on the findings, guide and strengthen measles elimination programmatic activities and reduce risk of outbreaks."[39] It is an Excel-based tool that uses programmatic data encompassing vaccination coverage, surveillance quality, program performance and indicators of outbreak threats such as population density and the presence of vulnerable groups. After inputting the required indicators, the tool classifies subnational areas into 4 categories of high and low risk. Data is meant to be input geographic areas representing the 2nd subnational administrative unit (e.g. districts) and then provides risk assessments at this administrative level.	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.	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.

[39] World Health Organization. Measles Programmatic Risk Assessment Tool. http://www.who.int/immunization/monitoring_surveillance/routine/measles_assessment/en/

	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			
Strengths	• Takes into account several data sources when evaluating a public health issue • 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	• Takes into account several data sources when evaluating a public health issue. • Provides overall risk estimates by administrative/geographic unit (2nd subnational administrative unit, e.g. districts) • Uses routinely available data • It is an Excel based tool that is available on the WHO website. • Several WHO regional offices have learned to support the tool •	• Uses underlying statistical models that take into account 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 • 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 •	• Can combine several sources of data including vaccination coverage, historical surveillance data, and others to model estimates of gaps in immunity and susceptibility • 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	• 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	• Does not focus on areas identified solely by low population immunity; takes into account many factors (this is not a limitation for its general use; but needs to be noted when using the tool as a method to assess population immunity). May need to concentrate on the parameters used to assess	• 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	• 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

	estimates are frequently based on 'expert opinion' and dependent on the skill and experience of the experts	vaccination coverage/population immunity if that is the area of interest. • Only uses data from the past 3 years. Hence vaccination coverage focuses on the youngest age cohorts.	• 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	• 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	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.	This is best used in countries that are closer to elimination and are trying to assess overall risk of outbreaks in subnational geographic areas. It does not directly estimate immunity gaps, but takes into consideration multiple risk factors to help countries tailor where they should concentration interventions geographically. Examination of individual risk components by geographic subunits may provide additional insight into specific immunity gaps and what factors are contributing to the gaps and resultant outbreaks.	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.	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.

Annex C: Stepwise framework in algorithm format



Executive Summary for SAGE Human papilloma virus (HPV) vaccines- Session 7- Wednesday, 24 October 2018

Background:

A SAGE working group was established in June 2018 to evaluate the potential contribution of HPV vaccines and immunization towards cervical cancer elimination. The working group will develop and propose interim goals that can be achieved through immunization as part of the efforts towards cancer elimination as well as to propose indicators to monitor the accomplishment of these interim goals.

Session Objective:

Present SAGE with updated evidence on HPV-related burden, HPV vaccines, impact of HPV immunization programmes, and modelling of impact of HPV immunization schedules and strategies.

SAGE is requested to consider the following questions:

1. What are the potential effect and cost effectiveness of various vaccination strategies towards the achievement of cervical cancer elimination?
2. What is the potential contribution of HPV vaccination towards cervical cancer elimination?
3. What are the interim goals that can be achieved through immunization as part of the efforts towards cancer elimination.
4. What are the indicators to monitor the accomplishment of these interim goals?
5. What is the additional research related to vaccines and immunization needed to attain these goals and outline potential innovations that may help enhance the achievement of these goals?

Session Summary:

1. Presentation: update on HPV vaccine introduction and programmatic perspective.
2. Presentation: an overview of HPV burden of disease and effects of HPV immunization strategies.
3. Presentation: review of the evidence regarding HPV immunization on different disease outcomes.
4. Presentation: compare the impact of different immunization strategies and scenarios towards cervical cancer elimination.

Background Reading (Web):

1- IVIR-AC recommendation 24-25th September meeting
2- SAGE WG meeting report 27-28th September meeting
3- HPV Background document
4- Systematic review of cost-effectiveness studies of human papillomavirus (HPV) vaccination: 9-Valent vaccine, gender-neutral and multiple age cohort vaccination. Siok Shen Ng a,b, Raymond Hutubessy c, Nathorn Chaiyakunapruk; Vaccine 2018.

5- Experiences of operational costs of HPV vaccine delivery strategies in Gavi-supported demonstration projects. Siobhan Botwright, Taylor Holroyd, Shreya Nanda, Paul Bloem, Ulla K. Griffiths4, Anissa Sidibe, Raymond C. W. Hutubessy. PLoS one 2017.
6- Costs of Introducing and Delivering HPV Vaccines in Low and Lower Middle Income Countries: Inputs for GAVI. Policy on Introduction Grant Support to Countries. Ann Levin, Susan A. Wang, Carol Levin, Vivien Tsu, Raymond Hutubessy. PLoS one 2014.
7- Costs of delivering human papillomavirus vaccination to schoolgirls in Mwanza Region, Tanzania. Wilm Quentin, Fern Terris-Prestholt, John Changalucha, Selephina Soteli, W John Edmunds, Raymond Hutubessy, David A Ross, Saidi Kapiga, Richard Hayes and Deborah Watson-Jones. BMC Medicine 2012.
8- A case study using the United Republic of Tanzania: costing nationwide HPV vaccine, delivery using the WHO Cervical Cancer Prevention and Control Costing Tool. Raymond Hutubessy, Ann Levin, Susan Wang, Winthrop Morgan, Mariam Ally, Theopista John and Nathalie Broutet. BMC Medicine 2012.
9- HPV vaccines in females over 25. Cochrane
10- Worldwide burden of cancer attributable to HPV by site, country and HPV type. Catherine de Martel, Martyn Plummer, Jerome Vignat and Silvia Franceschi. International Journal of Cancer, 2017.
11- HPV Vaccine - Global Market Study. Annecy, September 2018 – Tania Cernuschi

Executive Summary for SAGE Session on Ebola, Session 9 - Thursday, 25 October 2018

Current Ebola outbreaks and use of unlicensed candidate vaccines to respond to the outbreak

Background:

1- Epidemiology:

The 2014–2016 outbreak in West Africa was the largest and most complex Ebola outbreak since the virus was first discovered in 1976. There were more cases and deaths in this outbreak than all others combined. It also spread between countries, starting in Guinea then moving across land borders to Sierra Leone and Liberia. The virus causing the 2014–2016 West African outbreak belongs to the Zaire ebolavirus species.

Four measures have been in place to interrupt transmission of Ebola

I. infection control in health-care facilities and protection of health-care workers;
II. detection, management and isolation of patients;
III. surveillance (inclusive of back and forward contact tracing) and fever surveillance with rapid diagnosis and isolation; and
IV. community understanding with safe patient and body transport systems, safe burial and household/environmental decontamination

2- Additional measure to respond to Ebola - Vaccine development:

The major Ebola outbreak in West Africa has accelerated the development of a vaccine

Thirteen candidate Ebola vaccines (including monovalent, bivalent and multivalent candidates) have undergone or are currently undergoing clinical evaluation at different trial phases. Two vaccines were licensed, eight vaccines have completed or are in trials up to Phase I stage, two vaccines up to or in Phase II stage, and one vaccine has completed Phase III stage. Some vaccines are tested as single-dose regimen (Ad5-EBOV, ChAd3-EBOZ, rVSVΔG-ZEBOV-GP), while others include a priming and either homologous or heterologous boosting. When prime/boost regimens are tested, the interval between doses is at least 3–4 weeks.

Data on safety and immunogenicity are accumulating for all candidate vaccines under active clinical development. Trials have not reported serious adverse events definitely linked to any candidate vaccine. However, **safety profile** is still being characterized and additional safety information is being generated for children and special populations.

Session Objective:

To provide recommendations on the use of unlicensed vaccines and the anticipated impact of various vaccination strategies.

SAGE is requested to consider the following questions:

1- Is the current evidence sufficient for SAGE to adjust current recommendations regarding the use of Ebola vaccines in case of another Ebola outbreak? If yes, which recommendations can be proposed? And, what key data are missing?

2- what are the conclusions on the benefits and risk analysis of vaccination of pregnant women with rVSV-ZEBOV as part of Expanded Access/ Compassionate Use during Ebola outbreaks?

3- Are there remaining challenges that may prevent access to Ebola vaccines in future outbreaks, and, if yes, can SAGE make recommendations on how these might be addressed?

Session Summary:

1- the first presentation will be the on an overview of the epidemiology including an update of the current outbreak in DRC

2- the second presentation will provide an update on candidate Ebola vaccines: available data on R&D plans, immunogenicity, efficacy and safety, timelines for licensure and expanded access/compassionate use experience.

3. the third presentation will inform SAGE members on benefits and risk analysis of vaccination of pregnant women with rVSV-ZEBOV during outbreaks.

4- the forth presentation will provide projection on the impact of different Ebola candidate immunization strategies and targeted populations.

5- the chair of the WG will present the recommendations from the WG

Background Reading (Yellow Book and Web):

1- Ebola Vaccine development background doc

2- Interim SAGE recommendation for Ebola vaccines August 2018

Update with the development of Ebola vaccines and implications of emerging evidence to inform future policy recommendations

1. Policy questions and overall conclusions

1.1. Are there remaining challenges that may prevent access to Ebola vaccines in future outbreaks, and, if yes, can SAGE make recommendations on how these might be addressed?

- Thirteen candidate Ebola vaccines (including monovalent, bivalent and multivalent candidates) have undergone or are currently undergoing clinical evaluation at different trial phases. Two vaccines were licensed nationally under emergency use provisions, eight vaccines have completed or are in trials up to Phase I stage, two vaccines up to or in Phase II stage, and one vaccine has completed Phase III stage. The Phase III trial for an rVSV-vectored candidate vaccine (rVSVΔG-ZEBOV-GP) was undertaken in Guinea and is the only study that has so far been able to demonstrate clinical efficacy and effectiveness for any candidate Ebola vaccine.
- The two licensed vaccines are a prime/boost candidate vaccine based on rVSV- and Ad5-vectored components (GamEvac-Combi) and a monovalent candidate vaccine based on recombinant adenovirus type-5 vector (Ad5-EBOV).
- The rVSVΔG-ZEBOV-GP candidate vaccine with efficacy data was granted access to the Priority Medicine (PRIME) scheme by the European Medicines Agency (EMA) and Breakthrough Therapy Designation by the US Food and Drug Administration (FDA). This vaccine has also applied for the WHO Emergency Use Assessment and Listing (EUAL) procedure.
- The rVSVΔG-ZEBOV-GP candidate vaccine, a prime/boost candidate vaccine based on Ad26- and MVA-vectored components (Ad26.ZEBOV/MVA-BN-Filo) and the Ad5-EBOV candidate vaccine have submitted EUAL documentations to the WHO Secretariat. For all three vaccines, submissions were accepted and evaluated on a rolling basis and conclusions are expected to be available before the SAGE meeting.
- Potentially, various licensure options exist for candidate vaccines, e.g. animal rule (US), exceptional circumstances (EU), other provisions for licensure or deployment in emergencies.
- The WHO Secretariat is implementing the work plan of the Research and Development (R&D) Blueprint for Action to Prevent Epidemics, including experts' deliberations on future clinical trials for candidate Ebola vaccines. The Working Group recommended that there should be greater alignment of different initiatives (e.g. Coalition for Epidemic Preparedness Innovations [CEPI], and others) to support the development and licensure of Ebola vaccines and of other vaccines against epidemic-prone diseases, taking note of the mandates specific to each stakeholder.

1.2. Is the current evidence sufficient for SAGE to make recommendations regarding the use of Ebola vaccines in case of another Ebola outbreak (pre-licensure and/or post licensure)? If yes, which recommendations can be proposed? If not, what key data are missing?

- A single dose of rVSVΔG-ZEBOV-GP has shown 100% efficacy (95% confidence interval [CI]: 64%–100%) in a cluster randomized ring vaccination trial conducted in

Guinea (1). Ring vaccination with the same candidate vaccine was also carried out following the smaller flare-ups in 2016 in Guinea, Sierra Leone and Liberia and the most recent outbreak in the Democratic Republic of Congo (DRC).

- The duration of the immune responses elicited by the Ebola vaccines under development is currently documented for the observed follow-up periods of the trials. These periods remain short. As of July 2018, the information on the duration of protection for various candidate Ebola vaccines is up to 360 days post vaccination for the rVSVΔG-ZEBOV-GP (2), Ad26.ZEBOV/MVA-BN-Filo (3), and ChAd3-EBOZ vaccines (4). Although the understanding of the immune response to both natural infection and vaccination remains incomplete, it is expected that prime/boost vaccines offer better prospects of long-term protection to an Ebola virus infection than a single dose schedule. However, vaccines that elicit an earlier immune response after a single/first dose are likely to be more useful during outbreaks.
- Another uncertainty is whether vaccines protecting against Zaire Ebola virus species afford cross-protection against other species of Ebola virus and other filoviruses. Preliminary cross-protection data, assessed by enzyme-linked immunosorbent assays and virus neutralization assays results against other Ebola strains, was only reported for three candidate vaccines. There is no data on cross-protection against Marburg virus for any candidate vaccine.
- As no candidate Ebola vaccine has received regulatory approval for use to date, discussions are ongoing jointly with 13 African Member States to guarantee Expanded Access (compassionate use, while safeguarding ethical and good clinical practice precautions) to rVSVΔG-ZEBOV-GP in the event of an outbreak. Evidence from Phase I–III clinical trials and from the deployments during the 2018 outbreaks as well as modelling results comparing different vaccination strategies justify Expanded Access this candidate vaccine in a ring vaccination modality in outbreak responses. In addition to logistical arrangements, the preparation includes consultation and formal review of a protocol for an open-label, non-randomized, single arm study with the governments, national regulatory agencies and national ethics committees of the concerned 13 African countries.
- In the event of an outbreak in the near future, doses of rVSVΔG-ZEBOV-GP would be available from different sources. Researchers in West Africa have a few thousand doses left from the trials, currently stored under Good Clinical Practices conditions. The manufacturer reported that there are a few thousand doses in stock that are owned by the US Biomedical Advanced Research and Development Authority. In addition, the manufacturer committed to produce 300,000 doses for GAVI Alliance through an Advance Procurement Commitment (APC).

2. Key findings

2.1. Epidemiology

From 1976 to Sep 2018, 42 filoviruses outbreaks have been documented (**Appendix 1**). Zaire ebolavirus caused 28 of these outbreaks (30,294 reported cases in total), Sudan ebolavirus seven (792), Bundibugyo ebolavirus two (206), Taï Forest one (1), and Marburg marburgvirus four (425). When the 2013–2016 West African epidemic is omitted, the range of reported cases for the 24 remaining Zaire ebolavirus outbreaks

was 1–318 (median=31). **Figure 1** illustrates the epidemic curve of such an outbreak (5). The 2013–2016 Zaire ebolavirus epidemic in West Africa was unprecedented in its geographical spread and total number of reported cases, but this epidemic lasted slightly longer than a Marburg virus outbreak that began in October 1998 in Angola (109 vs. 100 weeks) (6;7). When these two occurrences are omitted, the outbreaks have lasted between 1 and 42 weeks, with a median duration of 8.5 weeks. Other filoviruses known to infect humans are Reston ebolavirus (asymptomatic infections only in persons exposed to nonhuman primates and pigs from the Philippines) (8).

Since the 1995 Kikwit outbreak, the **principles for interrupting transmission of Ebola and Marburg viruses** are well characterized (9). These four principles are:

1. infection control in health-care facilities and protection of health-care workers;
2. detection, management and isolation of patients;
3. surveillance (inclusive of back and forward contact tracing) and fever surveillance with rapid diagnosis and isolation; and
4. community understanding with safe patient and body transport systems, safe burial and household/environmental decontamination.

While these principles were probably not implemented with sufficient rigor and in the proper order initially in the 2013–2016 epidemics of West Africa, they eventually led to transmission interruption.

In the 2013–2016 epidemics of West Africa, reported incidence in children and adolescents was lower than in adults (**Figure 2**) and **health-care workers (HCWs) were initially at increased risk** (**Figure 3**). As already observed in previous outbreaks, HCWs can play a role in amplifying an early, low-level transmission of Ebola viruses.

Although already postulated earlier, the 2013–2016 West African epidemic also showed the possibility of **late transmission via semen of Ebola virus disease survivors** as well as transmission via breast milk from a sub-symptomatic mother to her baby (10-14).

There have been two Ebola outbreaks in DRC in 2018 (by Sep 2018). An earlier outbreak occurred from April to August 2018 and a later one was started in August 2018 and is still on going in September 2018.

Figure 1. Epidemic curve of Ebola virus disease cases, by transmission mode – Yambuku, Democratic Republic of Congo, 1976 (5)

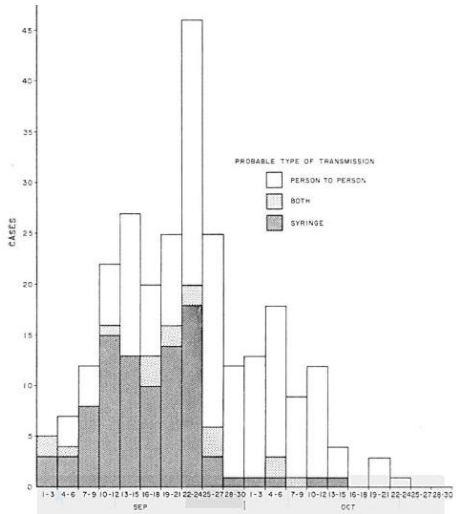


Figure 2. Age-specific cumulative incidence of confirmed and probable Ebola virus disease cases, by country – West Africa, 2013-2016 (15)

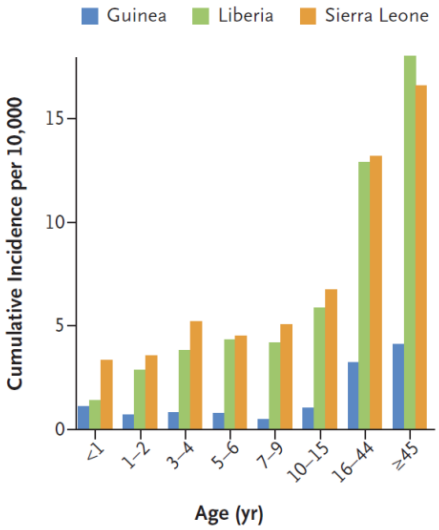
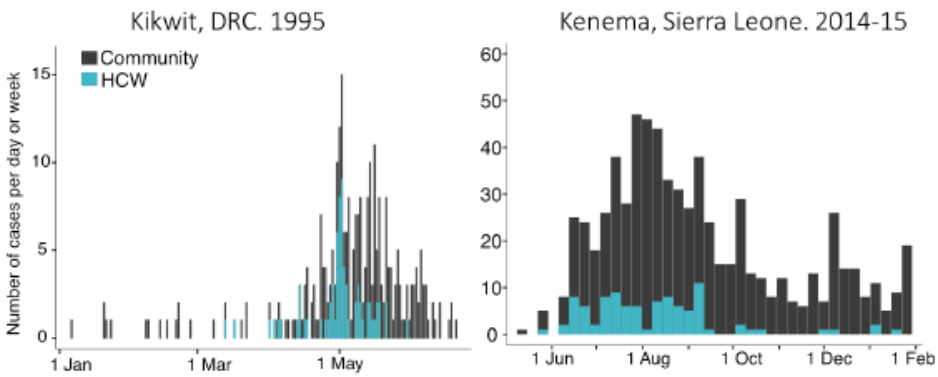


Figure 3. Epidemic curve of Ebola virus disease cases, by health-care workers (HCWs) and general population – Democratic Republic of Congo, 1995 and Sierra Leone, 2014-2015 (16;17)

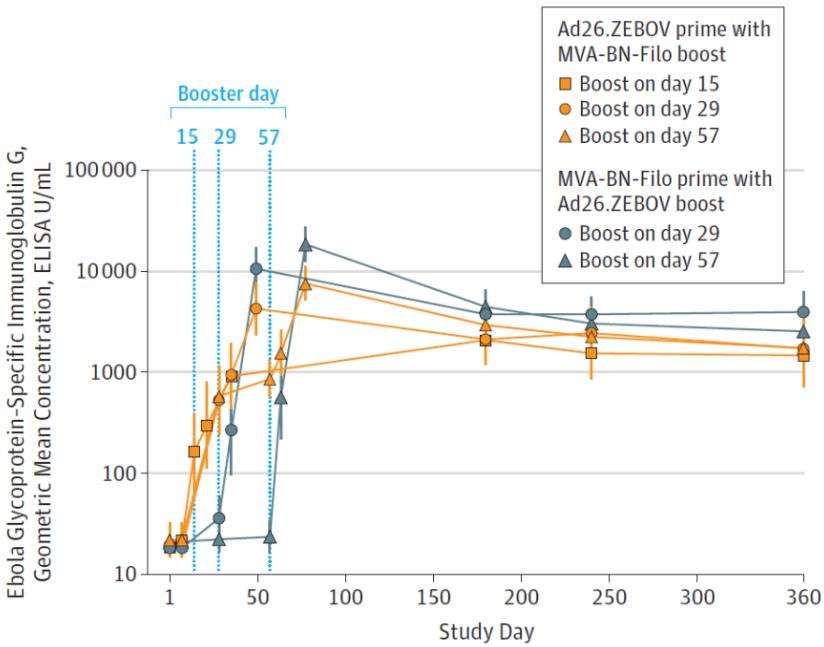


2.2. Vaccine development

Thirteen candidate Ebola vaccines (including monovalent, bivalent and multivalent candidates) have undergone or are currently undergoing clinical evaluation at different trial phases (**Table 1**). Two vaccines were licensed, eight vaccines have completed or are in trials up to Phase I stage, two vaccines up to or in Phase II stage, and one vaccine has completed Phase III stage. **Appendix 2** summarizes the published information on the clinical trials of all these vaccines or their combinations. Some vaccines are tested as single-dose regimen (Ad5-EBOV, ChAd3-EBOZ, rVSVΔG-ZEBOV-GP), while others include a priming and either homologous or heterologous boosting. When prime/boost regimens are tested, the interval between doses is at least 3–4 weeks.

Data on safety and immunogenicity are accumulating for all candidate vaccines under active clinical development (**Appendix 2**). Trials have not reported serious adverse events definitely linked to any candidate vaccine. However, **safety profile** is still being characterized and additional safety information is being generated for children and special populations. Limited systematic head-to-head comparisons are available. All vaccines show detectable humoral and cellular **immune responses** when measured after both priming and boosting (for instance, **Figure 4**). However, follow-up times over which maintenance of these immune responses are documented remain limited. As of July 2018, the longest available interval is 12 months, which refers to the Ad26.ZEBOV/MVA-BN-Filo, ChAd3-EBOV and rVSVΔG-ZEBOV-GP vaccines (2;3;18;19). Surrogates of protection are not defined yet.

Figure 4. Humoral immune response to Ad26.ZEBOV/MVA-BN-Filo vaccine in a Phase I trial (3)



Efficacy and effectiveness data are only available for rVSVΔG-ZEBOV-GP (1). In a Phase III trial mainly carried out in Guinea in 2015, this vaccine showed a 100% efficacy (95% CI: 64%–100%). **Table 2** details the efficacy and effectiveness results from this trial.

Table 1. Overview of candidate Ebola vaccines

Type of candidate vaccine	Strain(s) aimed to protect against	Current stage of clinical evaluation/regulatory status	Proposed vaccination schedule	Indication	Proposed target population	Storage	Current presentation
Candidate vaccines with updated data as of 5 June 2018							
Ad5-EBOV (monovalent) [1]	Monovalent Zaire (Makona)	- Phase II - Licensed based on Animal Rule by the Chinese Food and Drug Administration (FDA) - Submitting to WHO for Emergency Use Assessment and Listing (EUAL)	1 dose	Reactive	18 to 60 years	+2°C to +8°C for 12 months	2 vials of lyophilized powder + 1 vial of diluent
Ad26.ZEBOV & MVA-BN-Filo (prime/boost, VAC52150) [2]	Multivalent: Zaire (Mayinga), Sudan, Tai Forest and Marburg	- Phase II completed in Europe, the United States and Africa - Ongoing Phase II in Africa, Phase III in Sierra Leone and Phase I/II/III in multi-countries - Submitted dossier to the US FDA to request licensure using the Animal Rule - Submitting to WHO for EUAL	2 doses (prime + boost on 28 or 56 days)	Preventive	≥ 18 years (possibly ≥ 1 year)	Ad26.ZEBOV: -20°C to -60°C for 48 months and +2 to +8°C for 12 months MVA-BN-Filo: 20°C to -60°C for 42 months and +2 to +8°C for 6 months	- Liquid frozen - Separate single-dose vials
ChAd3 (monovalent, ChAd3-EBO-Z) [3]	Monovalent Zaire (Mayinga)	Phase II	1 dose	Reactive	≥ 1 year	≤ 60°C for 24 months	- Liquid frozen - Single-dose vials
GamEvac-Combi and GamEvac-Lyo [4]	Monovalent Zaire (Makona)	- Phase IV completed in Russia - Ongoing Phase I/II in Russia and Phase III in Guinea (Kindia) - Licensed in Russia based on Phase I/II trial	2 doses (prime + boost on 21 days)	Preventive	18 to 55 years	-16°C to -20°C for 12 months	- Liquid frozen and Lyophilized - Single-dose vials
rVSVΔG-ZEBOV-GP [5]	Monovalent Zaire (Kikwit 1995)	- Phase III completed in Africa, the United States, Canada and Europe and expanded access protocol in Guinea Forestiere - Ongoing expanded access protocol in DRC - Ongoing Phase II in Canada and Africa - Granted Breakthrough Therapy	1 dose	Reactive	≥ 18 years	- 60°C to -80°C for 36 months	- Liquid frozen - 10-dose vials

Type of candidate vaccine	Strain(s) aimed to protect against	Current stage of clinical evaluation/regulatory status	Proposed vaccination schedule	Indication	Proposed target population	Storage	Current presentation
		Designation by the US FDA and PRIME status by the European Medicines Agency (EMA) since 2016 - Submitting to WHO for EUAL					
DNA vaccine (INO-4212) [6]	Plasmid of the Guinea Makona strain	Phase I	2 doses	Reactive	≥ 18 years	+2°C to +8°C for 3 years and 25°C for 1 year	- Liquid - Separate single-dose vials
Candidate vaccines not having updated data (last update by Apr 2017)							
Ad5 (bivalent) [7]	Bivalent: Zaire (Mayinga), Sudan-Gulu	Phase I	1 dose	Preventive	18 to 50 years	-	Single-dose vials
ChAd3-EBOZ & MVA-BN-Filo (prime/boost) [8]	Multivalent: Zaire (Mayinga), Sudan, Tai Forest and Marburg	Phase I	2 doses	Preventive	18 to 50 years	-	- Liquid frozen - Separate single-dose vials
ChAd3 (bivalent) [9]	Bivalent: Zaire (Mayinga), Sudan-Gulu	Phase I	1 dose	Preventive	18 to 50 years	-	Single-dose vials
rVSV N4CT1 EBOVGP1 [10]	Trivalent: Zaire (Mayinga), Sudan (Boniface), Marburg (Angola)	Phase I	1 or 2 doses	Reactive and Preventive	≥ 1 year	<-70°C for more than 10 years	- Liquid frozen - Single-dose vials
Nanoparticle recombinant Ebola GP vaccine [11]	Monovalent Zaire (Makona)	Phase I	2 doses	Preventive	18 to 50 years	-	Separate single-dose vials
DNA plasmid vaccines [12]	Zaire (Mayinga), Marburg	Phase I	3 doses	Preventive	18 to 60 years	-	Separate single-dose vials
HPIV3-EbovZ GP [13]	Monovalent Zaire (Makona)	Phase I	2 doses	Preventive	18 to 50 years	-	Separate single-dose vials

Table 1 - Notes

[1] Ad5-EBOV (monovalent)

- Ad5-EBOV is a recombinant adenovirus type-5 vector-based Ebola vaccine which expresses envelope glycoprotein (GP) of Zaire Ebola virus species (Makona variant, monovalent).
- The formulation of Ad5-EBOV is lyophilized powder plus diluent; one dose with proposed 8 X 10^{10} vp per dose targeting adults aged 18 to 60 years.
- Two Phase I trials in China (120 and 61 healthy adults) (PMID: 25817373, 28017642, 2870962) and one phase II trial in Sierra Leone (500 healthy adults) (PMID: 28017399) were completed. The investigators reported good safety (the most common adverse events (AEs) reported included fever and mild injection site pain and no vaccine-related serious adverse events (SAEs) recorded) and immunogenicity profile (the geometric mean titre (GMT) of anti GP antibody peaked around 28 days after vaccination with a responder rate of 96% (95% CI: 91%-99%) but the vaccine-elicited antibody responses decreased on 168 days with a responder rate of 76% (95% CI: 67%-83%)) of Ad5-EBOV (PMID: 28017399).
- Ad5-EBOV has been licensed in China under the animal rule using data from 8 non-human primates challenged on day 28 (PMID: 27493239) and Phase II immunogenicity data for emergency use in the case of an outbreak (PMID: 28017399).
- EUAL application was submitted to WHO in July 2018, and is currently under review.
- WHO prequalification of Ad5-EBOV is planned in 2019-2020.

[2] Ad26.ZEBOV & MVA-BN-Filo (prime/boost, VAC52150)

- Ad26.ZEBOV is a monovalent replication-incompetent adenoviral vector serotype 26 (Ad26) vaccine, which expresses the full-length GP of the EBOV Mayinga variant, and is produced in the human PER.C6®cell line. MVA-BN-Filo is a multivalent Modified Vaccinia Ankara (MVA)-BN vaccine, which expresses the EBOV Mayinga GP, the Sudan virus (SUDV) Gulu GP, the Marburg virus (MARV) Musoke GP, and the Tai Forest virus (TAFV, formerly known as Côte d'Ivoire ebolavirus) nucleoprotein (NP). It is manufactured in chicken embryo fibroblast cells derived from specific pathogen-free eggs.
- The formulation of Ad26.ZEBOV/MVA-BN-Filo is liquid frozen. The vaccine regimen consists of a prime immunisation with Ad26.ZEBOV followed by a boost immunisation with MVA-BN-Filo 28 or 56 days later. The proposed doses of Ad26.ZEBOV and MVA-BN-Filo are 5 X 10^{10} and 1 X 10^{8} vp per dose respectively. The proposed target population includes adults, human immunodeficiency virus (HIV)-infected adults and possibly children aged ≥ 1 year.
- Four Phase I trials were completed: 87 healthy adults in Europe (PMID: 27092831, 28291882), 164 healthy adults in the United States (NCT02325050) and 72 and 72 healthy adults in Africa (NCT02376426, NCT02376400). Three Phase II trials were completed: 423 healthy adults in Europe (NCT02416453), 200 healthy adults and 200 HIV-infected adults in the United States and Africa (NCT02598388), and 669 healthy adults, 142 HIV-infected adults, 132 healthy adolescents and 132 healthy children in African countries (NCT02564523). Two Phase III trials in the United States (144 and 329 healthy adults) (NCT02543567, NCT02543268) were completed. The investigators reported good safety (the most common AEs reported was injection site pain and no vaccine-related SAEs recorded) and immunogenicity profile (93% (95% CI: 68%-100%) and 100% (95% CI: 77%-100%) responder rates on 28 and 56 days after Ad26.ZEBOV prime respectively and the vaccine-induced T-cell responses persisted on 360 days in 62% (95% CI: 32%-86%) and 83% (95% CI: 52%-98%) participants receiving MVA-BN-Filo boost on 28 and 56 days after prime respectively) of Ad26.ZEBOV/MVA-BN-Filo (PMID: 27092831, 28291882).
- In addition, one Phase II trial on populations aged older than 1 year in African countries (NCT02876328) and one Phase I/II/III trial on healthy children and adults aged less than 71 years in multi-countries in the United States, Europe and Africa (NCT02661464) are ongoing. The planned Phase III study originally focused on a staged approach in an Ebola-affected region

(Sierra Leone) (445 healthy adults, 192 healthy adolescents and 193 healthy children) (PMID: 27821112) with the aim of establishing safety and immunogenicity in adults, followed by an expanded safety and immunogenicity study in adults and children and an effectiveness study in preventing cases of Ebola Virus Disease. Since designing this Phase III effectiveness study, the epidemic waned and it is currently infeasible to conduct an effectiveness evaluation as part of this study, so this component has been removed. One additional trial was started in 2017, PREVAC (in partnership with NIAID, INSERM, LSHTM) (NCT02876328), to evaluate the safety and immunogenicity of the vaccine regimen in previously affected countries (Guinea, Liberia, and potentially Sierra Leone).

- Ad26.ZEBOV/MVA-BN-Filo has not been licensed yet but a dossier has been submitted to the US FDA to request licensure using the animal rule.
- A rolling EUAL submission including CMC data, non-clinical and clinical Phase I data was submitted to WHO in July/September 2016 and is annually updated.
- No WHO prequalification has been obtained.

[3] ChAd3 (monovalent, ChAd3-EBO-Z)

- ChAd3-EBO-Z vaccine consists of a recombinant replication-defective chimpanzee adenovirus Type 3 vector (ChAd3) engineered to express the WT GP antigen from Ebola virus Zaire (Mayinga strain).
- The formulation of ChAd3-EBO-Z is liquid frozen; one dose with proposed 1 X 10^{11} particle units (pu) per dose targeting population older than 1 year of age.
- Two Phase I trials, one in Europe (120 healthy adults) (PMID: 26725450) and one in the United States (91 healthy adults) (PMID: 26546548), and two Phase II trials in Africa (3024 healthy adults and 600 healthy persons aged from 1 to 17 years) (NCT02485301, NTC02548078) were completed. The investigators reported an acceptable safety profile (the most common AEs reported included injection site pain and tenderness, fatigue and headache and no vaccine-related SAEs recorded) and immunogenicity profile (different dose levels showed 96% (95% CI: 86%-100%) and 96% (95% CI: 87%-100%) responder rates on 28 days after vaccination but the antibody response decreased by roughly half by 180 days following vaccination; GMT decreased from 51ug/mL (95% CI: 41-63) to 26ug/mL (95% CI: 21-32) in the high-dose group and from 45ug/mL (95% CI: 26-56) to 22ug/mL (95% CI: 19-29) in the low-dose group) of ChAd3-EBO-Z (PMID: 26725450).
- ChAd3-EBO-Z has not completed Phase III efficacy testing (PMID: 25629663). With the Ebola outbreak declared over, and no opportunity to establish the clinical benefit of the candidate vaccine, the developer has decided not to submit the monovalent Zaire Ebola vaccine candidate for licensure at this time. The clinical, non-clinical, and stability studies already initiated will be continued until completion and the manufacturing and regulatory dossiers will be completed accordingly.
- ChAd3-EBO-Z has not been licensed and the developer has decided not to submit this candidate vaccine for licensure at the time.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[4] GamEvac-Combi and GamEvac-Lyo

- GamEvac-Combi and GamEvac-Lyo consist of live-attenuated recombinant vesicular stomatitis virus (VSV) and adenovirus serotype-5 (Ad5) expressing Ebola envelope GP of Zaire Ebola virus species (Makona).
- The formulation of GamEvac-Combi is liquid frozen but that of GamEvac-Lyo is lyophilized. The vaccine regimen consists of a priming immunisation with VSV followed by a boosting immunisation with Ad5 21 days later. The proposed dose of VSV and Ad5 are 0.5ml per dose targeting adults aged 18 to 55 years.
- One Phase I/II trial in Russia (84 healthy adults) (PMID: 28152326) and one Phase IV trial in Russia (60 healthy adults) (NCT02911415) were completed for GamEvac-Combi. The

investigators reported good safety (the most common AE reported was injection site pain and no vaccine-related SAEs recorded) and immunogenicity profile (antigen-specific response was detected in 93% (half dose) and 100% (full dose) on 28 days after vaccination, and 100% on 42 days) of GamEvac-Combi (PMID: 28152326).

- There is one Phase III trial of GamEvac-Combi in Guinea, Africa (2000 healthy adults) (NCT03072030) and one Phase I/II trial of GamEvac-Lyo in Russia (220 healthy adults) (NCT03333538) on-going.
- GamEvac-Combi has been licensed by the Ministry of Health of the Russian Federation for emergency use in the territory of the Russian Federation in December 2015 (registration number: LP-003390). The emergency license was based on Phase I and II clinical data of safety and immunogenicity (PMID: 28152326).
- No EUAL submission was initiated.
- Regarding WHO prequalification the company stated that a decision to submit will be made after completion of the phase III GamEvac-Combi clinical trial in Guinea.

[5] rVSVΔG-ZEBOV-GP

- rVSVΔG-ZEBOV-GP consists of a live, attenuated recombinant vesicular stomatitis virus-based vector expressing the envelope GP gene of Zaire Ebola virus (Kikwit 1995 strain).
- The formulation of rVSVΔG-ZEBOV-GP is liquid frozen; one dose with proposed 1ml per dose targeting adults.
- Eight Phase I trials in Europe and Africa (115 and 185 healthy adults and 40 healthy children aged 6 to 17 years) (PMID: 26248510, 29627147, 25830326, 28985239), Canada (40 healthy adults) (PMID: 28630358), and the United States (78 and 512 healthy adults) (PMID: 25830322, 28606591), one Phase II trial in Africa (1000 healthy adults) (NCT02344407), one Phase II/III trial in Africa (8673 healthy adults) (PMID: 27387395, 29788345), and two Phase III trials in Africa (5837 healthy adults) (PMID: 26215666, 26248676, 28017403), and in the United States, Canada and Europe (1197 healthy adults) (PMID: 28549145). The investigators reported acceptable safety profile (the most common AEs reported included injection site pain, headache, pyrexia, fatigue, myalgia and chills and few vaccine-related SAEs recorded) and 100% (95% CI: 69%-100%) efficacy (PMID: 28017403)of rVSVΔG-ZEBOV-GP in the ring-vaccination Guinea trial. The GMT were sustained with minimal change through 360 days after vaccination (PMID: 28606591) .
- Two Phase II trials on populations aged from 13 to 65 years in Africa and Canada (NCT03031912) and older than 1 year in Africa (NCT02876328) are ongoing.
- Granted Breakthrough Therapy Designation from FPA and PRIME status from EMA since 2016.
- The developer submitted an application for licensure to the US FDA and the EMA; the expected timeline to obtain regulatory approval is 2020. There is ongoing discussion with both regulatory authorities to shorten the timelines.
- EUAL application was submitted to WHO in 2015, and is currently under review.
- No WHO prequalification has been obtained.

[6] DNA vaccine (INO-4212)

- DNA vaccine (INO-4212) is a combination of INO-4201 and INO-4202. INO-4201 is a synthetic DNA plasmid construct expressing Ebola GP designed from consensus DNA sequences of Ebola outbreak strains from 1976-2006. INO-4202 is a DNA plasmid construct expressing Ebola GP from Ebola outbreak strain (Guinea) of 2014.
- The formulation of INO-4201 is liquid; two doses with proposed 2mg per dose in an interval of 4 weeks; targeting to adults aged over 18 years.
- One Phase I trial in the Unites States (75 healthy adults in the initial study) (NCT02464670) is ongoing. Interim analysis showed acceptable safety profile (the most common AEs reported included injection site pain, redness, swelling and itching and no vaccine-related SAEs recorded).

- Product currently in Phase I testing. Potential for application for licensure via Animal Rule by 2019/2020.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[7] Ad5 (bivalent)

- Ad5 is a recombinant adenovirus type-5 vaccine which expresses GP of Zaire strain of Ebola virus (Ad5.EBO.GP(Z).mt) and Gulu strain of Sudan Ebola virus species (Ad5.EBO.GP(S/G).mt).
- One dose of Ad5 (bivalent) is targeting adults aged 18 to 50 years.
- One Phase I trial of Ad5 (bivalent) in the United States (32 healthy adults) (21034824) was completed. The investigators reported acceptable safety profile (two of three AEs reported were asymptomatic prolongations in the activated partial-thromboplastin time in the 2 weeks following vaccination) of Ad5 (bivalent).
- Ad5 (bivalent) has not been licensed.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[8] ChAd3-EBOZ & MVA-BN-Filo (prime/boost)

- ChAd3-EBOZ vaccine consists of a recombinant replication-defective ChAd3 engineered to express the WT GP antigen from Ebola virus Zaire (Mayinga strain). MVA-BN-Filo is a multivalent Modified Vaccinia Ankara (MVA)-BN vaccine, which expresses the EBOV Mayinga GP, the Sudan virus (SUDV) Gulu GP, the Marburg virus (MARV) Musoke GP, and the Tai Forest virus (TAFV, formerly known as Côte d'Ivoire ebolavirus) nucleoprotein (NP). It is manufactured in chicken embryo fibroblast cells derived from specific pathogen-free eggs.
- The formulation of ChAd3-EBOZ/MVA-BN-Filo is liquid frozen. The vaccine regimen consists of a prime immunisation with ChAd3-EBOZ followed by a boost immunisation with MVA-BN-Filo 0, 7 or 14 days later. The target population is adults aged 18 to 50 years.
- Two Phase I trials of ChAd3-EBOZ/MVA-BN-Filo in the United Kingdom (60 healthy adults) (25629663) and in Mali (91 healthy adults) and the United States (20 healthy adults) (26546548) were completed. The investigators reported acceptable safety profile (the most common AE reported was mild injection site pain) of ChAd3-EBOZ/MVA-BN-Filo.
- ChAd3-EBOZ/MVA-BN-Filo has not been licensed.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[9] ChAd3 (bivalent)

- ChAd3 (bivalent) vaccine consists of cAd3-EBO glycoprotein Zaire and cAd3-EBO glycoprotein Sudan drug substances.
- One dose of ChAd3 (bivalent) is targeting adults aged 18 to 50 years.
- One Phase I trial of ChAd3 (bivalent) in the United States (20 healthy adults) (25426834) was completed. The investigators reported acceptable safety profile of ChAd3 (bivalent).
- ChAd3 (bivalent) has not been licensed.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[10] VSV N4CT1 EBOVGP1

- rVSV N4CT1 can be used individually or as a blended tri-valent vaccine. The monovalent vaccines are vectored by an attenuated replication competent rVSV vector. The Ebola vaccine (rVSV N4CT1 EBOVGP1) expresses the Mayinga strain GP of Zaire Ebola, the Sudan Ebola virus vaccine (rVSV N4CT1 SUDVGP1) expresses the GP from the Boniface strain and the Marburg vaccine (rVSV N4CT1 MARVGP1) expresses the GP from the Angola strain.
- The formulation of rVSV N4CT1 EBOVGP1 is liquid frozen; one dose of it is targeting adults aged 18 to 55 years.
- One Phase I trial of rVSV N4CT1 EBOVGP1 in the United States (39 healthy adults) (NCT02718469) was completed. The investigators reported acceptable safety profile (the most common AE reported was mild injection site pain) of rVSV N4CT1 EBOVGP1.

- rVSV N4CT1 EBOVGP1 has not been licensed.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[11] Nanoparticle recombinant Ebola GP vaccine

- Nanoparticle recombinant Ebola GP vaccine is an Ebola vaccine which expresses GP of Zaire Ebola virus species (Makona variant).
- Two doses of nanoparticle recombinant Ebola GP vaccine is targeting adults aged 18 to 50 years.
- One Phase I trial of nanoparticle recombinant Ebola GP vaccine in Australia (230 healthy adults) (NCT02370589) was completed. No published data on safety profile has been reported.
- Nanoparticle recombinant Ebola GP vaccine has not been licensed.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[12] DNA plasmid vaccines

- The Ebola DNA plasmid vaccine is composed of 2 plasmids including GP from the Zaire and Sudan-Gulu species. The Marburg DNA plasmid vaccine consists of one plasmid expressing GP of the Marburg Angola strain.
- One dose of DNA plasmid vaccine is targeting adults aged 18 to 60 years.
- Three Phase I trials of DNA plasmid vaccines in the United States (27 (16988008) and 20 (25225676) healthy adults) and Uganda (108 healthy adults) (25540891) were completed. The investigators reported acceptable safety profile (the most common AE reported was mild injection site pain and tenderness) of DNA plasmid vaccines.
    - DNA plasmid vaccines have not been licensed.
- No EUAL submission was initiated and no WHO prequalification have been obtained.

[13] HPIV3-EbovZ GP

- HPIV3-EbovZ GP vaccine is a live attenuated human parainfluenza virus type 3 vectored vaccine which expresses GP of Zaire Ebola virus species (Makona variant).
- Two doses of HPIV3-EbovZ GP vaccine is targeting adults aged 18 to 50 years.
- One Phase I trial of HPIV3-EbovZ GP vaccine in the United States (30 healthy adults) (NCT02564575) was completed and another Phase I trial in the United States (30 healthy adults) was started in March 2018 (NCT03462004). No published data on safety profile has been reported.
- HPIV3-EbovZ GP vaccine has not been licensed.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

Table 2. Effect of rVSVΔG-ZEBOV-GP vaccine on cases of Ebola virus disease in different study populations – Guinea and Sierra Leone (2)

	All clusters*				Randomised clusters†			
	1	2	3	4	5	6	7	8
	All vaccinated in immediate (group A) *vs* all contacts and contacts of contacts in delayed plus all never-vaccinated in immediate or non-randomised (group B)	All vaccinated in immediate (group A) *vs* all eligible in delayed plus all eligible never-vaccinated in immediate (group B)	All contacts and contacts of contacts in immediate (group A) *vs* delayed (group B)	All vaccinated in immediate (group A) *vs* all eligible never vaccinated in immediate (group B)	All vaccinated in immediate (group A) *vs* all eligible and consented on day 0 visit in delayed (group B)	All vaccinated in immediate (group A) *vs* all eligible in delayed (group B)	All eligible in immediate (group A) *vs* all eligible delayed (group B)	All contacts and contacts of contacts in immediate (group A) *vs* all contacts and contacts of contacts in delayed (group B)
Group A								
Number of individuals (clusters)	3775 (70)	3775 (70)	7241 (70)	3775 (70)	2108 (51)	2108 (51)	3212 (51)	4513 (51)
Cases of Ebola virus disease (clusters affected)	0 (0)	0 (0)	12 (7)	0 (0)	0 (0)	0 (0)	7 (4)	10 (5)
Attack rate	0%	0%	0·17%	0%	0%	0%	0·22%	0·22%
Group B								
Number of individuals (clusters)	7995 (116)	4507 (104)	4529 (47)	1432 (57)	1429 (46)	3075 (47)	3075 (47)	4529 (47)
Cases of Ebola virus disease (clusters affected)	34 (15)	23 (11)	22 (8)	7 (4)	10 (4)	16 (7)	16 (7)	22 (8)
Attack rate	0·43%	0·51%	0·49%	0·49%	0·7%	0·52%	0·52%	0·49%
Vaccine effect								
Vaccine efficacy/ effectiveness‡ (%, 95% CI)	100% (77·0 to 100·0)	100% (79·3 to 100·0)	70·1% (−4·9 to 91·5)	100% (−51·5 to 100·0)	100% (63·5 to 100·0)	100% (68·9 to 100·0)	64·6% (−46·5 to 91·4)	64·6% (−44·2 to 91·3)
p value§	0·0012	0·0033	0·2759	0·125	0·0471	0·0045	0·344	0·3761

2.3. Vaccine approval

To date, no vaccine has been WHO-prequalified or completed the WHO EUAL procedure. The rVSVΔG-ZEBOV-GP candidate vaccine, a prime/boost candidate vaccine based on Ad26- and MVA-vectored components (Ad26.ZEBOV/MVA-BN-Filo) and the Ad5-EBOV candidate vaccine have submitted EUAL documentations to the WHO Secretariat. For all three vaccines, submissions were accepted and evaluated on a rolling basis and conclusions are expected to be available before the SAGE meeting.

With regard to regulatory agencies, two candidate vaccines, GamEvac-Combi and Ad5-EBOV are licensed in the Russian Federation and China respectively, their countries of origin. Also, rVSVΔG-ZEBOV-GP vaccine was granted access to the PRIME scheme by the EMA and Breakthrough Therapy Designation by the US FDA.

2.4. Modelling of vaccination strategies

The following pre-emptive and reactive vaccination strategies were modeled to assess and compare their impact in controlling Ebola outbreaks:

1. **Pre-emptive vaccination**
   - Targeted vaccination: HCWs, front-line workers (FLWs) are not included because they are recruited after an outbreak is declared; and
   - Mass vaccination: random allocation among people living in areas at risk of Ebola.
2. **Reactive vaccination**
   - Ring vaccination: contacts and contacts of contacts (CCCs) of Ebola virus disease cases;
   - Targeted vaccination: HCWs and/or FLWs; and

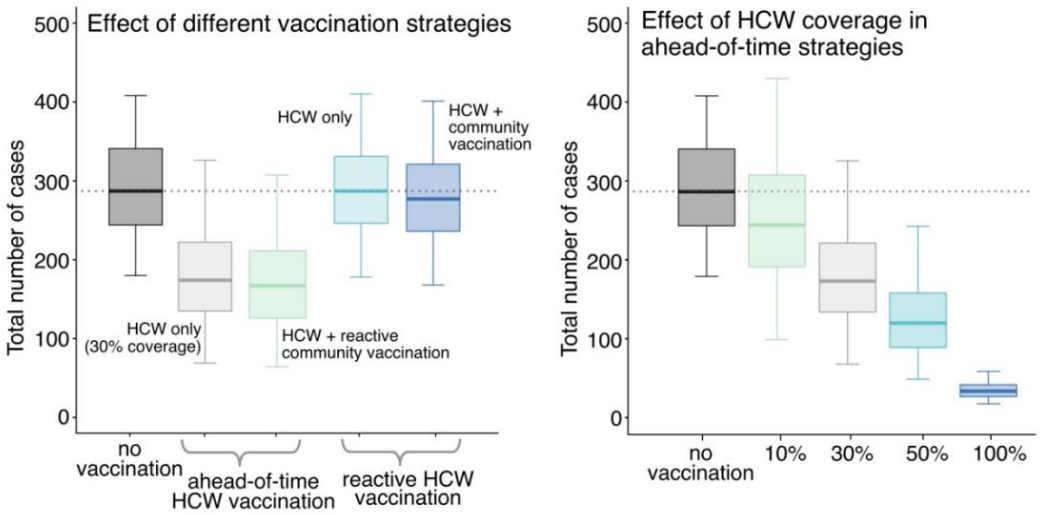
- Mass vaccination: random allocation among people living in areas reporting Ebola virus disease cases.

The strategies were assessed on both **localized outbreaks** similar to historical Ebola outbreaks (less than 300 cases and 6 months duration) as well as **widespread outbreaks**, similar to the 2013–16 West African outbreak (30,000 cases and 2-year duration).

Targeted vaccination

Figure 5 shows that the pre-emptive vaccination of HCWs, even at 30% coverage, can lead to a reduction around 40% of the total number of cases in a scenario similar to the one in Kikwit in 1995, where HCWs played an important role in amplifying the early spread of Ebola virus (see also **Figure 3**). By contrast, reactive vaccination targeting HCWs and/or mass-vaccination (70% coverage, 140,000 doses) has a negligible impact due to inherent implementation delays and the rapid control of the outbreak through classical control measures. And the total number of cases decreases by increasing the vaccination coverage in HCWs in ahead-of-time strategies.

Figure 5. Impacts of different vaccination strategies and health-care workers (HCWs) coverage in ahead-of-time strategies on the 1995 Ebola outbreak in Kikwit (Democratic Republic of Congo), while accounting for classical control measures implemented during the outbreak



Notes: Each boxplot represents the distribution of the total number of cases expected for a given vaccination strategy (left panel) and for a given vaccination coverage in HCWs (right panel), in comparison to the baseline scenario without vaccination (but with classical control measures). Variability arises from multiple stochastic simulations.
Source: Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, presented to the SAGE Working Group on 5 June 2018.

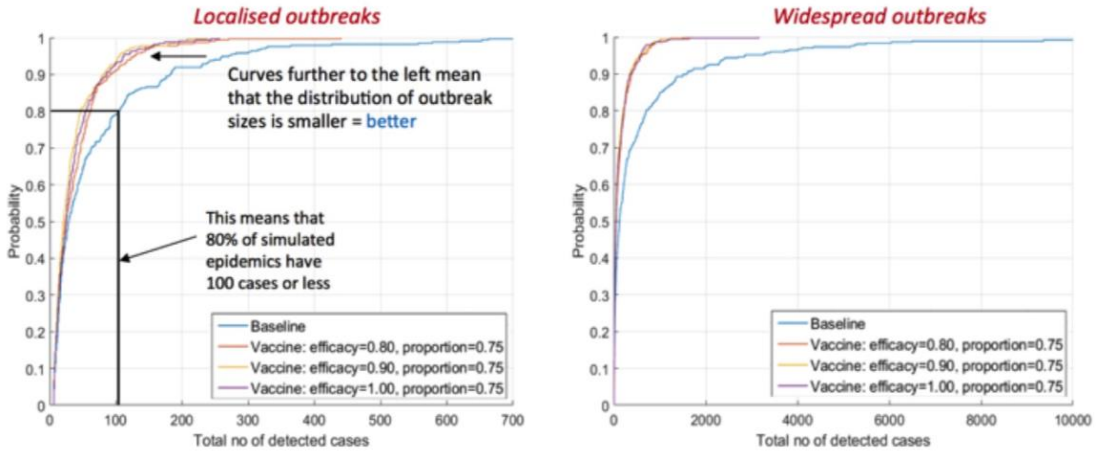
Ring vaccination

Figure 6 shows that ring vaccination of CCCs is an effective reactive strategy for preventing large outbreaks (>300 cases) when used in conjunction with classical control measures. For instance, in a scenario of localized outbreaks (up to 670 cases),

ring vaccination led to a reduction of the probability of observing a large outbreak from 4% to 1%. In a scenario of widespread transmission (up to 10,000 cases), the probability dropped from 33% to 12%, with 95% of the outbreaks having less than 600 cases.

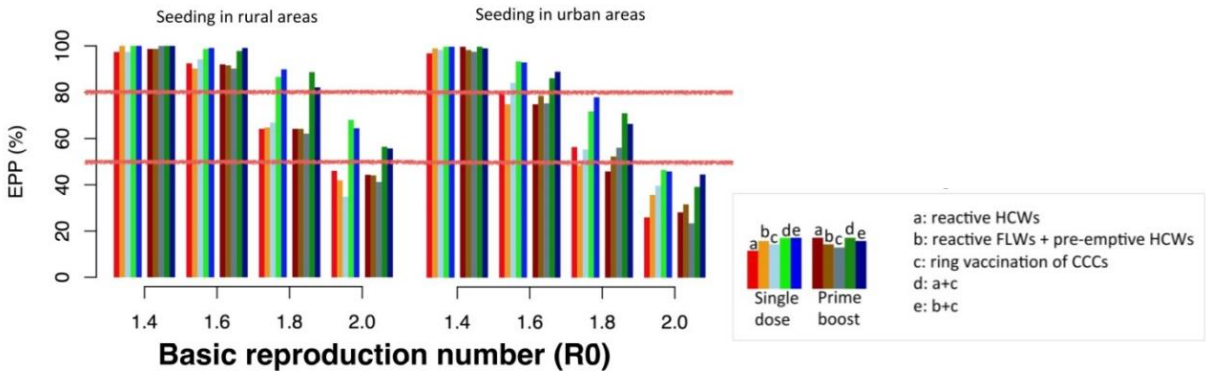
Figure 7 compares the impact of different combinations of pre-emptive and reactive strategies, including ring vaccination, for both single-dose and prime/boost vaccines in either rural or urban areas and for different intensity of transmission (as measured by the basic reproduction number R0). This model is gauged to a baseline with poor or zero initial infrastructures for classical control measures.

Figure 6. Cumulative probability distribution of the total number of cases with and without ring vaccination and for localized (left panel) and widespread (right panel) outbreaks



Notes: Classical control measures are also implemented in this model.
Source: Centre for Outbreak Analysis and Modelling, Imperial College London, presented to the SAGE Working Group on 5 June 2018.

Figure 7. Comparison of the epidemic prevention potential (EPP) for different vaccination strategies, urban Vs rural areas, single dose Vs prime/boost and for different R0 values



Note: EPP is defined as the reduction of the risk of observing a large outbreak (>300 cases).
Source: Center for Inference & Dynamics of Infectious Diseases, presented to the SAGE Working Group on 5 June 2018.

Mass vaccination

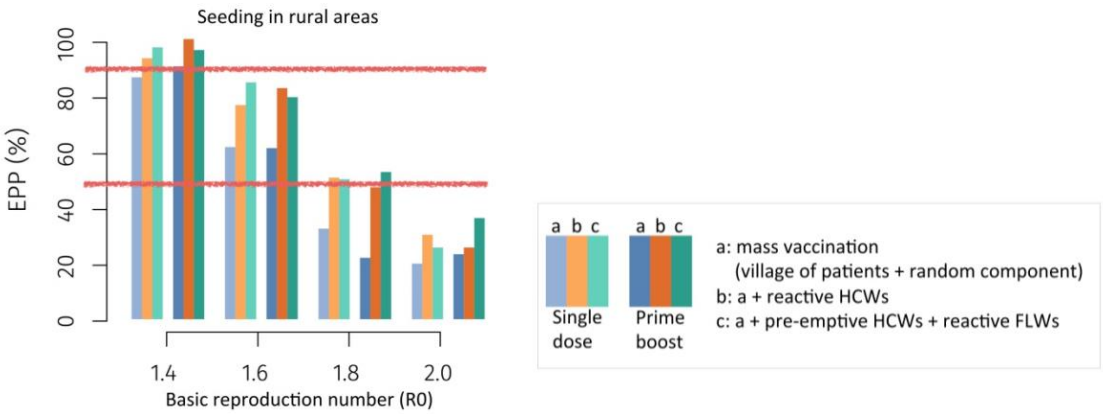
Figure 8 shows similar comparison for mass vaccination strategies.

Herd immunity to Ebola viruses is not a realistic target for current vaccination strategies (20). A 90% effective vaccine would require more than 80% coverage in the general population to establish herd immunity. This makes pre-emptive mass vaccination be an unrealistic strategy because of the resistance against vaccinations, financial/ logistical challenges, and a lack of vaccines that provide long-term protection against all human-pathogenic Ebola viruses.

Although the number of doses needed for pre-emptive vaccination of HCWs depends on the health system of each country, modelling can provide estimates of the number of doses required for the reactive vaccination strategies. Using a ring vaccination strategy, 10,000 doses were sufficient to contain simulated localized outbreaks, whereas 50,000 doses were sufficient to contain simulated widespread outbreaks. By contrast, mass vaccination required a tenfold number of doses.

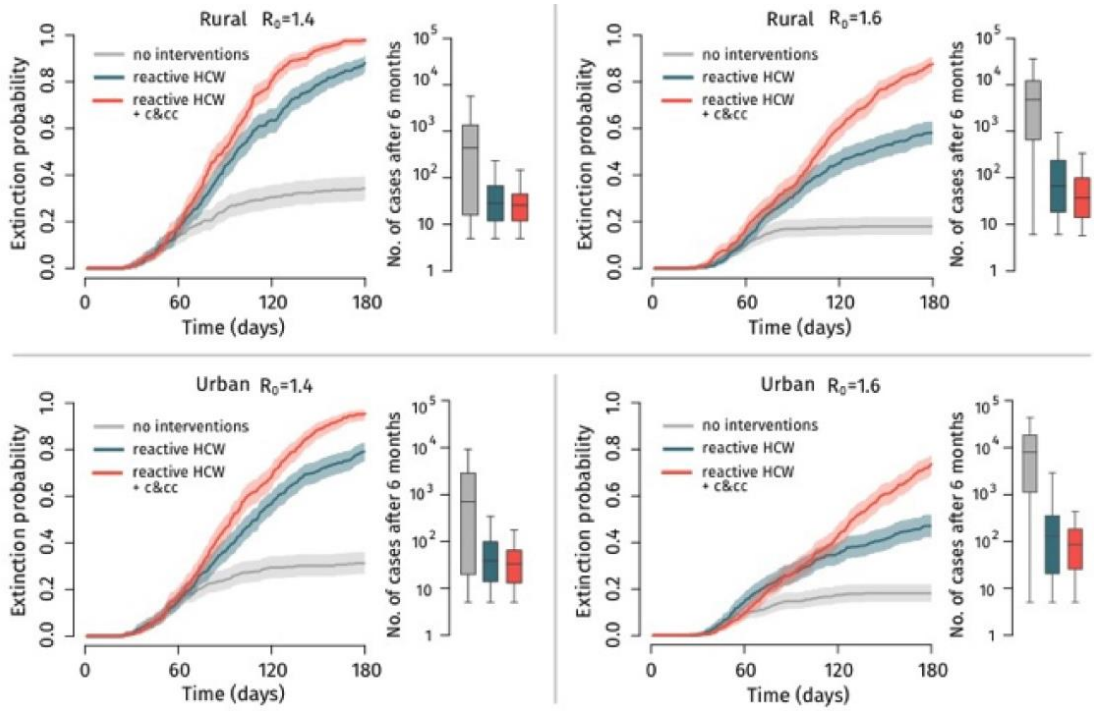
Overall, modelling suggests that pre-emptive vaccination of HCW combined with a reactive ring vaccination strategy is the most effective strategy to contain future Ebola outbreaks (**Figure 9**). Replacing ring vaccination by mass vaccination is less efficient as it reduces the chances of preventing large outbreaks (e.g. from 80% to 50% for R0 = 1.8, see **Figure 8**). This is because ring vaccination targets people at high risk of infection that mass vaccination might miss. It also appears that reducing the risk of large outbreaks is more difficult in urban than in rural areas, due to increased connectivity. Both single-dose and prime/boost (with boosting 28 days after priming) regimens with a similar vaccine efficacy of 90% lead to similar reduction of the risk of large outbreaks. Importantly, ring vaccination requires effective case detection and contact tracing, thus acting synergistically with classical control measure of Ebola virus transmission.

Figure 8. Comparison of the epidemic prevention potential (EPP) from a rural seeding, for different mass vaccination strategies, single dose Vs prime/boost and for different R0 values



Note: EPP is defined as the reduction of the risk of observing a large outbreak (>300 cases).
Source: Center for Inference & Dynamics of Infectious Diseases, presented to the SAGE Working Group on 5 June 2018.

Figure 9. Impact of ring vaccination and reactive vaccination in health-care workers (HCWs) for different vaccination strategies, urban Vs rural areas, and for different R0 values



Note: This model is gauged to a baseline with poor and zero initial infrastructure for classical control measures.
Source: Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, presented to the SAGE Working Group on 5 June 2018.

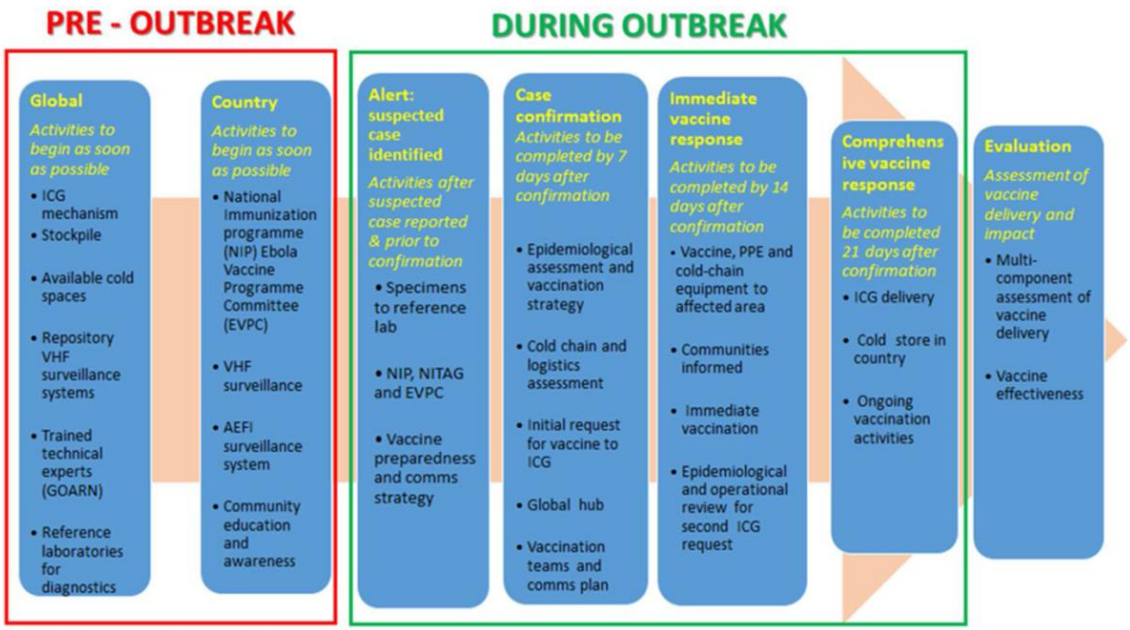
2.5. Emergency and post-licensure access

Because no candidate Ebola vaccine has received regulatory approval for use to date, discussions are ongoing jointly with 13 African Member States to guarantee **Expanded Access** (compassionate use, while safeguarding ethical and good clinical practice precautions) to rVSVΔG-ZEBOV-GP in the event of an outbreak. In addition to logistical arrangements, the preparation includes consultation and formal review of a protocol for an open-label, non-randomized, single arm study with the governments, national regulatory agencies and national ethics committees of the concerned 13 African countries. Under expanded access/ compassion use study protocols, the primary study objective is to measure the incidence of laboratory-confirmed EVD cases 84-days after vaccination; the secondary study objectives are to assess adverse events over 21 days after vaccination. Immunization is by ring vaccination of contacts and of contacts of those contacts around a confirmed case. Only persons who consented after information and who are eligible are vaccinated.

For post-licensure access, the **Global Ebola Vaccine Implementation Team (GEVIT)** has submitted into public consultation a practical guidance on the use of Ebola vaccines in an outbreak response. Its objectives are to improve understanding of the technical specificities of Ebola vaccines and the possible strategies for outbreak

response vaccination and to guide global partners and countries on preparedness plans to facilitate rapid vaccination response activities in the event of a future Ebola outbreak. The guide outlines phases that cover both preparation and implementation (**Figure 10**).

Figure 10. Outline of Ebola vaccination phases proposed by the Global Ebola Vaccine Implementation Team



3. Recommendations proposed by SAGE Working Group

Thirteen candidate Ebola vaccines (including monovalent, bivalent and multivalent candidates) have undergone or are currently undergoing clinical evaluation at different trial phases. The Working Group reviewed the published data as well as the unpublished data submitted by the candidate vaccine developers (**Table 1**) and, together additional confidential data and information presented during closed meetings between the SAGE Working Group members and the individual developers.

Should an Ebola disease outbreak occur, the Working Group members reiterated that the current SAGE recommendation remains pertinent i.e. the rVSVΔG-ZEBOV-GP vaccine should be promptly deployed under the Expanded Access/Compassionate Use cohort protocol, with informed consent and in compliance with Good Clinical Practice. Ring vaccination remains the recommended delivery strategy. This should be adapted to the social and geographic conditions of the outbreak-affected areas and include people at risk including but not limited to: (i) contacts, and contacts of contacts; (ii) local and international health-care and FLWs in the affected areas; and (iii) health-care and FLWs in areas at significant risk of expansion of the outbreak. The implementation of a protocol using rVSVΔG-ZEBOV-GP and the ring vaccination strategy offers an important opportunity to accumulate additional information on vaccine safety, efficacy and effectiveness, and long-term immunogenicity.

The modelling results on the effect of various preventive and reactive vaccination strategies (conducted by three independent groups and presented during the meeting) supports the above recommendations. Model results suggest that ring vaccination would have greater impact in reducing the duration of outbreak and the number of cases if implemented in conjunction with reactive vaccination of health-care and FLWs and, together with full implementation of other non-vaccine outbreak control measures. Under scenarios of poor case detection and contact tracing, model results suggest that ring vaccination may need to be adjusted to a more geographically targeted reactive vaccination approach. The Working Group encouraged modelers to consider including additional assumptions and parameters that could help better understand and predict the potential effect that sociocultural dynamics of affected communities have on the course of an outbreak.

The Working Group members noted that the rVSVΔG-ZEBOV-GP vaccine contains a replicating viral vector. A very limited number of pregnant women have received rVSVΔG-ZEBOV-GP vaccine, not aware they were pregnant at the time of vaccination, in previous randomized clinical trials or in the compassionate use/expanded access cohort study being implemented in the Democratic Republic of the Congo (DRC) (as recommended by the Ethics Review Committee in DRC). Therefore, the Working Group members emphasized the importance of maintaining a pregnancy registry to compile the safety data on vaccination during pregnancy including the data on women unaware of their pregnancy at the time of vaccination. This may inform future recommendations for the use of the vaccine in pregnant women. A similar registry approach is recommended for documenting vaccine safety in children.

In the context of the ongoing outbreak in the DRC and future outbreaks linked to the Zaire strain where a ring vaccination strategy is implemented using the rVSVΔG-ZEBOV-GP vaccine, consideration should be given to the potential for assessing the effect on disease outcomes of other Ebola candidate vaccines which target the Zaire strain. Access to other candidate vaccines might be relevant in terms of: manufacturing safety and stockpiling capacity, cold chain, multiple Ebola virus strain protection, cellular immunologic response or long-term protection. Target populations involved in such studies might include health-care and FLWs and other groups who may be at risk of further spread and who would not otherwise be eligible to receive the rVSVΔG-ZEBOV-GP vaccine under the current recommendations. To assess other candidate vaccines in such settings, given uncertainties of the direction of outbreak spread and likely low attack rates at the population level, consideration should be given to innovative randomized trial designs that have the potential to provide robust evidence on candidate vaccine efficacy and/or effectiveness and safety if the changing epidemiology of the disease would permit this. These trials should be designed to at least generate additional safety and immunogenicity data among populations at risk of Ebola.

If the outbreak is caused by an Ebola virus species other than Zaire species, then robust randomized trial designs to assess candidate vaccines which target the relevant putative viral species should be implemented. Presently, one multivalent vaccine is currently in Phase II of clinical development (Ad26.ZEBOV/MVA-BN-Filo).

The Working Group members considered that available unpublished evidence on various candidate Ebola vaccines concerning duration of protection and cross-

protection are still insufficient to support policy recommendation(s) for routine preventive vaccination of the general population or vaccination of HCWs and/or FLWs in the absence of an outbreak. The current information on the duration of protection for various candidate Ebola vaccines is up to 360 days post vaccination for the rVSVΔG-ZEBOV-GP, Ad26.ZEBOV/MVA-BN-Filo and ChAd3-EBOZ vaccines. Preliminary reports for these 3 candidate vaccines suggest that Ebola antibody geometric mean titers (GMT) were initially high (with peaks at 56 or 84 days post vaccination and 21 and 14 days post boost respectively) and slightly decline over time, but a relatively high GMT was maintained at the end of these follow-up periods for each candidate vaccine. However, in the absence of a correlate of protection and given that different assays were used, it is challenging to interpret these data. Evidence on cross-protection against different Ebola virus species remains uncertain for all candidate vaccines. Preliminary cross-protection data, assessed by enzyme-linked immunosorbent assays and virus neutralization assays results against other Ebola strains, was only reported for three candidate vaccines (Ad26.ZEBOV/MVA-BN-Filo, GamEvac-Combi and INO-4212 DNA vaccines). There is no data on cross-protection against Marburg virus for any candidate vaccine. The Working Group encouraged developers and researchers to design studies that would generate additional information on long term immunogenicity and cross-protection with a view to contribute to potential market authorization for a preventive indication.

The Working Group recommended that the WHO Secretariat continue to encourage the dialogue between national regulatory authorities and developers and, to explore expedited regulatory processes by supporting national regulatory authorities to develop a consensus on the regulatory pathways for the evaluation and potential market authorization of candidate Ebola vaccines. The Working Group also recommends that manufacturers and sponsors seek proactive feed-back on generic protocols for efficacy/effectiveness trials and market authorization requirements from relevant regulatory authorities in affected countries.

The Working Group noted that there is an ongoing systematic review of vaccination acceptability in health-care workers. The review outcomes will provide additional evidence to inform future SAGE recommendations regarding health-care worker vaccination strategies. Additional safety data among other target populations such as children, HIV-positive individuals and pregnant women is required. Moreover, additional social behavioral research is essential to provide further insights into the context and determinants of expanding outbreaks, especially the dynamic responses of the communities involved, and how this might impact on future outbreak dynamics and response.

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5. Appendices

Appendix 1. Characteristics of Ebolavirus and Marburg virus outbreaks, 1976–2018 (1)

Year	Country	Virus species	Weeks to 1st peak	Weeks to extinction	Cases	Deaths	Case fatality rate (CFR) %	Reference
1976	South Sudan	Sudan	5	20	284	151	53%	WHO/International Study Team, 1978 (2)
1976	Democratic Republic of Congo	Zaire	5	9	318	280	88%	Report of an International Commission, 1978 (3)
1977	Democratic Republic of Congo	Zaire	N/A	1	1	1	100%	
1979	South Sudan	Sudan	2	10	34	22	65%	Baron et al., 1983 (4)
1994	Gabon	Zaire	4	13	52	31	60%	Georges et al., 1999 (5)
1994	Côte d'Ivoire	Taï Forest	N/A	1	1	0	0%	
1995	Democratic Republic of Congo	Zaire	17	27	315	254	81%	Khan et al., 1999 (6)
1996 (Jan-Apr)	Gabon	Zaire	0	5	31	21	68%	Georges et al., 1999 (5)
1996 (Jul-Dec)	Gabon	Zaire	18	27	60	45	75%	Georges et al., 1999 (5)
1996	South Africa (ex-Gabon)	Zaire	N/A	1	1	1	100%	
1998	Democratic Republic of Congo	Marburg	13	100	154	125	81%	Bausch et al., 2006 (7)
2000	Uganda	Sudan	5	20	425	224	53%	Okware et al., 2002 (8)
2001-2002	Gabon	Zaire	6	21	65	53	82%	World Health Organization, 2003 (9) Nkoghe et al., 2005 (10)
2001-2002	Congo	Zaire	N/A	20	59	44	75%	Chippaux et al., 2014 (11)
2003 (Jan-Apr)	Congo	Zaire	N/A	19	143	128	90%	Formenty et al., 2003 (12)
2003 (Nov-Dec)	Congo	Zaire	5	7	35	29	83%	Boumandouki et al., 2005 (13)
2004	Angola	Marburg	24	42	252	227	90%	World Health Organization, 2005 (14, 15)

Year	Country	Virus species	Weeks to 1st peak	Weeks to extinction	Cases	Deaths	Case fatality rate (CFR) %	Reference
								US CDC, 2005 (16) Towner et al., 2006 (17)
2004	Sudan	Sudan	1	10	17	7	41%	World Health Organization, 2005 (18)
2005	Congo	Zaire	N/A	6	12	10	83%	
2007	Democratic Republic of Congo	Zaire	13	15	264	187	71%	World Health Organization, 2007 (19) Leroy et al., 2009 (20) Grard et al., 2011 (21)
2007	Uganda	Marburg	N/A	13	4	1	25%	Adjemian et al., 2001 (22)
2007	Uganda	Bundibugyo	14	18	149	37	25%	MacNeil et al., 2011 (23)
2008	Democratic Republic of Congo	Zaire	3	5	32	14	44%	World Health Organization, 2009 (24) Rosello et al., 2015 (25)
2011	Uganda	Sudan	N/A	1	1	1	100%	
2012	Uganda	Marburg	N/A	3	15	4	27%	Albariño et al., 2013 (26)
2012	Uganda	Sudan	N/A	1	24	17	71%	Albariño et al., 2013 (26)
2012	Uganda	Sudan	N/A	1	7	4	57%	Albariño et al., 2013 (26)
2012	Democratic Republic of Congo	Bundibugyo	N/A	8	57	29	51%	Albariño et al., 2013 (26)
2014-2016	Guinea	Zaire	22	109	3811	2543	67%	WHO Ebola Response Team 2014, 2015 & 2016 (27-29) Boisen et al., 2016 (30)
2014-2016	Liberia	Zaire	10	92	10675	4809	45%	
2014-2016	Sierra Leone	Zaire	18	88	14124	3956	28%	
2014	Nigeria	Zaire	N/A	N/A	20	8	40%	
2014	Mali	Zaire	N/A	N/A	8	6	75%	
2014	Senegal	Zaire	N/A	1	1	0	0%	
2014	USA	Zaire	N/A	N/A	4	1	25%	
2014	UK	Zaire	N/A	1	1	0	0%	
2014	Spain	Zaire	N/A	1	1	0	0%	
2014	Democratic Republic of Congo	Zaire	4	10	66	49	74%	Maganga et al., 2014 (31)

Year	Country	Virus species	Weeks to 1st peak	Weeks to extinction	Cases	Deaths	Case fatality rate (CFR) %	Reference
2015	Italy	Zaire	N/A	1	1	0	0%	
2017	Democratic Republic of Congo	Zaire	4	7	8	4	50%	World Health Organization, 2017 (32)
2018	Democratic Republic of Congo	Zaire	4	16	54	33	61%	World Health Organization, 2018 (33)
2018	Democratic Republic of Congo	Zaire	4	ongoing	142	97	68%	World Health Organization, 2018 (34)

* include suspect, probable and confirmed Ebola virus disease cases

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Appendix 2. Summary of published data on efficacy, immunogenicity and safety of candidate Ebola vaccines in clinical development (by 9 May 2018)

#	Candidate Ebola vaccine under clinical development	Developer	Published data available	Data updated
01	Ad5-EBOV (monovalent)	CanSino Biologics Inc. & Beijing Institute of Biotechnology, China	Yes	Yes
02	Ad5 (bivalent)	National Institute of Allergy and Infectious Diseases (NIAID), USA	Yes	
03	Ad26.ZEBOV & MVA-BN-Filo (prime/boost, VAC52150)	Janssen Vaccines & Prevention B.V, The Netherlands	Yes	Yes
04	ChAd3 (monovalent, ChAd3-EBOZ)	GlaxoSmithKline, Belgium	Yes	Yes
05	ChAd3-EBOZ & MVA-BN-Filo (prime/boost)	University of Oxford, UK and National Institute of Allergy and Infectious Diseases (NIAID), USA	Yes	
06	ChAd3 (bivalent)	National Institute of Allergy and Infectious Diseases (NIAID), USA	Yes	
07	GamEvac-Combi	Gamaleya Research Institute of Epidemiology and Microbiology, Russia	Yes	Yes
09	rVSVΔG-ZEBOV-GP	Merck, USA	Yes	Yes
10	rVSV N4CT1 EBOVGP1	Profectus BioSciences, USA	Yes	
11	Nanoparticle recombinant Ebola GP vaccine	Novavax, USA	No	
12	DNA vaccine (INO-4212)	Inovio Pharmaceuticals, USA	No	
13	DNA plasmid vaccines	National Institute of Allergy and Infectious Diseases (NIAID), USA	Yes	
13	HPIV3-EbovZ GP	National Institute of Allergy and Infectious Diseases (NIAID), USA	No	

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Ad5 expressing envelope GP of Zaire Ebola virus species (Makona variant, monovalent) with or without homologous boost							
Zhu et al., 2015 (1) Li et al., 2016 (2) (PMID: 25817373 and 28017642; NCT02326194 and NCT02533791)	1	China	120 healthy adults aged 18-60y; both men and women, but not pregnant or breast-feeding women. 60% participants had pre-existing Ad5 immunity (titres >1:200).	Randomised, placebo-controlled, double-blind trial; 1:1:1 randomisation to 1.6×1011, 4.0×1010 viral particles [vp], or placebo; follow-up to 168d (5.6m); unmasking after preliminary analysis. At 168d, 110 participants re-recruited and received 2nd dose of same intervention (the same vaccine & dose, or placebo; follow-up to 12m (18m after 1st dose). Enrolment 12/2014–1/2015.	After priming: Glycoprotein (GP) specific antibody titres were significantly increased at d14 and d28 in both vaccine groups; they peaked at d28 and persisted by d168. T-cell responses peaked at d14 in both vaccine groups. Immunogenicity was greater in high-dose than in low-dose vaccine group. After boosting: >20-fold increase in titres at d28 in both vaccine groups; titres persisted at m18. At lower dose, immunogenicity seemed more vulnerable to pre-existing Ad5	Mild and moderate solicited adverse reactions within 7d of vaccination reported at higher rate in both vaccine groups. No serious events recorded.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					immunity. Boosting provided greater antibody response, possibly with longer duration.		
Zhu et al., 2016 (3) (PMID: 28017399; PACTR201509001259869)	2	Sierra Leone	500 healthy adults aged 18-50y; both men and women, but not pregnant or breast-feeding women; HIV negative, no EVD history, no previous Ebola immunisation. 45% participants had pre-existing Ad5 immunity (titres >1:200).	Randomised, placebo-controlled, double-blind trial; 2:1:1 randomisation to 8.0x1010, 1.6x1011 vp, or placebo; safety follow-up at 7d, immunogenicity follow-up at d14, 28 and 168. Enrolment 10/2015.	GP-specific antibodies detected from d14, peaked at d28, and later declined by d168 (still approx. 40-fold greater than in placebo group). Although immunogenicity was greater in high-dose than in low-dose vaccine group, candidate vaccine was highly immunogenic at both dose levels in healthy Sierra Leonean adults. Lower dosage was chosen for further development also on basis of results from preclinical animal studies.	Rates of ≥1 adverse reaction within 7d of vaccination were similar in 3 groups; most reactions mild and self-limiting. Injection-site reactions were more frequent in vaccine groups. No serious events related to vaccine.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Wu, et al.2017(4), (PMID: 28708962; NCT02401373)	1b	China	61 healthy African aged 18-40y; both men and women, but not pregnant or breast-feeding women. HIV negative,64% participants had pre-existing Ad5 immunity (titres >1:200).	A dose-escalation, open-label trial, 31 participants receiving one shot intramuscular injection of 8.0x1010, and 30 participants receiving a double-shot regimen of 1.6x1011 vp. safety and immunogenicity follow-up at d14, 28. Enrolment 04/2015-08/2015.	Ebola glycoprotein-specific antibodies appeared in all 61 participants and antibodies titers peaked after 28 d of vaccination. The antibodies titers were similar between these 2 groups. The glycoprotein-specific T-cell responses rapidly peaked after 14 d of vaccination and then decreased, however, the percentage of subjects with responses were much higher in the high-dose group . Pre-existing Ad5 neutralizing antibodies could dampen the specific humoral immune response and cellular response to the	86.89% of participants reported at least one adverse reaction within 28 d of vaccination. The most common reaction was fever and the mild pain at injection site, and there were no significant difference between these 2 groups. No serious events recorded.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					vaccine		
Ad5 expressing envelope GP of Sudan and Zaire Ebola virus species (bivalent)							
Ledgerwood et al., 2010 (5) (PMID: 21034824; NCT00374309)	1	USA (Maryland)	31 healthy adults, both men and women; mean age 31y. Half of participants had a high level of pre-existing Ad5 immunity (titres >1:500)	Randomised, placebo-controlled, double-blind trial; 3: 1 randomisation to either 2×1011 or 2×1010 vp and placebo; follow-up for 48w. Enrolment 9/2006–11/2007.	Actual randomization 11:12:8, Sudan and Zaire GP-specific seropositivity peaked at 58% and 50% at w4 and was 42% and 33% at w48, respectively; response rates were higher in low-dose vaccine group, but magnitudes were non-statistically higher in high-dose group. Ad5-seronegative vaccinees had significantly higher response rates and magnitude of response than Ad5-seropositive vaccinees. Sudan and Zaire GP-specific T-cell responses were	Self-limited reactogenicity without sequelae was observed. Three adverse events related to vaccination (two cases of partial thromboplastin time, a case of Grade 3 fever with 24h).	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					present in both low- and high-dose vaccinees.		
Ad26 expressing envelope GP of Zaire Ebola virus species (Mayinga variant, as prime) and modified vaccinia Ankara expressing 4 filoviruses nucleoproteins (MVA-BN-Filo, as boost)							
Milligan et al., 2016 (6) (PMID: 27092831; NCT02313077)	1	United Kingdom (Oxford)	87 healthy adults aged 18–50y (median age 38.5y); both men and women, but not pregnant or breast-feeding women; 67% participants were women. 3.4% participants had pre-existing Ad26 immunity 8tires threshold not defined).	Randomised, placebo-controlled, observer-blind trial; 5:1 randomisation, with 4 vaccine groups: primed with either Ad26 5×1010 vp or MVA 1×108 infective dose and boosted with alternative vaccine at either d28 or d56; and primed with Ad26 and boosted by MVA at d14 (open-label). Follow-up for 8m after priming. Enrolment 12/2014–2/2015.	Seropositivity at d28 in 97% and 23% vaccinees primed with Ad26 and MVA, respectively; all vaccinees had detectable GP-specific IgG at d21 after boost and at 8m follow-up. Conclusion was that Ad26 priming induces immune response and MVA boosting sustained and specific immunity.	In randomised groups, 5% participants experienced fever after Ad26, none after MVA. In open-label group, 27% experienced fever. No vaccine-related serious adverse events occurred.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Enria et al., 2016 (7) (PMID: 27821112; NCT02509494)	3	Sierra Leone (Kambia)	*Stage 1:* 43 healthy adults aged ≥18y. *Stage 2:* 976 persons aged ≥1y.	Study denominated EBOVAC-Salon; reported as phase 3 trials, but stage description only reports safety/immunogenicity evaluation. *Stage 1:* open label, primed with Ad26 5×1010 vp and boosted with MVA 1×108 infective dose at d28; vaccinated from 10/2015. *Stage 2:* randomised, controlled, double-blind trial; randomization to same prime/boost regimen as stage 1 or MCV as control; allocation not detailed. 3rd dose for children aged <2 at 3m after boost. Follow-up for 56d (28d after boost), but for	N/A	N/A	Currently recruiting. Data collection for primary outcome measure finalized by 11/2019

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				serious adverse events for 36/12m for stage 1/2, respectively. Additional stages are being consulted with national and international stakeholders.			
Vandebosch et al., 2016 (8) (PMID:26768568)	3 (design)	Not applicable	Not appplicable	This manuscript aims to present the statistical and modeling considerations, design rationale and challenges encountered due to the emergent, epidemic setting that led to the selection of a cluster-randomized phase 3 study design under field conditions.	Not applicable	Not applicable	Not applicable
Shukarev, G et al., 2017 (9) (PMID: 27925844)	Overall program and Phase I, 1001, durability 8 months (Commentary)	Not applicable (Commentary)	Not applicable (Commentary)	Not applicable (Commentary)	Not applicable (Commentary)	Not applicable (Commentary)	Not applicable (Commentary)

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Camacho A, et al. 2017 (10) (PMID: 28024952)	3 (design)	3 Regions in Sierra Leone	Not applicable (modelling)	In real-time, we fitted, forecasted, and simulated a proposed phase 3 cluster-randomized vaccine trial for a prime-boost EVD vaccine in three candidate regions in Sierra Leone. The aim was to forecast trial feasibility in these areas through time and guide study design planning.	Not applicable	Not applicable	Not applicable
Winslow RL et al. 2017 (11) (PMID: 28291882)	1 (Durability)	United Kingdom (Oxford)	87 healthy adults aged 18–50y (median age 38.5y); both men and women, but not pregnant or breast-feeding women; 67% participants were women. 3.4% participants had pre-existing Ad26 immunity 8tires threshold not	Randomised, placebo-controlled, observer-blind trial; 5:1 randomisation, with 4 vaccine groups: primed with either Ad26 5×1010 vp or MVA 1×108 infective dose and boosted with alternative vaccine at either	All of the active vaccine recipientsmaintained Ebola virus–specific immunoglobulin G responses at day 360. Vaccine-induced T-cell responses persisted in 60% to 83% of participants receiving	No serious adverse events were recorded from day 240 through day 360.	completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
			defined). Of 75 active vaccine recipients, 64 attended follow-up at day 360 (median age, 39 years; women, 66%). Eleven participants withdrew (1-3 per group) and missing data were not imputed	d28 or d56; and primed with Ad26 and boosted by MVA at d14 (open-label). Follow-up at 1 year. Enrolment 12/2014–2/2015.	Ad26.ZEBOV first followed by MVA-BN-Filo as a booster compared with 69% to 100% of those receiving the reverse regimen.		
ChAd3 expressing envelope GP of Zaire Ebola virus species (Mayinga variant, monovalent)							
De Santis et al., 2016 (13) (PMID: 26725450; NCT02289027)	1/2a	Switzerland (Lausanne)	120 healthy adults aged 18–65y. Also, individual potentially deployable to areas with ongoing transmission.	Randomised, placebo-controlled, double-blind, dose-finding trial; 2:2:1 randomisation to ChAd3-EBOZ 2.5×1010 pu (low dose), 5×1010 pu (high dose) or placebo. Allocation not concealed for deployable participants. Follow-up for	GP-specific antibody response rate in vaccinees was 96% (5% in placebo). Ab-level peaked at d28 and halved by d180. CD4/8 cell responses were 60–70%. ChAd3-EBO-Z was safe and well tolerated, although mild/ moderate systemic adverse events were common. No	>75% vaccinees reported local adverse events. Fatigue or malaise was most reported systemic event (60%) and 25–30% vaccinees reported fever within 24h after vaccination. No serious vaccine-related adverse events reported.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				180d.	significant differences related to two dosages.		
Tapia et al., 2016 (14) (PMID: 26546548; NCT02231866)	1	USA (Maryland), Mali	In total 91 healthy participants aged 18–65y: ChAd3-EBOZ at 1×1010 pu (N=10), at 2.5×1010 pu (N=35), at 5×1010 pu (N=35) and at 1×1011 pu (N=11). Malian subjects were invited to participate to a nested, placebo-controlled MVA booster extension.	Randomized, open-label and double-blind trial.	Anti-GP ELISA response observed in 83 to 100% of vaccinees at d28 after ChAd3-EBO-Z vaccination. Titres were higher in the 1×1011 pu group. Antibody and	Local pain and tenderness, fatigue and headache were most frequently reported adverse events. No serious safety concerns identified.	Completed
Ewer et al., 2016 (15) (PMID: 25629663; NCT02240875)	1	UK	In total 76 healthy participants aged 18–50y: ChAd3-EBOZ at 1×1010 pu (N=20), at 2.5×1010 pu (N=36), at 5×1010 pu (N=20). Subjects were invited to	Randomized, open-label	Induction of anti-GP ELISA (standardized glycoprotein and whole-virion assays) responses 28 days after ChAd3-EBO-Z vaccination. Low levels of	The majority of adverse events were self-limited and mild. Local pain was the most common local event. Moderate systemic adverse events were fever, myalgia,	Active, not recruiting

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
			participate to an MVA booster extension.		neutralizing antibody titers to live Zaire Ebola (Mayinga) strain, as well as Polyfunctional EBOV-specific CD4+ and CD8+ T-cell responses also observed at Day 30. All vaccine responses boosted by the MVA.	arthralgia, headache, fatigue, nausea, and malaise. No severe systemic solicited adverse events were reported. No fever persisted for more than 24 hours.	
EBOLA Z CHAD3-005 (NCT02485301)	2	Senegal, Mali, Nigeria, Cameroon	Healthy adults aged 18 years and above (N=3000)	Single vaccination with ChAd3-EBO-Z. Randomized 1:1 ChAd3-EBO-Z 1×1011 pu vs. placebo. Observer-blind (until D30); single-blind (until M6); open label (until M12).	Approximately 25% of the subjects were seropositive for anti-GP-EBOV ELISA antibodies on Day 0 before vaccination. Anti-GP EBOV ELISA antibodies were induced at 30 days after vaccination and persisted until the end of the study follow-up (Month 12). Polyfunctional EBOV-specific CD4+ and CD8+ T-	The ChAd3-EBO-Z vaccine candidate was generally well tolerated in the subjects. Vaccination with ChAd3-EBO-Z was mainly associated with transient and non-severe local pain, headache and fatigue. No SAEs were considered related to the study vaccination by the Investigator. Drops from baseline platelet levels, the	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					cell responses were observed at Day 30 in the EBO-Z group. A ChAd3 neutralizing antibody response above the threshold of positivity was observed in 58.3% subjects in the EBO-Z group and 27.2% subjects in the Placebo/ EBO-Z group at Day 30. At Month 6, it was observed in 35% of subjects of the EBO-Z group and 24.5% of subjects of the Placebo/ EBO-Z groups. The GMC value was just above the threshold of positivity at Day 30 in the EBO-Z group and below the threshold in the Placebo/ EBO-Z group. At Month	majority of them occurring within the normal range, were observed in both the EBO-Z and the Placebo/ EBO-Z groups without notable differences between both groups, and no clinical signs of thrombocytopenia (AESI) were reported within the first 7 days post-vaccination in either of the groups. No other clinically significant laboratory abnormalities related to the vaccination were noted.	

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					6, GMC values were below the threshold of positivity in the two groups.		
EBOLA Z CHAD3-004 (NCT02548078)	2	Senegal, Mali	Children aged 1 to 17 years (13-17y [N=200], 6-12y [N=200], 1-5y [N=200])	Randomized 1:1 ChAd3-EBO-Z 1×1011 pu vs. MenACWY. Observer-blind (until D30); single-blind (until M12).	Approximately 17% of the subjects were seropositive for anti-GP-EBOV ELISA antibodies on Day 0 before vaccination. Anti-GP EBOV ELISA antibodies were induced at 30 days after vaccination with ChAd3-EBO-Z and persisted until the end of the study follow-up (Month 12). Poly-functional EBOV CD4+ and CD8+ T-cell responses were observed at 30 days post ChAd3-EBO-Z vaccination. A ChAd3 neutralising antibody response	The ChAd3-EBO-Z vaccine candidate was generally well tolerated in the subjects. Vaccination with ChAd3-EBO-Z was mainly associated with transient and non-severe local pain (except Grade 3 pain for one subject aged 6 to 12 years and three subjects aged 1 to 5 years), fever, headache and fatigue. No SAEs were considered related to the study vaccination by the Investigator. Drops from baseline platelet levels, the majority of them occurring within	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					above the threshold of positivity was observed in 57% subjects in the EBO-Z/ MENACWY-TT group and 14.6% subjects in the MENACWY-TT/ EBO-Z group at Day 30. At Month 6, it was observed in 41.2% of subjects of the EBO-Z/ MENACWY-TT group and 20.5% of subjects of the MENACWY-TT/ EBO-Z groups. The GMC value was 304 at Day 30 in the EBO-Z/ MENACWY-TT group and below the threshold in the MENACWY-TT/ EBO-Z group. At Month 6, GMC values were below the threshold of	the normal range, were observed in both the EBO-Z/ MENACWY-TT and the MENACWY-TT/ EBO-Z groups without notable differences between both groups, and no clinical signs of thrombocytopenia (AESI) were reported within the first 7 days post-vaccination in either of the groups. No clinically significant laboratory abnormalities were related to vaccination.	

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					positivity in the two groups.		
ChAd3 (monvalent) boosted with MVA-BN-Filo							
Tapia et al., 2016 (14) (PMID: 26546548; NCT02267109)	1b	Mali	91 adults aged 18–50y (52 participants boosted with either MVA-BN-Filo [27] or saline [25]). Males & females not breast-feeding, not pregnant & not planning to become pregnant.	Open-label and double-blind, dose-escalation trial (ChAd3 prime); nested, randomised, placebo-controlled and double-blind trial (MVA boost). 1:3:3:1 randomisation to ChAd3 1×1010, 2.5×1010, 5×1010 or 1×1011 vp. 52 participants were further 1:1 randomised to boost MVA 2×108 pfu or placebo. Follow up for 180d after primary or booster vaccination. Enrolment 11/2014 (prime) and 2/2015 (boost).	83–100% vaccinees showed humoral response after ChAd3 at d28, unrelated to dose level. 100% vaccinees showed humoral response after MVA boost at both d7 and d28. T-cell responses after ChAd3 priming were of small magnitude, but stable at time of boosting. In contrast, cellular response was high-magnitude in 85% after boosting. Results suggest use of 1×1011 ChAd3 dose for reactive vaccination and MVA boosting for conferring long-	Most adverse events were mild. Predominant solicited adverse event was fever (10/11 episodes resolved within 24h). Only one serious event observed in a Malian participant, but deemed unrelated to vaccine.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					lived protection.		
Ewer et al., 2016 (15) (PMID: 25629663; NCT02240875)	1	UK (Oxford)	76 healthy adults aged 18–50y.	Open-label trial. *Priming:* 20:36:20 participants each received ChAd3 at 1×1010, 2.5×1010 and 5×1010 vp. *Boosting:* 46 participants in total boosted with MVA. At w1–2, 16 participants of ChAd3 2.5×1010 dose boosted with MVA 1.5×108 plaque forming units (pfu). At w3–10, 10 participants of 3 ChAd3 dose groups boosted at either MVA 1.5×108 (18 participants) or 3x108 (12), stratified per priming dose group. Follow-up for 29d (primed only) or 180d (if boosted). Also, comparison of neutralizing	After MVA boost, GP-specific antibody response increased by d7 compared to pre-boost level, peaked at d14, and remained higher at d180 days. At w4, MVA boosting also increased virus-specific (12-fold) and neutralizing antibodies titres and CD8 cell response (5-fold). At d180, 100% boosted and less than half primed-only vaccinees remained positive for GP-specific antibodies; titres in boosted were 4-fold greater. ChAd3 boosted with MVA elicited humoral and cellular immune responses that	Majority of adverse events were self-limited and mild. Moderate systemic adverse events included fever, myalgia, arthralgia, headache, fatigue, nausea and malaise. No severe systemic solicited adverse reported. No safety concerns were identified at any of the dose levels studied.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				antibody activity with that observed in ph1 trial of rVSV-ZEBOV. Enrolment in late 2014.	were superior to those induced by ChAd3 alone		
ChAd3 expressing envelope GP of Zaire (Mayinga variant) and Sudan Ebola virus species (bivalent)							
Ledgerwood et al., 2014 & 2017 (16, 17) (PMID: 25426834; NCT02231866)	1	USA (Maryland)	20 healthy participants aged 18–50, both sexes (55% women)	Open-label, dose-escalation trial. Participants sequentially enrolled in groups of 10 to receive ChAd3 (bivalent) at doses 2×1010 and 2×1011 vp. Followed-up for 48w. Enrolment 9/2014.	At w4, 90/100%, 90/90% & 70/80% vaccinees showed Zaire/Mayinga, Zaire/Makona & Sudan GP-specific humoral response (low/high dose), respectively. At w48, Zaire/Mayinga titres remained eleveated. T-cell responses were dose-dependent (20-80% at w4 & 10-50% at w8). Pre-existing ChAd3 & Ad5 antibodies had no correlation with immune responses.	No safety concerns were identified. Fever reported in 2 participants in higher dose group. No serious adverse events were reported.	Completed
GamEvac-Combi and GamEvac-Lyo (rVSV & Ad5, prime & heterologous boost) expressing Zaire Ebola virus species (Makona variant)							
Dolzhikova et al., 2017 (15) (PMID:	1/2	Russia	84 healthy volunteers aged	Open-label, dose-escalation trial.	100% prime-boost vaccinees of both	Pain at the injection site was	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
28152326; zakupki.gov.ru no. 0373100043 215000055)			18–55y, both sexes (76% men)	GamEvac-Combi (rVSV prime & heterologous Ad5 boost), each component alone or in combination at full (rVSV 2.5×107 pfu & Ad5 2.5×1011 vp) or half dose. For safety evaluation, an initial group was assigned to receive either rVSV (12 participants) or Ad5 (12) at half dose. For safety and immunogenicity evaluation, a second group of 60 participants received rVSV followed by Ad5 at d21 at either full or half dose. Followed up for 42d. Enrolment 9–11/2015.	dose groups showed GP-specific immune response at d42. Titres were 1.25-fold greater in full-dose vaccinees at d42 compared to half-dose vaccinees. In full-dose vaccinees, titres were 5-fold lower in rVSV only vaccinees compared to prime-boost vaccinees. Preexisting neutralizing Ad5 antibodies adversely influenced GP-specific response in half-dose group, but not in full-dose group. 93% prime-boost vaccinees in full-dose group showed neutralizing Mayinga, taken as indication of	most frequently reported adverse event. No serious adverse event were reported.	

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					crossreactive immunogenicity from Makona. 59–83% prime-boost vaccinees of both dose groups showed Tcell responses at d28, with lower percentages at d42. Vaccine showed high immunogenicity and had good safety profile. Accordingly, it was registered in Russia in 12/2015.		
Only information from clinical trial registry entry (N.F. Gamaleya FRCEM, Russia) (PMID: N/A; NCT02911415)	4	Russia	60 healthy volunteers aged 18–56y, both sexes. (NCT02911415)	Open Study of the Duration of Immunity After Vaccination With Medicinal Product GamEvac-Combi - Combined Vector-Based Vaccine Against Ebola Virus Disease, 0.5 ml+0.5 ml/Dose Observational, prospective cohort study to evaluate	100% prime-boost vaccinees of both dose groups showed GP-specific immune response at 12 months. Average titers were 1.29-fold greater in full-dose vaccinees at 12 month compared to half-dose vaccinees.	No serious adverse events were reported.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				duration of immunity after earlier vaccination (that occurred 10–11/2015) at two dose levels. Follow-up visits at 12, 18 & 24m after vaccination. Enrolment from 10/2016.	The GP-specific antibody titre was detected in 96% of volunteers in full-dose group and in 93% of volunteers in half-dose group at 18 month. Average titers were 1,5-fold greater in full-dose vaccinees at 18 month compared to half-dose vaccinees. The GP-specific antibody titer was detected in 89% of volunteers in full-dose group and 53% of volunteers in half-dose group at 24 months. Average titers were 8-fold greater in full-dose vaccinees at 24 month compared to half-dose vaccinees.		
Russian Federation	3	Guinea (Kindia)	2,000 healthy	GamEvac-Combi:	in progress	The data obtained	Recruiting.

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
MOH briefing at WHO Executive Board meeting of 2/2016 (PMID: N/A; NCT03072030 & PACTR201702002053400)			volunteers aged 18–60y, both sexes	rVSV prime, 2.5x107 pfu; Ad5 boost at d21, 2.5x1011 vp. Randomized, placebo-controlled, double-blind trial. 19:1 randomization to either prime/boost (1,900 participants) or placebo (100). According to epidemiological situation, option for ring vaccination around confirmed EVD cases. Follow-up for 12m.		during the clinical trial about adverse events after administration of the vaccine correspond to the available safety information specified in the official instructions for medical use, approved by the Ministry of health of the Russian Federation, and in Investigators Brochure. No serious adverse events were reported. In the structure of adverse events, systemic reactions were mainly represented by temperature increase, fever, which in a number of volunteers was accompanied by concomitant symptoms of	Actual study started at 8/2017; data collection for primary analysis will be obtained up to 12/2019.

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
						intoxication. Local reactions were noted in the form of hyperemia and edema at the site of the vaccine injection. Clinical manifestations of allergic reactions (urticaria, rash, anaphylactic reactions) associated with vaccine administration, were not recorded.	
Only information from clinical trial registry entry (N.F. Gamaleya FRCEM, Russia) ClinicalTrials.gov Identifier: NCT03333538	1/2	Smorodintsev research Institute of Influenza Sankt-Peterburg, Russian Federation	220 healthy volunteers aged 18–55y, both sexes	A Double-blind Randomized Placebo-controlled Study of Safety and Immunogenicity of Medicinal Product GamEvac-Lyo, Vector-Based Vaccine Against Ebola Virus Disease, Lyophilisate for Preparation of Solution for	in progress	During the first stage of the study, mild adverse events (temperature increase, fever, headache, malaise, pain at the injection site) were recorded. All reported adverse events were resolved within 1-2 days without the use of	Recruiting. Actual study started at 11/2017; data collection for primary outcome measure will be finaled to 12/2018. Currently, the investigation of immunogenicity of the drug "GamEvac-Lyo" with 200

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				Intramuscular Injection. This clinical trial is designed as a double blind randomized placebo-controlled study to evaluate immunogenicity of medicinal product GamEvac-Lyo-Vector-Based Vaccine against Ebola Virus Disease The study consist of two stages At the first stage were studied the safety and tolerability of one dose of component A and B vaccine against Ebola in 20 healthy volunteers: 10 for component A and 10 to component B. In the first stage, the placebo will not be used. The duration of		symptomatic therapy. The frequency and nature of the adverse events recorded after the administration of the vaccine, are corresponding to the available safety information for the vaccine-analog "GamEvac-Combi".	volunteers, which will be determined by the tension of humoral and T-cellular immunity in response to vaccination is ongoing

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				screening up to 10 days. After interim analysis of safety data was obtained permission of the local ethics Committee of the Research Centre about the possibility of further studies of the drug. the second phase of the study was started, which, along with continued security research, provides the definition of the parameters of immunogenicity of the study drug. The second phase of the study will includ 200 participants, including 150 people will receive the vaccine and 50 will get a placebo.			
rVSV expressing envelope GP of Zaire Ebola virus species (Mayinga variant, rVSVΔG-ZEBOV-GP) with or without homologous boost							
Huttner et al.,	1	Switzerland	115 healthy adults	Randomized,	Huttner 2015	Mild, early-onset	Completed and

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
2015 (19) (PMID: 26248510; NCT02287480) Huttner et al., 2018 (20) (PMID: 29627147)		(Geneva)	aged 18–65 years	placebo-controlled, double-blind trial (deployable subjects not randomized to placebo) of rVSV doses ranging from $3x10^5$ –$5x10^7$ pfu; Follow-up for 28d (safety) and 180d (immunogenicity).	interim results reported seropositivity rates were similar (>90%), but GP-specific and neutralising Ab titres were 3 times lower in low-dose versus high-dose vaccinees. Lowering rVSV dose improved early tolerability, but also lowered antibody responses and did not prevent vaccine-induced arthritis, dermatitis, or vasculitis. Huttner 2018 reported sustained GP-ELISA responses and decreased PsVNA responses at 2 years	reactogenicity reported in 88%, 98% and 15% of low-, high-dose and placebo participants, respectively. 25% vaccinees at dose $1x10^7$ pfu w/ had objective fever. 25% low-dose vaccinees experienced oligoarthritis with median onset d10, associated with increasing age. No serious adverse events reported. Huttner 2018 reported vaccine related arthritis is associated with increased IgG GMCs beyond 6 months.	published
Agnandji et al., 2016 (21) (PMID: 25830326; NCT02283099,	1	Africa (Lambaréné, Gabon; Kilifi, Kenya) and Europe (Hamburg,	*Gabon, Kenya, Germany:* 185 healthy adults aged 18–55y, both	*Gabon, Kenya, Germany:* Open-label, uncontrolled,	All vaccinees showed GP-specific antibody responses; similar	Within 1st day, mild-to-moderate adverse events, with fever being	Completed and published

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
NCT02287480, NCT02296983, and PACTR201411000919191) Agnandji et al., 2017 (22) (PMID: 28985239)		Germany; Geneva, Switzerland) Data from Switzerland captured in prior row	sexes (75% men). 40 children aged 6-17 y.	dose-escalation trials of single rVSV dose ranging from $3x10^3$–$2x10^7$ pfu.	titres for different doses that were sustained at 180d. Most vaccinees showed neutralizing antibodies, with higher titres at higher doses.	most frequent (up to 30% vaccinees). Two (3%) vaccinees experienced arthritis. No serious vaccine-related adverse events reported. Vaccine viremia higher in children than adults and higher proportion of children than adults with PCR positive saliva through day 7 (latest timepoint tested).	
Regules et al., 2015 & 2017 (23, 24) (PMID: 25830322; NCT02269423 and NCT02280408)	1	USA (Maryland)	78 healthy adults aged 18–50y, both sexes (71% men)	Placebo-controlled, double-blind, dose-escalation trials. Consecutive enrolment to $3x10^6$, $2x10^7$ and $1x10^8$ pfu (60 participants) or placebo (18). In one of two studies, participants	100% vaccinees seroconverted for GP-specific antibodies by d28. Higher titres in vaccinees with two higher dose levels. 2nd dose at d28 increased titres by d56, but titres were diminished at 6m. Results support	Injection-site pain, fatigue, myalgia, and headache were reported most frequently. Rates of adverse events were lower after 2nd dose. No serious adverse events observed.	Completed and published

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				received 2nd dose at d28. Follow-up for 28d (after either 1st or 2nd injection).	further evaluation of rVSV at dose $2x10^7$ pfu and indicate that 2nd dose boosts antibody responses.		
El Sherif et al., 2018 (25) (PMID: 28630358)	1	Canada	40 healthy adults aged 18–65y, both sexes (43% men)	Randomized, Single-Center, Double-Blind, Placebo Controlled, Dose-Ranging Study to Evaluate the Safety and Immunogenicity of $1x10^5$, $5x10^5$ and $3x10^6$ pfu (30 participants) or placebo (10)	ZEBOV rGP ELISA seroconversions Day 28 were 70% in participants who received the 1×10^5 pfu or 5×10^5 pfu dose and 100% in participants who received the 3×10^6 pfu dose.	Solicited AEs were primarily characterized as mild to moderate, with only 3 severe events (headache and diarrhea in the 5×10^5 pfu group; fatigue in the 3×10^6 pfu group). Arthralgia during the first 14 days postvaccination was infrequent and not severe. Arthritis was not reported.	Completed and published
Heppner et al., 2017 (26) (PMID: 28606591)	1b	USA	512 healthy eligible subjects between the ages of 18 and 61 years received vaccine or placebo	Randomized, multi-center, double-blind, placebo controlled, dose-ranging study to evaluate the	On day 28 at the 2×10^7 PFU dose, the geometric mean IgG ELISA endpoint titre was 1624 (95% CI 1146–	At the 2×10^7 PFU dose the most common local adverse events versus placebo within the first 14 days were arm	Completed and published

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				safety and immunogenicity of a broad dose range from $3x10^3$ to $1x10^8$ pfu	2302) and seroconversion was 95·7% (95% CI 85·5–98·8); the geometric mean neutralising antibody titre by $PRNT_{60}$ was 250 (176–355) and seroconversion was 95·7% (85·5–98·8)	pain and local tenderness. The most common systemic adverse events were headache, fatigue, myalgia, subjective fever, shivering or chills, sweats, joint pain, objective fever, and joint tenderness or swelling. Self-limited, post-vaccination arthritis occurred in 4.5% of vaccinees. Post-vaccination dermatitis occurred in 5.7% of vaccinees.	
Halperin et al., 2017 (27) (PMID: 28549145) Simon et al., 2017 (28)	3	USA, Canada, Spain	1,197 Healthy eligible subjects between the ages of 18 and 65 years	Randomized, double-blind, placebo-controlled study to evaluate safety and lot consistency of $2x10^7$ pfu standard dose and $1x10^8$ pfu high dose	Using validated assays day 28 geometric mean titer comparisons among subjects randomized to the 3 lots of standard dose vaccine demonstrated lot-	Fever (≥38.0°C) was observed in 20.2% of combined lots, 32.2% of high-dose, and 0.8% of placebo recipients. Incidences of AEs of interest (days	Completed and published

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					to-lot consistency. Seroconversion defined as ≥ 2-fold increase in antibody over baseline and ≥200 EU/ml was achieved by more than 94% of subjects who received any standard dose and 98% of subjects who received the high dose. At Month 6, more than 95% of subjects who received any standard dose and 96% of subjects who received the high dose met these criteria. Geometric mean titers increased by more than 58-fold from baseline by Day 28 and were increased by more than 52 fold from baseline at Month	1–42) were arthralgia (17.1% combined lots, 20.4% high-dose, 3.0% placebo), arthritis (5.1% combined lots, 4.2% high-dose, 0.0% placebo), and rash (3.8% combined lots, 3.8% high-dose, 1.5% placebo). Twenty-one SAEs and 2 deaths were reported, all assessed by investigators as unrelated to vaccine.	

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					6 in subjects that received standard dose or high dose of vaccine.		
Ebola ça suffit ring vaccination trial consortium, 2015 (29) Henao-Restrepo et al., 2015 & 2017 (30, 31) Soumah et al., 2016 (32) (PMID: 26215666, 26248676 & 28017403; PACTR201503001057193)	3	Guinea, Sierra Leone	5837 vaccinated participants out of 11, 841 people enumerated in 117 clusters total in communities with confirmed EVD. Initially aged ≥18y and not pregnant, breastfeeding, or severely ill; later age lowered to ≥6y. Both sexes (60% women). 2,016 healthy adults, front-line workers aged ≥18y. Both sexes (75% men)	*Cluster-randomized trial:* Ebola Ça Suffit! trial. Cluster-randomized (ring) trial; single rVSV dose of $2x10^7$ pfu; randomization by cluster into immediate or 21d delayed vaccination. No immunological testing. Follow up for 84d. Following DSMB recommendation randomization stopped and children down to 6 years enrolled. Enrolled 3/2015–1/2016. *Front-line worker trial:* non-randomized, open-label trial for safety and	*Cluster-randomized trial:* Vaccine efficacy was 100.0% (95% CI: 68.9–100.0%). *Front-line worker trial:* Only preliminary results are available. 29% and 70% of participants were whole virion ELISA positive at d0 and 28, respectively; 0% and 8% showed cellular response at d0 and 28, respectively.	*Cluster-randomized trial:* 54% of participants reported at ≥1 adverse event in 14d after vaccination; 88% of all adverse events were mild; 80 serious adverse events were identified, of which two were judged to be related to vaccination. *Front-line worker trial:* 70% participants reported adverse events. Headache and fatigue were most frequently reported. No serious adverse event was vaccine-related.	*Cluster-randomized trial:* completed and published Front-line *worker trial:* completed but not yet published

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				immunogenicity; subgroup w/ immunological assessment (112 participants): 5 blood drawings (at inclusion and w2, 4, 12, 24). Follow-up for 24w. Enrolled 4–8/2015.			
Widdowson et al., 2016 (33) Goldstein et al., 2016 (34) Samai et al., 2018 (35) (PMID: 27387395 & N/A; NCT02378753)	2/3	Sierra Leone	8,673 clinical and nonclinical workers and other Ebola front-line workers (e.g., surveillance, burial, and ambulance personnel) enrolled and randomized; 8651 with valid consent	STRIVE trial (Sierra Leone Trial to Introduce a Vaccine against Ebola). Single rVSV dose of $2x10^7$ pfu. Initially planned as modified stepped-wedge trial: facilities randomized to receive vaccine at a specified time over a 6m period. Implemented as individually randomized trial of workers assigned to receive vaccine immediately or	8,651 vaccinees in 5 districts, of whom 4,319 (50%) immediately vaccinated. 44 participants became EVD suspect, but no cases were laboratory confirmed.	No serious vaccine-related adverse events or deaths report among vaccinees. 91.2% reported systemic adverse events within 7 days of vaccination.	Completed and published

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				delayed by 18–24w. Follow-up monthly for 6m. 436 participants in safety sub-study.			
Günther et al., 2011 (35) (PMID: 21987751; N/A)	N/A	USA	1 (post -exposure vaccination of biosafety level 4 laboratory worker)	Case report related to emergency vaccination of BL4 worker who got a needlestick injury with syringe containing Zaire Ebola virus species; single dose of rVSV $5.3x10^7$ pfu 48h after accident.	Person remained healthy. Except for the glycoprotein gene expressed in the vaccine, Ebola virus was never detected in serum and peripheral blood mononuclear cells during 3w observation period.	Patient developed fever and myalgia 3d after accident (1d after vaccination).	N/A
Lai et al., 2015 (36) (PMID: 25742465; N/A)	N/A	USA	1 (post -exposure vaccination of HCW)	Case report related to emergency vaccination of a physician who got a needlestick injury while working in an Ebola treatment unit in Sierra Leone in 9/2014. Vaccine administered 43h after accident	Ebola virus glycoprotein gene (included in the vaccine), Cytokine secretion and T lymphocyte and plasmablast activation were detected shortly after vaccination. Later, GP- specific antibodies and T cells were detected, but not	Fever and moderate to severe symptoms observed 12h after vaccination and lasted 3-4d.	N/A

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					antibodies against Ebola viral matrix protein 40 (not generated from vaccine). PCR was consistently negative for Ebola virus nucleoprotein gene (not in the vaccine).		
Wong et al., 2016 (37) (PMID: 27118786; N/A)	N/A	USA	5 (post-exposure vaccination of healthcare workers)	Case report related to emergency vaccination of HCWs who had potential exposures while working in Ebola treatment units in West Africa. Vaccine administered 24h to 3 days post-exposure	No subjects had RT-PCR evidence of Ebola infection	Fever, headache, and nausea were the most common AEs reported. 1 or 2 subjects reported diarrhea, vomiting, rash, arthralgia, or pain at injection site	N/A
rVSV expressing envelope GP of Zaire Ebola virus species (Mayinga variant, rVSV N4CT1 EBOVGP1)							
Matassov et al., 2016 (38) (PMID: N/A; NCT02718469)	1	USA	39 healthy adults, aged 18–55, both sexes	Randomized, placebo-controlled, double-blind, truncated dose escalation trial.	Preliminary results are from still blinded groups. GP-specific antibody responses	Adverse events across all dose groups were generally mild. Most frequently reported events	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				10:3 randomization in 3 groups to either vaccine (at doses 2.5x104, 2.5x105 & 2.0x106 pfu for each group) or placebo. Second dose administered at 28d interval. Follow-up for 26w (4m). Enrolment early 2016.	detected in 10/13, 9/12 & 10/13 participants in low-, mid- and high-dose groups, respectively. Similarly, T cell responses detected in 8/13, 8/12 & 9/13 participants.	were pain at injection (13/39) and fatigue (5/39).	
DNA plasmid vaccines							
Martin et al., 2006 (39) (PMID: 16988008; NCT00072605)	1		27 healthy adults aged 18–44 years	1st generation DNA vaccine, protocol VRC 204. Three-plasmid DNA vaccine encoding GP from Zaire and Sudan/Gulu species and nucleoprotein (VRC-EBODNA012-00-VP). Randomized, controlled, double-blind trial. 5:8:8:6 randomization to three injections	100% vaccinees showed GP-specific humoral and cellular responses detected at 4w after 3rd dose. Responses were also detectable after 2nd dose. Results of cellular responses also reported. Candidate DNA vaccine was immunogenic.	Vaccine was well-tolerated, with no significant adverse events.	Completed in 8/2005

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				(d0, d28, d56) of vaccine at doses 2, 4, 8mg or placebo. Followed for 12m. Enrolment in 11/2003–7/2004.			
Kibuuka et al., 2015 (40) (PMID: 25540891; NCT00997607)	1b	Uganda (Kampala)	108 healthy adults aged 18–50y	Two DNA plasmid vaccines: one encoding Zaire and Sudan Ebola virus species GP (EBO, VRC-EBODNA023-00-VP) and one Marburg virus (MAR, VRC-MARDNA025-00-VP). Randomised, placebo-controlled, double-blind trial. 5:1 randomization to 3 injections of vaccine or placebo at d0, w4 and w8, with vaccine allocations divided equally b/w EBO only, MAR only, and both. Follow-up for 2y. Enrolled 11/2009–4/2010.	GP-specific humoral and T-cell immune responses were similar between separate and concomitant use of two vaccines at w4 after 3rd dose (humoral: approx. 50% EBO and 25% MAR; cellular: 30–60% EBO and 40–50% MAR). Both vaccines given alone or jointly elicited antigen immune responses. Responses were not cross-reactive between EBO and MAR vaccines.	Vaccines were well tolerated. No significant differences in local or systemic reactions observed between groups.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Sarwar et al., 2015 (41) (PMID: 25225676; NCT00605514)	1	USA (Maryland)	20 healthy adults aged 18–60 y	Same vaccine as previous trial. Open-label trial. Vaccination at d0, w4and w8, with optional homologous boost at ≥w32. Follow-up for 32/44w (w/o or w/ boost). Enrolled 6/2008–6/2009.	80% vaccinees showed GP-specific humoral response at w4 after 3rd dose. Titres peaked at w4 and were decreased at w24. Cellular responses observed at less frequently (CD4+ T-cell 13–30% at w4 after 3rd dose). 4th dose boosted humoral response to near peak levels and T-cell responses slightly.	Vaccines were well tolerated and no serious adverse events were reported.	Completed
Multiple vaccines (Ad26, ChAd3, MVA [MVA-BN-Filo], rVSV [rVSVΔG-ZEBOV-GP])							
Kennedy et al., 2016 (42) Bolay, 2016 (43) (PMID: 26768572 & N/A; NCT02344407)	2	Liberia	1,500 healthy adults aged ≥18y; not pregnant or breastfeeding or EDV history (median age 30y, 37% female)	PREVAIL-I, as part of Partnership for Research on Ebola Vaccines in Liberia. Originally also intended as Phase 3 trial (w/ enrolment of 28,000 participants). Randomisation 1:1:1 to ChAd3 and rVSV, and	At 1m post-vaccination, ChAd3 and rVSV immunogenic for 87% and 94% participants, respectively. At enrolment, 6.3% of participants had Ebola virus antibodies, but no reported EVD. 98.6% completed	Both vaccines well-tolerated; differences in report of adverse events between 2 vaccine and placebo groups after 1w, but not after 1m.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				placebo; follow-up 8–12m. Enrolment 2–4/2015.	follow-up, which ended in 4/2016.		
Published reference N/A (PMID: N/A; NCT02876328)	2/3	Guinea & Liberia	4,900 healthy persons aged ≥1y; not pregnant, breast-feeding, EDV history, Ebola vaccination or HIV-positive	PREVAC (Partnership for Research on Ebola VACcinations). Randomization to Ad26, MVA, rVSV (single or boost at 56d), placebo. Follow-up for 12m and possibly 5y.	Primary outcome measures relate to immunogenicity. Study start in 1/2017, final data collection for primary outcome measure by 9/2018.	N/A	Not yet recruiting; data collection for primary outcome measure finalized by 9/2018.
Kennedy et al., 2017 (44) (PMID: 29020589; NCT02344407)	2	Liberia	1500 adults aged 18 years and above were randomized 1:1:1 between ChAd3-EBO-Z 1×1011 pu, rVSV and placebo. Follow-up of 12 months.	Randomized, double-blind, placebo-controlled study of 2x107 pfu dose rVSV, 1x1011 particles ChAd3-EBO-Z, or placebo	Induction of anti-GP ELISA responses in 71% of ChAd3-EBO-Z recipients one month after vaccination. Responses persisted in 63.5% of ChAd3-EBO-Z recipients until Month 12. By 1 month, an antibody response developed in 83.7% of subjects in the rVSV	Symptoms most commonly reported were headache, muscle pain, feverishness, and fatigue. Adverse events occurred significantly more often with the active vaccine than with placebo and included injection-site reactions in 30.9%, headache in 31.9%, muscle	Completed and published; long term follow-up continuing

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					vaccine group, as compared with 2.8% of those in the placebo group	pain in 26.9%, feverishness in 30.5%, and fatigue in 15.4% of subjects at 1 week. Serious adverse events within 12 months after injection were seen in 9.4% in the vaccinated group and 11.8% of the placebo group.	

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Interim recommendation Ebola vaccines

On 1 August 2018, the Ministry of Health of the Democratic Republic of the Congo declared a new outbreak of Ebola virus disease in North Kivu Province. The Ministry of Health, WHO and partners are responding to this event, and working to establish the full extent of this outbreak[1].

This new outbreak of Ebola virus disease is affecting north eastern provinces of the Democratic Republic of the Congo, which border Uganda. The province of North Kivu is among the most populated provinces, with eight million inhabitants. It shares borders with four other provinces (Ituri, South Kivu, Maniema and Tshopo) as well as with Uganda and Rwanda. The subregion has been experiencing intense insecurity and worsening humanitarian crisis, with over one million internally displaced people and a continuous efflux of refugees to the neighboring countries, including Uganda, Burundi and Tanzania.

Therefore, potential risk factors for transmission of EVD at national and regional levels include the transport links between the affected areas, the rest of the country, and neighboring countries; the internal displacement of populations; and displacement of Congolese refugees to neighboring countries. The country is concurrently experiencing several epidemics and a long-term humanitarian crisis. Additionally, the security situation in North Kivu may hinder the implementation of response activities. Based on this context, the public health risk is considered high at the national and regional levels and low globally.

This context puts limitations to the implementation of the ring vaccination strategy based on the identification of contacts, as recommended by SAGE in April 2017[2]. Hence, there was a need to urgently review options for alternative strategies for the use of rVSVΔG-ZEBOV-GP vaccine should ring vaccination strategy become unfeasible.

Given the urgency of the matter, the members Strategic Advisory Group of Experts (SAGE) Working Group on Ebola vaccines and the SAGE members have reviewed the epidemiological situation and the evidence available to the Working Group with regard to the different candidate Ebola vaccines and the impact of different interventions.

While ring vaccination remains the preferred strategy (as stated in the April 2017 SAGE report [3]), geographic targeted approach was proposed as an exceptional alternative if the ring vaccination around a laboratory confirmed case of Ebola proves unfeasible. The following interim recommendation was agreed upon:

"Should an Ebola disease outbreak occur before the candidate vaccine is licensed, SAGE recommended that the rVSVΔG-ZEBOV-GP vaccine be promptly deployed under the Expanded Access framework, with informed consent and in compliance with Good Clinical Practice. If the outbreak is caused by an Ebola virus species other than Zaire, consideration should be given to the use of other candidate vaccines that target the putative viral species.

Ring vaccination, as used in the Phase 3 study in Guinea, is the recommended delivery strategy. This should be adapted to the social and geographic conditions of the outbreak areas and include people at risk including but not limited to: (i) contacts and contacts of contacts; (ii) local and international health-care and front-line workers in the affected areas and (iii) health-care and front-line workers in areas at risk of expansion of the outbreak."

A geographically targeted vaccination strategy can be considered in settings where it is not possible to identify the individuals making up the ring vaccination cohorts because of serious security, social or epidemiological issues. In this case, the geographic area immediately around an Ebola case, such as a village or a neighborhood, is most likely to include those individuals who were the contacts or contacts-of-contacts of the index case.

An expanded strategy to vaccinate all individuals in this defined geographic area will require a larger number of vaccinations than would be used in a ring vaccination intervention in the same area. Even in this setting, informed consent and compliance with Good Clinical Practice will be required, but the intensity of follow up of vaccinated individuals will be determined by the context of the intervention.

In this geographically targeted approach, the intent remains to immunize those people most at risk of secondary spread from an identified Ebola case."

Further discussions, including on the available evidence and potential use of other Ebola vaccines, will take place at the forthcoming SAGE meeting in October 2018.

[1] http://apps.who.int/iris/bitstream/handle/10665/273640/SITREP_EVD_DRC_20180807-eng.pdf?ua=1

[2] http://apps.who.int/iris/bitstream/handle/10665/255611/WER9222.pdf;jsessionid=84A8710145124E5C537187BEFD46D5DC?sequence=1

[3] http://apps.who.int/iris/bitstream/handle/10665/255611/WER9222.pdf;jsessionid=84A8710145124E5C537187BEFD46D5DC?sequence=1

Executive Summary for SAGE Session 10:
Opportunities for early warning and preventive action.
Case study: Diphtheria outbreak in Cox's Bazaar.

Background:
Despite overall high vaccination coverage in most countries, pockets with low coverage can leave significant parts of populations vulnerable to outbreaks of vaccine preventable diseases (VPD). The recent past has provided evidence of significant VPD outbreaks. Vaccination campaigns conducted during an outbreak represent a reactive response and until these measures are fully implemented there is unnecessary suffering and death of susceptible individuals. Outbreak response measures also have significant cost implications both in terms of opportunity costs and finances.

Session Objective:
The objective of this session is to discuss programme data available for identifying populations at risk for VPD outbreaks and ways to improve the data or analysis to better anticipate or prevent outbreaks.

Session Summary:
The session will be broken down into five parts:

1) Introduction. The introduction section of the session will review the objectives and frame the session. The presenter will provide examples of different outbreaks that have occurred recently and common themes among these outbreaks. Since our time is limited, we will only look in detail at the Diphtheria outbreak in Cox's Bazaar.
2) Case study. A second presenter will provide a quick overview of the outbreak in Cox's Bazaar and consider the factors that came together to create an environment where this outbreak was able to occur and flourish. Specific attention will be given to the challenges that occurred in managing this outbreak. The presenter will consider what interventions could have pre-emptively prevented this outbreak and what actions could have diminished the impact and resource mobilization required.
3) Mapping of global programme data and gaps. In the next section we will map the characteristics of data we would ideally need in order to optimally prevent and or anticipate outbreaks. We will consider three different domains of data: immunization coverage, surveillance and policy tools. The presenter will review the data that currently exists at the international level within these three different domains and highlight work that is being done and current opportunities to improve this data in order to better inform our ability to anticipate VPD outbreaks.
4) Risk assessment tool to analyse the current available data for vaccination coverage, case reporting and disease burden from the time-period 2007-2016; data, vaccination strategies and country instability information. This risk assessment tool could help to predicted epidemics during the period
5) Another approach is to use subnational vaccination coverage rates and disease surveillance data are now available for many countries. In the United States, many states have recently made school-level vaccination coverage data publicly available and at WHO, district-level vaccination

coverage data are being collected since 2016. Using subnational data for risk analysis to strengthen vaccination strategy recommendations.

6) Discussion.

Background Reading (Yellow Book):

- Diphtheria Position Paper (2017) – This document provides the most recent WHO position paper on Diphtheria. It provides recommendations on the optimal number of doses of diphtheria vaccine, timing of administration, the use of combination vaccines and their alignment in the routine immunization schedule and provides guidance on the use of diphtheria boosters later in life.
- Vaccination in Acute Humanitarian Emergencies (2017). Only the executive summary of this document is included. This document is a framework for vaccination in humanitarian emergencies and is intended to assist users to thoughtfully, deliberately, ethically, and rationally determine whether or not the delivery of one or more vaccines to specific target populations during the acute phase of an emergency would result in an overall saving of lives, a reduction in the population burden of disease, and generally more favourable outcomes than would otherwise be the case.
- Update on Supply of Diphtheria Antitoxin (DAT) and the Ad-Hoc Working Group on DAT: This note provides background on the supply issues related to DAT and an update on the activities of the Ad-Hoc Group on DAT.

Background Reading (Web):

- Diphtheria Surveillance Standards – These recently published surveillance standards provide the WHO recommended standards for conducting surveillance for diphtheria.
- Concept note on Vaccine Decision Information System
- Narrative description of the risk assessment tool to anticipate outbreaks
- WHO/UNICEF guidance note ensuring sustained protection against diphtheria: replacing TT with Td vaccine.

Update on Supply of Diphtheria Antitoxin and the Ad-Hoc Working Group on DAT

BACKGROUND

Diphtheria was one of the leading causes of childhood death in the pre-vaccine era[1]. The development of diphtheria toxoid vaccine in 1923 and its subsequent large-scale use in many industrialised countries in the 1940s-1950s provided a significant turning point for diphtheria control. With the inclusion in 1977 of diphtheria toxoid vaccine (D) in WHO's list of recommended immunizations for its Expanded Programme on Immunization (EPI), global incidence of diphtheria dropped significantly from 384,540 cases in 1980 (see fig. 1) to a steady state rate of around 18,000 reported cases since 2006[2]. There has, however, been an increase in the number of cases noted in 2016 to early 2018 due to outbreaks (fig. 2).

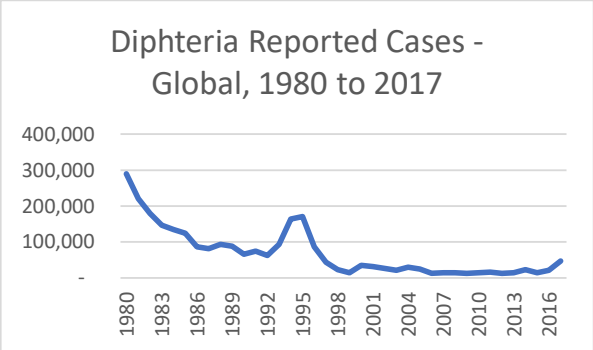


Figure 1: diphtheria reported cases 1980 - 2017[3]

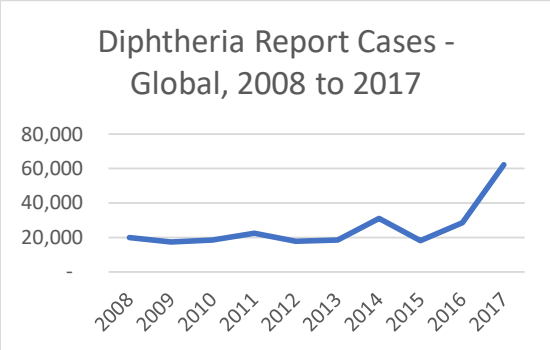
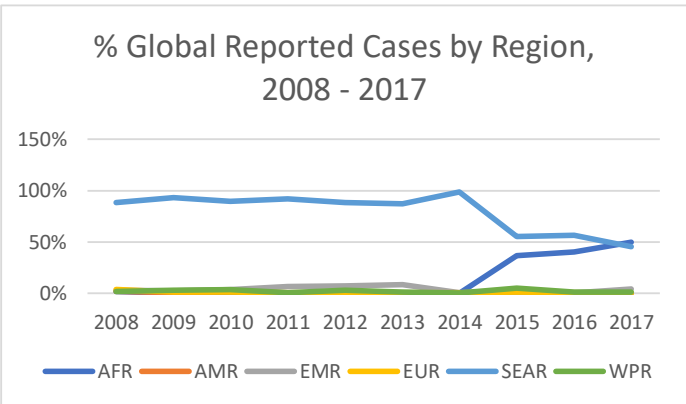


Figure 2: diphtheria reported cases 2008 - 2017[3]

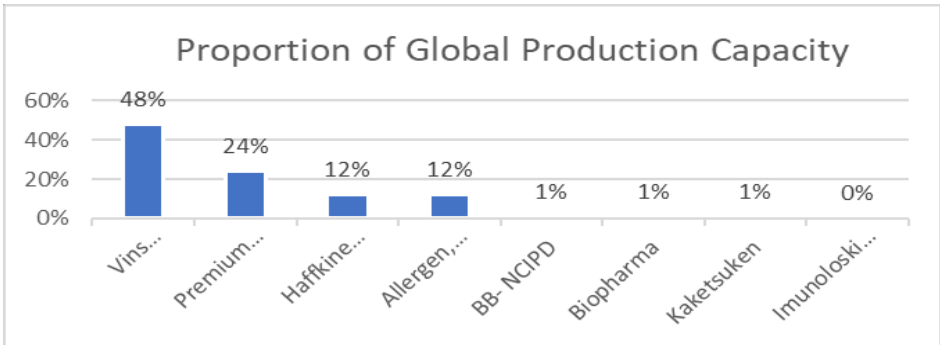
Globally, 76 countries have reported cases of diphtheria at some point in the last 10 years. Of these, the reported cases are systematically concentrated either in a limited number of countries, or are related to outbreaks including Bangladesh, Haiti, Indonesia, Venezuela and Yemen in late 2017 and early 2018.

WHO Region	Nr of Countries reporting diphtheria cases any time from 2008 to 2017
AFRO	14 / 47
AMRO / PAHO	10 / 35
EMRO	11 / 21
EURO	27 / 53
SEARO	7 / 11
WPRO	7 / 27



[1] Zakikhany K, Efstratiou A. Diphtheria in Europe: current problems and new challenges. Future Microbiology 2012; 7(5): 595-607.
[2] WHO vaccine-preventable diseases: monitoring system 2018 global summary http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencediphtheria.html
[3] Source: WHO vaccine-preventable diseases: monitoring system 2018 global summary http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencediphtheria.html

Until the development and use of diphtheria vaccine, Diphtheria anti-toxin (DAT) was the primary intervention for the treatment of diphtheria. DAT is a biological product obtained by immunizing horses with inactivated diphtheria toxin and subsequently purifying their immunoglobulins. The fall in global incidence of disease has led to a decrease in the supply of DAT, with a number of manufacturers leaving the market and unpredictable demand for remaining suppliers. Analysis carried out by WHO indicates that the total global production capacity is around 83,000 vials, distributed among 8 major manufacturers. Of these, 4 suppliers represent approximately 92% of the global market. Price ranges from around USD 5/vial to USD 1,100/vial.



The WHO Essential Medicines List recommends DAT injection: 10 000 IU; 20 000 IU in vial. The global short-term need for DAT is estimated at around 32,000 vials based on an estimated need for 8,000 treatment courses requiring 40,000 IU, with an average of 5 vials per patient / treatment (from a range of 10,000 – 100,000 IU / treatment)[4].

PROBLEM STATEMENT

With a limited number of suppliers, production lead time, variable product quality and highly fluctuating demand as a result of outbreaks, there is a need to ensure rapid access to DAT for the treatment of diphtheria cases. In light of this, the issue of supply of DAT was considered by SAGE at its meeting in April 2017. SAGE provided the following recommendation to WHO:

"SAGE expressed its grave concern about the limited DAT supplies worldwide, and stressed that DAT is urgently needed for managing suspected cases of diphtheria. SAGE therefore advised that WHO collaborate closely with partners to establish and manage a global procurement mechanism and a physical or virtual DAT stock-pile 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."

Estimating demand for DAT may face three major unknowns:

- total number of cases, including unforeseen outbreak situations
- total product requirement per case (i.e. based on stage at which the treatment is given)

[4] http://www.who.int/immunization/sage/meetings/2017/april/3_Diphtheria_anti_toxin.pdf?ua=1

- product potency; WHO specifications recommend 10,000 IU / vial but product testing indicates that some products show lower potency levels, sometimes reaching only 50% of required levels

An additional consideration issue is the absence of quality assured products compliant with required quality standards. Quality testing of DAT is available and carried out on request at the National Institute of Biological Standard and Control[5] (NIBSC) in the UK and the Paul-Ehrlich-Institute[6] (PEI) in Germany.

Predictability of demand influences not only current production capacity, but also impacts on producers' production plans and investment decisions, including decisions around investment in new products and/or the quality of existing products. Unpredictable demand combined with 4-6 months production lead time highlights the importance of better planning, demand forecasting or establishing regional or global stockpile.

WHO uses a number of different models for global stockpiles; stocks of product may be held at the manufacturer site, at a centralized location (e.g. WHO Headquarters) or at regional level. Possible governance mechanisms include the International Coordination Group[7] (ICG) approach provides a process of making decisions on vaccine allocation for outbreak response when supply is very limited, or the Humanitarian Mechanism[8] (HM), which ensures that defined government, NGO or UN actors responding to emergencies have access to selected vaccines at affordable prices. These different options will be carefully considered to take into account the specificity of DAT, including quality assurance.

WORKPLAN OF THE AD-HOC WORKING GROUP ON DAT SUPPLY

In November 2017, WHO has established an Ad-Hoc Working Group to address this SAGE recommendation. The membership of this working group includes CDC; EMA; European Commission; ECDC; FDA; MSF; MHRA; NIBSC; PAHO; PEI; PHE; UNICEF SD; WHO HQ; WHO Regional Offices. The Terms of Reference are available on the WHO website[9].

The objective of the Working Group follows the priorities highlighted by SAGE. The priorities have been further developed into a workplan as follows:

1) **Short term (2019)**: procurement / contracting with manufacturers to ensure availability of DAT for 2019, product selection criteria, and partner coordination
2) **Medium term (2 to 3-year horizon)**: develop a formal process for quality assessment and supply response option (i.e. stockpile or other solution)
3) **Long term (3 to 5-year horizon)**: availability of new products or improvement of existing options

[5] https://nibsc.org/
[6] https://www.pei.de/EN/home/node.html
[7] http://www.who.int/csr/disease/icg/en/
[8] http://www.who.int/immunization/programmes_systems/policies_strategies/vaccination_humanitarian_emergencies/en/
[9] http://www.who.int/immunization/diseases/diphtheria/en/

1) Short term (2019)

The most immediate concern of the SAGE, the Working Group and countries is to ensure that they have access to sufficient quantities of quality DAT to respond to their needs. Coordinating information is therefore a first step in addressing the situation. In response, WHO has:

- coordinated with partners to identify existing stock on hand, estimated needs and product specifications. Estimated demand for 2019 is 10,000 to 12,000 vials across three major procuring agencies (WHO, PAHO Revolving Fund and MSF), based on historical data notably 2018
- WHO (HQ and Regions) have worked with individual countries to address specific requests for DAT supply, for example facilitating information sharing to countries in SEARO and WPRO
- quality tested DAT supplied by three manufacturers, including potency tests
- continued to work with partners to identify the most appropriate structures for addressing access to DAT in outbreak situations. The Ad-Hoc Working Group is working on two-phased approach, taking into account product quality issues. The first, for the short term, focuses on improved communication around estimated need where the WG has coordinated estimates across members and communicates these to suppliers. The second, a medium-term action, will assess any additional need for a stockpile, taking into account currently available stocks, product specifications and quality components

As indicated above, one of the key issues is to balance the requirements of small, steady state demand versus outbreaks which require more significant volumes in a very short time period. To address this:

- the US Centers for Disease Control (CDC) and WHO are working to develop a risk-assessment tool which seeks to identify areas at risk of outbreaks
- partners, notably WHO, MSF and CDC, are working to improve data collection around the number and outcomes of DAT cases, including patient profiles, product used, clinical outcome and adverse events. A standardized case report form (CRF) has been. It is important to work closely with national authorities and Ministries of Health to facilitate relevant data sharing and respect confidentiality
- the WHO Pre-Qualification team has reviewed WHO assessment reports of DAT manufacturers in the past 5 years (since 1 January 2012). Six of the eight manufacturers have been inspected in this time period for other products. This review will help to plan future good manufacturing practice (GMP) site inspections for DAT producers

Next steps will focus the following activities:

- confirm product specifications for the 2019 procurement cycle
- communicate the 2019 demand estimate to manufacturers in order to ensure sufficient supply
- agree on quality aspects, including potency testing for products procured in 2019 (and beyond)

2) Medium term (2 to 3-year horizon)

The main medium-term concern raised by SAGE and the Ad Hoc Working Group is the absence of quality assured products. Four of the eight current manufacturers have local GMP certification, but there is currently no WHO Pre-Qualification process or quality evaluation for DAT products. The priority over the medium term is therefore to ensure DAT of assured quality is available. To move forward on this process, over the past year WHO has:

- agreed on a short-term plan with the WHO PQ team to carry out inspections for the three manufacturers with the highest production capacities, as well as one new manufacturer which may enter the market in the near future

Next steps including the following:

- standardized potency test using the same reference standard among the suppliers
- WHO will define the minimum product characteristics for DAT, taking into existing International Biological Reference Standards[10] and develop a formal quality assessment process (WHO Pre-Qualification or alternative procedure)
- an inspection schedule shall be defined and implemented with the WHO Pre-Qualification team
- WHO and partners represented through the DAT Ad-Hoc Working Group will define the specifications required of a stockpile, define procurement strategies, and establish an appropriate mechanism, replicating existing models if possible. This mechanism will include a decision making process for DAT allocation, and may include options such as a global or regional stockpile, advance commitments or other alternatives

3) Long term (3 to 5-year horizon)

Research into a new monoclonal antibody has progressed, with one organization ready to start Phase I trials. Defining the regulatory requirements for such clinical trials will be essential for the successful future development of such products. In the long term, WHO and partners will focus on the following:

- understanding and agreeing the requirements for moving new monoclonal antibody products into Phase II and Phase III trials
- working with relevant manufacturers to evaluate the potential for improving the production of fragment antigen binding (Fab) products
- providing technical assistance to existing and potential producers of existing and new products to ensure that these are available within the defined product characteristics including price. Such technical assistance may ultimately lead to technology transfer if required

[10] http://www.who.int/bloodproducts/catalogue/Vacc.pdf?ua=1

Conclusion

Existing production capacity is sufficient to meet steady-state needs for DAT, albeit recognizing the need for a 4-6 lead time in production. Key partners including WHO, MSF and CDC currently have access to total stock of approximately 3,000 vials and will coordinate access to up to an additional 8,000 vials in total for 2019. The Ad-Hoc Working Group will define stockpile requirements, including the quality component, and propose mechanisms to ensure rapid coordination of demand and procurement to address diphtheria outbreak situations from 2019 forward.

The issue of product quality remains a priority, and WHO will prioritise inspections of the main manufacturers and potency test (and one new entrant) in 2019.

This work will be complemented by further progress identifying areas at risk of outbreaks and to collect clinical outcome data in order to better understand product use.

Geneva, 7th September 2018

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

4 AUGUST 2017, 92th YEAR / 4 AOÛT 2017, 92e ANNÉE
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Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes. They summarize essential background information on diseases and vaccines and conclude with the current WHO position on the use of vaccines worldwide.

The papers are reviewed by external experts and WHO staff, and reviewed and endorsed by the WHO Strategic Advisory Group of Experts (SAGE) on immunization (http://www.who.int/immunization/sage/en). The GRADE methodology is used to systematically assess the quality of the available evidence. The SAGE decision-making process is reflected in the evidence-to-recommendation table.[1] A description of the processes followed for the development of vaccine position papers is available at: http://www.who.int/immunization/position_papers/position_paper_process.pdf

The position papers are intended for use mainly by national public health officials and managers of immunization programmes. They may also be of interest to international funding agencies, vaccine advisory groups, vaccine manufacturers, the medical community, the scientific media, and the general public.

[1] Guidance for the development of evidence-based vaccine-related recommendations. http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf, accessed January 2017.

Vaccin antidiphtérique: Note de synthèse de l'OMS – août 2017

Introduction

Conformément à son mandat, qui prévoit qu'elle conseille les États Membres en matière de politique sanitaire, l'OMS publie une série de notes de synthèse régulièrement mises à jour sur les vaccins et les associations vaccinales contre les maladies ayant une incidence sur la santé publique internationale. Ces notes, qui portent essentiellement sur l'utilisation des vaccins dans les programmes de vaccination à grande échelle, résument les informations essentielles sur les maladies et les vaccins correspondants et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation de ces vaccins à l'échelle mondiale.

Ces notes sont examinées par des experts externes et des membres du personnel de l'OMS, puis évaluées et approuvées par le Groupe stratégique consultatif d'experts sur la vaccination (SAGE) de l'OMS (http://www.who.int/immunization/sage/fr). La méthodologie GRADE est utilisée pour évaluer de manière systématique la qualité des données disponibles. Le processus de décision du SAGE est reflété dans le tableau des données à l'appui des recommandations.[1] La procédure suivie pour élaborer les notes de synthèse sur les vaccins est décrite dans le document: http://www.who.int/immunization/position_papers/position_paper_process.pdf

Les notes de synthèse s'adressent avant tout aux responsables nationaux de la santé publique et aux administrateurs des programmes de vaccination, mais elles peuvent également présenter un intérêt pour les organismes internationaux de financement, les groupes consultatifs sur la vaccination, les fabricants de vaccins, le corps médical, les médias scientifiques et le grand public.

[1] Guidance for the development of evidence-based vaccine-related recommendations. Disponible sur http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf; consulté en janvier 2017.

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This position paper replaces the 2006 WHO position paper on diphtheria vaccine.[2] It incorporates recent evidence on diphtheria and provides revised recommendations on the optimal number of doses and timing of diphtheria vaccination. In view of the widespread use of combination vaccines, it provides guidance on the alignment of vaccination schedules for different antigens included in routine childhood immunization programmes.[3,4] The recommendations concerning diphtheria vaccine booster doses later in life are also updated. Recommendations on the use of diphtheria vaccines were discussed by SAGE in April 2017;[5] evidence presented at the meeting can be accessed at: http://www.who.int/immunization/sage/meetings/2017/april/presentations_background_docs/en/.

Background

Epidemiology

Throughout history, diphtheria has been one of the most feared infectious diseases globally, which caused devastating epidemics, mainly affecting children. During major diphtheria epidemics in Europe and the United States of America (USA) in the 1880s, the case-fatality rates of respiratory diphtheria reached 50% in some areas. Case-fatality rates in Europe had dropped to about 15% during the First World War, mainly as a result of widespread use of diphtheria antitoxin (DAT) treatment. Diphtheria epidemics also ravaged Europe during the Second World War, causing about 1 million cases and 50 000 deaths in 1943. Diphtheria toxoid-based vaccines became available in the late 1940s in Europe and North America and were shown to reduce outbreaks in vaccinated populations. In the 1970s, before these vaccines became easily accessible and used worldwide, an estimated 1 million cases of diphtheria including 50 000–60 000 deaths occurred each year in low and middle income countries.[6,7]

After the establishment of the Expanded Programme on Immunization (EPI) in 1974, with diphtheria vaccine as one of the original 6 EPI vaccines, the incidence of diphtheria decreased dramatically worldwide. The total number of reported diphtheria cases was reduced by >90% during the period 1980–2000.[8,9,10]

La présente note de synthèse sur le vaccin antidiphtérique remplace celle qui avait été publiée par l'OMS en 2006.[2] Elle présente de nouveaux éléments d'information sur la diphtérie et donne des recommandations révisées sur le nombre optimal de doses et le calendrier d'administration du vaccin antidiphtérique. Compte tenu de l'utilisation généralisée des vaccins combinés, ce document fournit également des orientations sur l'harmonisation des calendriers de vaccination pour les différents antigènes inclus dans les programmes de vaccination systématique de l'enfant.[3,4] Les recommandations relatives à l'administration des doses de rappel de vaccin antidiphtérique à un stade ultérieur de la vie ont également été actualisées. Les recommandations relatives à l'utilisation des vaccins antidiphtériques ont été examinées par le SAGE en avril 2017;[5] les éléments présentés lors de cette réunion peuvent être consultés à l'adresse: http://www.who.int/immunization/sage/meetings/2017/april/presentations_background_docs/en/.

Généralités

Épidémiologie

Tout au long de l'histoire, la diphtérie a compté parmi les maladies infectieuses les plus redoutées dans le monde, donnant lieu à des épidémies dévastatrices frappant principalement les enfants. Lors des grandes épidémies de diphtérie survenues en Europe et aux États-Unis d'Amérique dans les années 1880, les taux de létalité de la diphtérie respiratoire pouvaient atteindre 50% dans certaines régions. Ces taux avaient chuté à environ 15% en Europe au cours de la Première Guerre mondiale, principalement grâce à l'adoption à grande échelle du traitement par l'antitoxine diphtérique. Des épidémies de diphtérie ont également ravagé l'Europe au cours de la Seconde Guerre mondiale, provoquant environ 1 million de cas et 50 000 décès en 1943. À la fin des années 1940, des vaccins à base d'anatoxine diphtérique sont devenus disponibles en Europe et en Amérique du Nord et se sont montrés efficaces pour réduire les flambées parmi les populations vaccinées. Dans les années 1970, avant que ces vaccins ne deviennent aisément accessibles et ne soient utilisés à l'échelle mondiale, on estime qu'environ 1 million de cas de diphtérie, dont 50 000 à 60 000 mortels, se produisaient chaque année dans les pays à revenu faible ou intermédiaire.[6,7]

Suite à l'établissement du Programme élargi de vaccination (PEV) en 1974, qui comptait 6 vaccins initiaux dont le vaccin antidiphtérique, l'incidence de la diphtérie a baissé de manière spectaculaire à l'échelle mondiale. Le nombre total de cas notifiés a chuté de >90% entre 1980 et 2000.[8,9,10]

[2] See No. 3, 2006, pp. 21–32.

[3] See No. 6, 2017, pp. 53–76.

[4] See No. 35, 2015, pp. 433–460.

[5] See No. 22, 2017, pp. 301–320.

[6] Walsh JA and Warren KS. Selective primary health care: an interim strategy for disease control in developing countries. N Engl J Med. 1979;301(18):967–974.

[7] Tiwari TSP and Wharton M. Chapter 19: Diphtheria Toxoid. In Plotkin's Vaccines, 2017;Seventh Edition:261–275.

[8] Review of the Epidemiology of Diphtheria- 2000-2016. Available at http://www.who.int/immunization/sage/meetings/2017/april/1_Final_report_Clarke_april3.pdf?ua=1, accessed April 2017.

[9] WHO. Diphtheria reported cases. Available at http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencediphtheria.html, accessed April 2017.

[10] WHO/UNICEF. Joint Reporting Form. Available at http://www.who.int/immunization/monitoring_surveillance/routine/reporting/reporting/en/, accessed April 2017.

[2] Voir N° 3, 2006, pp. 21-32.

[3] Voir N° 6, 2017, pp. 53-76.

[4] Voir N° 35, 2015, pp. 433-460.

[5] Voir N° 22, 2017, pp. 301-320.

[6] Walsh JA and Warren KS. Selective primary health care: an interim strategy for disease control in developing countries. N Engl J Med. 1979;301(18):967–974.

[7] Tiwari TSP and Wharton M. Chapter 19: Diphtheria Toxoid. In Plotkin's Vaccines, 2017;Seventh Edition:261–275.

[8] Review of the Epidemiology of Diphtheria- 2000-2016. Disponible à l'adresse: http://www.who.int/immunization/sage/meetings/2017/april/1_Final_report_Clarke_april3.pdf?ua=1; consulté en avril 2017.

[9] OMS. Cas notifiés de diphtérie. Données disponibles sur: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencediphtheria.html; consulté en avril 2017.

[10] OMS/UNICEF. Formulaire de rapport commun. Disponible à l'adresse: http://www.who.int/immunization/monitoring_surveillance/routine/reporting/reporting/en/; consulté en avril 2017.

The largest outbreak of the recent past was reported from the Russian Federation and former Soviet Republics in the 1990s. More than 157 000 cases and 5000 deaths were reported during 1990–1998.[11]

Diphtheria remains a significant health problem in countries with poor routine vaccination coverage. The annual number of reported cases of diphtheria (laboratory or clinically confirmed or epidemiologically linked) has remained relatively unchanged over the last 11 years. According to the most recent estimate, 86% of children worldwide receive the recommended 3 doses of diphtheria-containing vaccine in the infant schedule, leaving 14% with no or incomplete vaccination. There are pockets of unvaccinated children in all countries.[12] Case-fatality rates exceeding 10% have been reported, in particular where DAT is unavailable.[13] In regions with temperate climates, most cases occur during the cold season, whereas in warmer climates transmission takes place throughout the year.

In the period 2011–2015, India had the largest total number of reported cases each year, with a 5-year total of 18 350 cases, followed by Indonesia and Madagascar with 3203 and 1633 reported cases respectively. The South-East Asia Region was the source of 55–99% of all reported cases each year during this period. The analysis further showed a significant under-reporting of cases to WHO, particularly from the African and Eastern Mediterranean Regions. The true burden of disease is therefore likely to be greater than reported.

A recent review of diphtheria epidemiology showed that among cases with information on age, the age distribution shifts and the majority of cases occur in adolescents and adults, reflecting the decline in incidence due to increasing vaccination coverage in children. In high incidence countries (≥10 cases per year in ≥3 years during 2000–2015) 40% were aged >15 years while in low incidence countries (<10 cases per year in ≥3 years during 2000–2015) 66% of cases were aged >15 years. Among cases with known vaccination status most were unvaccinated, and a lower proportion were incompletely vaccinated; very few cases had received ≥5 vaccine doses.[8]

After the introduction of a primary series of childhood diphtheria vaccination in a population where diphtheria is endemic, 2 epidemiologic stages have been described. In the first stage, disease incidence shifts from predominantly pre-school pattern to a greater proportion of cases in school-age children. In the second stage, cases are seen primarily in adolescents and young adults aged >15 years.[14] Infection in infants younger than 6 months

[11] Dittmann S et al. Successful control of epidemic diphtheria in the states of the former Union of Soviet Socialist Republics: Lessons learned. J Infect Dis. 2000;181(1):S10-S22.

[12] World Health Organization. Immunization coverage fact sheet. Available at http://www.who.int/mediacentre/factsheets/fs378/en/, accessed June 2017.

[13] Centers for Disease Control and Prevention, Epidemiology and Prevention of Vaccine-Preventable Diseases, 13th Edition, Immunology and Vaccine-Preventable Diseases – Pink Book – Diphtheria. Available at https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/dip.pdf,accessed June 2017.

[14] Galazka A. The Changing Epidemiology of Diphtheria in the Vaccine Era. J Infect Dis. 2000;181(Suppl 1):52–59.

La plus grande flambée enregistrée récemment est celle qui a sévi en Fédération de Russie et dans les pays de l'ancienne Union soviétique dans les années 1990. Plus de 157 000 cas, dont 5000 mortels, ont été signalés dans la période 1990-1998.[11]

La diphtérie demeure un problème de santé important dans les pays où la couverture de la vaccination systématique est faible. Le nombre annuel de cas de diphtérie notifiés (confirmés par laboratoire, par compatibilité clinique ou par lien épidémiologique) est resté relativement inchangé au cours des 11 dernières années. Selon les estimations les plus récentes, 86% des enfants du monde reçoivent les 3 doses de vaccin contenant l'anatoxine diphtérique recommandées dans le calendrier vaccinal des nourrissons, les 14% restants étant soit non vaccinés, soit partiellement vaccinés. On relève dans tous les pays des poches dans lesquelles les enfants ne sont pas vaccinés.[12] Des taux de létalité dépassant 10% ont été signalés, en particulier dans les zones où le traitement par l'antitoxine diphtérique n'est pas disponible.[13] Dans les régions de climat tempéré, la plupart des cas se produisent durant la saison froide, tandis que dans les climats plus chauds, la transmission a lieu tout au long de l'année.

Dans la période 2011-2015, l'Inde a été le pays signalant le plus grand nombre annuel de cas, avec un total de 18 350 cas sur 5 ans, suivi de l'Indonésie et de Madagascar, qui ont notifié respectivement 3203 et 1633 cas. La Région de l'Asie du Sud-Est compte 55-99% de tous les cas notifiés chaque année durant cette période. L'analyse des données révèle en outre une sous-notification considérable des cas à l'OMS, en particulier dans la Région africaine et la Région de la Méditerranée orientale. La charge de morbidité réelle de la diphtérie est donc probablement plus importante que les notifications l'indiquent.

Une récente analyse épidémiologique de la diphtérie montre que parmi les cas dont l'âge a été renseigné, la répartition selon l'âge évolue, avec une majorité de cas chez les adolescents et les adultes, ce qui est révélateur du déclin de l'incidence suite à l'augmentation de la couverture vaccinale chez les enfants. La proportion de cas âgés de >15 ans s'établissait à 40% dans les pays à forte incidence (≥10 cas par an pendant ≥3 ans dans la période 2000-2015), tandis qu'elle s'élevait à 66% dans les pays de faible incidence (<10 cas par an pendant ≥3 ans dans la période 2000-2015). Parmi les cas dont le statut vaccinal était connu, la plupart n'étaient pas vaccinés, et une proportion plus faible était partiellement vaccinée; très peu de cas avaient reçu ≥5 doses de vaccin.[8]

Deux phases épidémiologiques ont été décrites après l'introduction d'une série de primovaccination antidiphtérique chez l'enfant dans les zones d'endémie. Dans la première phase, on constate une évolution de l'incidence de la maladie qui, au lieu de rester prédominante chez les enfants d'âge préscolaire, se caractérise par une proportion accrue de cas parmi les enfants d'âge scolaire. Dans la deuxième phase, la majorité des cas sont des adolescents et des jeunes adultes de >15 ans.[14] Protégés par

[11] Dittmann S et al. Successful control of epidemic diphtheria in the states of the former Union of Soviet Socialist Republics: Lessons learned. J Infect Dis. 2000;181(1):S10-S22.

[12] Organisation mondiale de la Santé. Aide-mémoire sur la couverture vaccinale. Disponible à l'adresse: http://www.who.int/mediacentre/factsheets/fs378/en/; consulté en juin 2017.

[13] Centers for Disease Control and Prevention, Epidemiology and Prevention of Vaccine-Preventable Diseases, 13th Edition, Immunology and Vaccine-Preventable Diseases – Pink Book – Diphtheria. Disponible à l'adresse: https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/dip.pdf; consulté en juin 2017.

[14] Galazka A. The Changing Epidemiology of Diphtheria in the Vaccine Era. J Infect Dis. 2000; 181(Suppl 1):52–59.

is rare due to the presence of maternal antibodies. In the pre-vaccination era, no gender differences in incidence were observed. However, a higher incidence in women was reported in several outbreaks among adults in the 1940s and a female predominance was also observed in the outbreak in the Russian Federation and other countries of the former Soviet Union in the 1990s. This gender imbalance may reflect lower susceptibility among men vaccinated during military service and/ or a higher rate of injury in men who then receive combined diphtheria-tetanus vaccine.[7]

The control of diphtheria is based on primary prevention of disease by ensuring high population immunity through vaccination, and secondary prevention of spread by the rapid investigation of close contacts to ensure prompt treatment of those infected.

Pathogen

Corynebacterium is a genus of gram-positive bacteria. Various species of the genus *Corynebacterium* exist. Diphtheria is caused by *Corynebacterium diphtheriae*, a club-shaped facultative anaerobic species that exists in 4 biotypes (gravis, mitis, belfanti and intermedius). The 4 biotypes differ slightly in their colonial morphology and biochemical parameters, but no consistent differences have been found in the prevalence or the severity of disease caused by the different types.[7]

The most important virulence factor of *C. diphtheriae* is the diphtheria toxin, its exotoxin. This is encoded by a highly conserved sequence of the *tox* gene of the *ß*-corynebacteriophage, which is integrated in the circular bacterial chromosome. The exotoxin consists of 2 fragments: A and B. Following attachment mediated by the non-toxic B fragment and penetration of the host cell, the highly toxic fragment A is detached, and inhibits protein synthesis leading to cell death. Outside the host cell, the exotoxin is relatively inactive. In addition to the bacterial exotoxin, cell-wall components such as the O- and K-antigens are important in the pathogenesis of the disease.

The ß-corynebacteriophage can infect nontoxigenic strains of 2 other species of *Corynebacterium*, *C. ulcerans* and *C. pseudotuberculosis*, which leads to production of the diphtheria toxin and transformation to a toxigenic strain.[7] Both are zoonotic agents without documented human-to-human transmission. Humans are the natural host for *C. diphtheriae*, although it has been occasionally isolated from cattle[15] and horses.[16]

Disease

Transmission of *C. diphtheriae* occurs from person to person through droplets and close physical contact. Transmission may also occur via contagious cutaneous diphtheria lesions, as has been documented in some

[15] Dhanashekar R et al. Milk-borne infections. An analysis of their potential effect on the milk industry. Germs. 2012;2:101–109.

[16] Leggett BA et al. Toxigenic *Corynebacterium diphtheriae* isolated from a wound in a horse. Vet Rec. 2010;166:656–657.

les anticorps maternels, les nourrissons de moins de 6 mois sont rarement infectés. Avant l'introduction de la vaccination, aucune différence d'incidence n'avait été observée entre les sujets de sexe féminin et masculin. Cependant, on a constaté une incidence accrue chez la femme lors de plusieurs flambées touchant la population adulte dans les années 1940, ainsi que dans le cadre de la flambée survenue en Fédération de Russie et dans d'autres pays de l'ancienne Union soviétique dans les années 1990. Ce déséquilibre entre les sexes peut être le reflet d'une sensibilité réduite des hommes ayant été vaccinés durant leur service militaire et/ou de la survenue plus fréquente, chez l'homme, de blessures conduisant à l'administration du vaccin combiné antidiphtérique-antitétanique.[7]

La lutte contre la diphtérie repose sur des efforts de prévention primaire visant à garantir une forte immunité de la population au moyen de la vaccination, ainsi que sur une prévention secondaire de la propagation de la maladie, consistant en une recherche rapide des contacts proches afin d'offrir rapidement un traitement aux personnes infectées.

Agent pathogène

Corynebacterium est un genre de bactérie à Gram positif qui regroupe plusieurs espèces. La diphtérie est due à *Corynebacterium diphtheriae*, une espèce anaérobie facultative de forme légèrement incurvée qui comprend 4 biotypes (gravis, mitis, belfanti et intermedius). Ces 4 biotypes présentent de légères différences en termes de morphologie des colonies et de paramètres biochimiques, mais aucune différence systématique n'a été observée dans la prévalence ou la sévérité de la maladie provoquée par ces types différents.[7]

Le facteur de virulence le plus important de *C. diphtheriae* est son exotoxine, la toxine diphtérique. Cette dernière est codée par une séquence hautement conservée du gène *tox* du corynephage *ß*, qui est intégré dans le chromosome bactérien circulaire. L'exotoxine est constituée de 2 fragments: A et B. Le fragment B non toxique permet la fixation et la pénétration de l'exotoxine dans la cellule hôte, puis le fragment hautement toxique A se détache et inhibe la synthèse des protéines, entraînant la mort de la cellule. En dehors de la cellule hôte, l'exotoxine est relativement inactive. Outre l'exotoxine produite par la bactérie, les constituants de la paroi cellulaire, tels que les antigènes O et K, jouent un rôle important dans la pathogenèse de la maladie.

Le corynephage ß peut infecter des souches non toxinogènes de 2 autres espèces de *Corynebacterium*, *C. ulcerans* et *C. pseudotuberculosis*, consuisant à la production de toxine diphtérique et rendant ces souches toxinogènes.[7] Il s'agit dans les deux cas d'agents zoonosiques, sans transmission interhumaine constatée à ce jour. L'homme est l'hôte naturel de *C. diphtheriae*, bien que la bactérie ait occasionnellement été isolée chez les bovins[15] et les chevaux.[16]

Maladie

C. diphtheriae se transmet d'une personne à l'autre par l'intermédiaire de gouttelettes respiratoires ou d'un contact physique proche. La transmission peut également s'opérer par des lésions cutanées diphtériques contagieuses, comme cela a été observé

[15] Dhanashekar R et al. Milk-borne infections. An analysis of their potential effect on the milk industry. Germs. 2012;2:101–109.

[16] Leggett BA et al. Toxigenic *Corynebacterium diphtheriae* isolated from a wound in a horse. Vet Rec. 2010;166:656–657.

areas of the tropics and under conditions of poor hygiene. Cutaneous diphtheria is more common in warmer climates and in settings with poor hygiene and overcrowding.[7] *C. diphtheriae* replicates on the surface of the mucous membrane but can also manifest as a cutaneous form. Together, aural, vaginal, conjunctival and cutaneous diphtheria account for approximately 2% of cases.[7] Morbidity and mortality due to toxigenic *C. diphtheriae* are mediated by the diphtheria toxin. Transmission of nontoxigenic *C. diphtheriae* to susceptible individuals frequently results in transient asymptomatic pharyngeal carriage or mild clinical disease.

Infection can cause respiratory or cutaneous diphtheria and in rare cases can lead to systemic diphtheria. Respiratory diphtheria usually occurs after an incubation period of 2–5 days (range 1–10 days). Depending on the anatomical location, respiratory disease may be nasal, pharyngeal, or laryngeal, or any combination of these. Pharyngeal diphtheria is the most common form. The onset is usually relatively slow and characterized by mild fever and an exudative pharyngitis initially with progression of symptoms over 2 to 3 days. In classic cases, the exudate organizes into a pseudo-membrane that gradually forms in the nose, pharynx, tonsils, or larynx. The pseudo-membrane is typically asymmetrical, greyish-white in appearance and is firmly attached to the underlying tissue. Attempts to remove the pseudo-membrane result in bleeding at the site. The pseudo-membrane may extend into the nasal cavity and the larynx causing obstruction of the airways, which is a medical emergency that often requires tracheotomy. Anterior cervical lymph nodes become markedly enlarged and in some patients there is considerable inflammation and oedema of surrounding tissues ("bull-neck" appearance) with greater morbidity and mortality.[7]

Absorption of diphtheria toxin into the bloodstream results in toxic damage to organs such as the heart, kidneys and peripheral nerves. The extent of toxin absorption in respiratory disease depends largely on the anatomical site of infection, extent of the mucosal lesions, and duration of untreated illness.

Diagnosis

Clinical diagnosis of diphtheria usually relies on the presence of pseudo-membranous pharyngitis. Although laboratory investigation of suspected cases is recommended for case confirmation, treatment should be started immediately without waiting for the laboratory results. Material for culture should be obtained by swabbing the edges of the mucosal lesions, placed in appropriate transport media (Amies or Stuart media in ice packs; or dry swabs in silica gel satchets) and followed by prompt inoculation onto blood agar and tellurite-containing media, e.g. Tinsdale media. Suspected colonies may be tested for toxin production using the modified Elek immunoprecipitation test for detection of toxin; this standard assay takes 24–48 hours. A positive culture with toxin-producing *C. diphtheriae* confirms the etiologic diagnosis. Diphtheria toxin gene (*tox*) can be detected directly in *C. diphtheriae* isolates using polymerase chain reaction (PCR) techniques.[7] However,

dans certaines régions tropicales et dans de mauvaises conditions d'hygiène. La diphtérie cutanée est plus fréquente dans les climats chauds et dans des conditions de surpeuplement ou d'hygiène inadéquate.[7] *C. diphtheriae* se multiplie à la surface des muqueuses, mais peut aussi se manifester sous forme cutanée. Environ 2% des cas sont atteints de diphtérie auriculaire, vaginale, conjonctivale ou cutanée.[7] La toxine diphtérique est responsable de la morbidité et de la mortalité dues à la bactérie *C. diphtheriae* toxinogène. La transmission de *C. diphtheriae* non toxinogène à des sujets sensibles entraîne dans la plupart des cas un portage pharyngé transitoire asymptomatique ou des manifestations cliniques bénignes.

L'infection peut provoquer une diphtérie respiratoire ou cutanée, menant dans de rares cas à une diphtérie systémique. La diphtérie respiratoire apparaît généralement après une période d'incubation de 2-5 jours (plage de 1-10 jours). Selon le site anatomique atteint, la maladie respiratoire peut être nasale, pharyngée, laryngée, ou une combinaison. La diphtérie pharyngée est la forme la plus courante de la maladie. En général, elle démarre assez lentement et se caractérise dans un premier temps par une fièvre modérée et une pharyngite exsudative bénigne, avec une progression des symptômes sur une période de 2 à 3 jours. Dans les cas classiques, l'exsudat forme progressivement une pseudo-membrane dans le nez, le pharynx, les amygdales ou le larynx. Cette pseudo-membrane est généralement asymétrique, de couleur grise-blanche et est solidement ancrée dans les tissus sous-jacents. Toute tentative de retrait de la pseudo-membrane entraîne un saignement du site concerné. La pseudo-membrane peut s'étendre jusqu'à la cavité nasale et au larynx, provoquant une obstruction des voies aériennes, ce qui constitue une urgence médicale nécessitant souvent une trachéotomie. Les ganglions lymphatiques cervicaux antérieurs enflent et certains patients présentent une inflammation et un œdème importants des tissus environnants (aspect de «cou de taureau»), associés à une morbidité et une mortalité accrues.[7]

L'absorption de la toxine diphtérique dans la circulation sanguine entraîne une atteinte toxique de certains organes tels que le cœur, les reins et les nerfs périphériques. Le degré d'absorption de la toxine lors d'une diphtérie respiratoire dépend en grande partie du site anatomique de l'infection, de l'étendue des lésions muqueuses et de la période de temps pendant laquelle le sujet a été malade sans être traité.

Diagnostic

Le diagnostic clinique repose généralement sur la présence d'une pharyngite pseudomembraneuse. Bien qu'une confirmation en laboratoire des cas suspects soit recommandée, il convient de démarrer le traitement immédiatement, sans attendre les résultats d'analyse. Le matériel destiné à la mise en culture doit être prélevé par écouvillonnage en bordure des lésions muqueuses, placé dans un milieu de transport approprié (milieu Amies ou Stuart entre des blocs réfrigérants; ou écouvillons secs dans des sachets contenant du gel de silice) et ensemencé rapidement dans un milieu de gélose au sang à base de tellurite, tel que le milieu Tinsdale. On peut déterminer si les colonies suspectes sont productrices de toxine en utilisant le test d'Elek modifié d'immunoprécipitation visant à détecter la toxine; cette épreuve standard prend 24-48 heures. L'obtention d'une culture positive de *C. diphtheriae* productrice de toxine confirme le diagnostic étiologique. Le gène de la toxine diphtérique (*tox*) peut être détecté directement dans les isolats de *C. diphtheriae* au moyen des techniques d'amplification en

in some cases the presence of *tox* gene does not confirm production of toxin; positive PCR results should therefore be confirmed with an immunoprecipitation test.[7]

Treatment

Intravenous or intramuscular administration of equine-derived DAT (polyclonal IgG antibody) is highly effective and is the gold standard for diphtheria treatment. Diphtheria toxin that has already entered the host cells is unaffected by DAT. Therefore, to reduce complications and mortality DAT should be administered as soon as possible after disease onset, preferably intravenously in serious cases.[17]

The entire therapeutic dose should be administered at one time. The amount of antitoxin recommended varies between 20 000 and 100 000 units, with larger amounts recommended for persons with extensive local lesions and with longer interval since onset. The dose is the same for children and adults. Adverse events such as anaphylaxis may occur.[18] Global access to DAT is limited as most manufacturers have ceased production and episodes of delayed or non-availability of equine DAT have been reported recently in Europe and elsewhere.

Novel approaches to passive immunization include the development of monoclonal antibodies to diphtheria toxin, and development of recombinant modified diphtheria toxin receptor molecules to bind diphtheria toxin. Efficacy of monoclonal antibodies has been demonstrated in preclinical models but clinical development will take several more years.[19]

Antibiotics (penicillin or erythromycin) eliminate the bacteria and toxin production, prevent further transmission to uninfected individuals, and limit carriage that can persist even after clinical recovery. Treatment should be continued for 2 weeks.[7]

Airway management is crucial for patients with impending respiratory difficulty or the presence of laryngeal membranes. Interventions to prevent the risk of sudden asphyxia involve tracheotomy or mechanical removal of tracheobronchial pseudo-membranes and/or intubation, ventilator and possibly extracorporeal membrane oxygenation (ECMO) where available. Patients should also be monitored continuously for development of cardiac complications.[7]

Post-exposure prophylaxis

For susceptible exposed individuals, active immunization with diphtheria toxoid-containing vaccine is

chaîne par polymérase (PCR).[7] Cependant, dans certains cas, la présence du gène *tox* ne confirme pas la production de toxine; les résultats positifs de PCR doivent donc être confirmés par un test d'immunoprécipitation.[7]

Traitement

L'administration intraveineuse ou intramusculaire d'antitoxine diphtérique d'origine équine (anticorps IgG polyclonaux) est très efficace et constitue le traitement de référence contre la diphtérie. L'antitoxine n'a pas d'effet sur la toxine diphtérique qui a déjà pénétré dans les cellules hôtes. Ainsi, afin de réduire les risques de complications et de mortalité, l'antitoxine diphtérique doit être administrée dès que possible après l'apparition de la maladie, de préférence par voie intraveineuse dans les cas graves.[17]

La dose thérapeutique complète doit être administrée en une seule fois. La quantité d'antitoxine recommandée varie entre 20 000 et 100 000 unités, les doses les plus importantes étant préconisées pour les sujets présentant des lésions locales étendues ou chez lesquels un intervalle plus long s'est écoulé depuis l'apparition de la maladie. Les enfants et les adultes reçoivent une dose identique. Des manifestations indésirables, telles qu'une anaphylaxie, peuvent survenir.[18] L'accès mondial à l'antitoxine diphtérique est limité car la plupart des fabricants en ont cessé la production. Des situations d'indisponibilité ou de retard d'approvisionnement de l'antitoxine diphtérique d'origine équine ont récemment été signalées en Europe et ailleurs.

De nouvelles méthodes d'immunisation passive ont été élaborées, reposant notamment sur l'utilisation d'anticorps monoclonaux contre la toxine diphtérique et la mise au point de molécules réceptrices recombinantes modifiées qui fixent la toxine diphtérique. L'efficacité des anticorps monoclonaux a été démontrée par des modèles précliniques, mais leur développement clinique nécessitera encore plusieurs années.[19]

Les antibiotiques (pénicilline ou érythromycine) éliminent la bactérie et la production de toxine, évitent que la maladie soit transmise à des sujets non infectés et limitent le portage, qui peut persister même après la guérison clinique. Le traitement doit se poursuivre pendant 2 semaines.[7]

L'assistance respiratoire est cruciale pour les patients présentant des difficultés respiratoires imminentes ou des membranes laryngées. La prévention du risque d'asphyxie soudaine repose sur des interventions telles que la trachéotomie ou le retrait mécanique des pseudomembranes trachéobronchiques et/ou l'intubation, la ventilation assistée et éventuellement l'oxygénation par membrane extracorporelle, si cette option est disponible. Il convient en outre d'assurer une surveillance continue des patients pour déceler toute complication cardiaque.[7]

Prophylaxie postexposition

Chez les personnes sensibles qui ont été exposées, la vaccination par un vaccin contenant l'anatoxine diphtérique est forte-

[17] World Health Organization. Management of the child with a serious infection or severe malnutrition. Guidelines for care at the first-referral level in developing countries. Geneva, 2000. Available at http://apps.who.int/iris/bitstream/10665/42335/1/WHO_FCH_CAH_00.1.pdf, accessed July 2017.

[18] World Health Organization. Model Formulary 2008. Available at http://apps.who.int/medicinedocs/documents/s16879e/s16879e.pdf, accessed June 2017.

[19] World Health Organization. Diphtheria anti-toxin (DAT) supply issues: brief review and proposition. SAGE meeting, 2017. Available at http://www.who.int/immunization/sage/meetings/2017/april/3_Diphtheria_anti_toxin.pdf?ua=1, accessed June 2017.

[17] Organisation mondiale de la Santé. Prise en charge de l' enfant atteint d'infection grave ou de malnutrition sévère: directives de soins pour les centres de transfert de premier niveau dans les pays en développement. Genève, 2000. Disponible à l'adresse: http://apps.who.int/iris/bitstream/10665/66929/1/WHO_FCH_CAH_00.1_fre.pdf; consulté en juillet 2017.

[18] Organisation mondiale de la Santé. Model Formulary 2008. Disponible à l'adresse: http://apps.who.int/medicinedocs/documents/s16879e/s16879e.pdf; consulté en juin 2017.

[19] Organisation mondiale de la Santé. Diphtheria anti-toxin (DAT) supply issues: brief review and proposition. SAGE meeting, 2017. Disponible à l'adresse: http://www.who.int/immunization/sage/meetings/2017/april/3_Diphtheria_anti_toxin.pdf?ua=1; consulté en juin 2017.

strongly recommended. Swabs should be taken from contacts and the samples cultured for *C. diphtheriae*, and a course of penicillin or erythromycin should be administered for 7 days. DAT is not recommended for post-exposure prophylaxis, as evidence regarding its benefit is limited.[7] During outbreaks, vaccination records of all contacts of each case should be reviewed. Unvaccinated contacts should receive a full course of diphtheria toxoid-containing vaccine and under-vaccinated contacts should receive the doses needed to complete their vaccination series.

Naturally-acquired immunity

Immunity to disease depends mainly on the presence of diphtheria anti-toxin antibodies (IgG). Cell-mediated immunity may also play a role. In general, there is a good correlation between clinical protection and the level of diphtheria antitoxin antibodies in the blood, whether this results from disease or from vaccination. When measured using a toxin neutralization test, a diphtheria antibody concentration of 0.01 IU/mL is considered to be the minimum level required for some degree of protection. Antibody levels of 0.1 IU/mL or higher confer full protection and levels of 1.0 IU/mL or higher are associated with long-term protection against diphtheria.[20] Rarely, diphtheria has been reported in persons having higher than protective levels of antibodies.

Occasionally, protective immunity does not develop after recovery from the disease. Individuals recovering from diphtheria should therefore receive a complete course of diphtheria toxoid vaccination during convalescence.[21]

Transplacental maternal antibodies provide passive immunity to the newborn infant during the first few months of life.[21]

Diphtheria vaccines

Diphtheria toxoid-containing vaccines are among the oldest vaccines in current use. The first approaches to active immunization against diphtheria were based on a mixture of toxin and antitoxin. Such vaccines were widely used in the USA in 1914. In 1923, diphtheria toxoid vaccine was developed by formaldehyde detoxification of diphtheria toxin. In 1926, a more immunogenic alum-precipitated diphtheria toxoid was developed. In the 1940s diphtheria toxoid, tetanus toxoid and pertussis antigens were combined in the diphtheria-tetanus-pertussis vaccine (DTP) used widely throughout the world.[7]

ment recommandée. Des écouvillons devront être prélevés auprès des contacts, les échantillons devront être mis en culture pour *C. diphtheriae*, et un traitement par la pénicilline ou l'érythromycine devra être administré pendant 7 jours. L'administration d'antitoxine diphtérique n'est pas recommandée à titre de prophylaxie postexposition, car peu d'éléments permettent de penser que cette approche soit avantageuse.[7] En situation de flambée, il convient d'examiner les carnets de vaccination de tous les contacts de chaque cas. Les contacts n'ayant jamais été vaccinés devront recevoir la série complète de vaccins contenant l'anatoxine diphtérique et ceux qui n'ont été que partiellement vaccinés se verront administrer les doses nécessaires pour compléter la série.

Immunité acquise naturellement

L'immunité contre la maladie dépend principalement de la présence d'anticorps (IgG) contre la toxine diphtérique. L'immunité à médiation cellulaire pourrait également jouer un rôle. On observe en général une bonne corrélation entre la protection clinique et le titre d'anticorps antitoxine diphtérique dans le sang, que ces anticorps aient été induits par la maladie ou la vaccination. On considère que le titre d'anticorps antidiphtériques, tel que mesuré par un test de neutralisation de la toxine, doit être au minimum de 0,01 UI/ml pour conférer un certain degré de protection. Les titres de 0,1 UI/ml ou plus sont pleinement protecteurs et ceux de 1,0 UI/ml ou plus sont associés à une protection à long terme contre la diphtérie.[20] Il est arrivé dans de rares cas que la maladie soit observée chez des sujets dont le titre d'anticorps est supérieur au seuil de protection.

Parfois, les patients n'acquièrent pas d'immunité protectrice après avoir guéri de la diphtérie. Les personnes en phase de convalescence doivent donc recevoir une série complète de vaccination par l'anatoxine diphtérique.[21]

Le passage transplacentaire des anticorps maternels confère une immunité passive au nourrisson au cours de ses premiers mois de vie.[21]

Vaccins antidiphtériques

Les vaccins contenant l'anatoxine diphtérique comptent parmi les vaccins les plus anciens actuellement utilisés. Les premières méthodes de vaccination contre la diphtérie faisaient appel à un mélange de toxine et d'antitoxine. Ces vaccins ont largement été employés aux États-Unis d'Amérique en 1914. En 1923, le vaccin à base d'anatoxine diphtérique a été mis au point par détoxification de la toxine diphtérique par le formaldéhyde. En 1926, une anatoxine diphtérique plus immunogène précipitée par l'alun a été élaborée. Dans les années 1940, l'anatoxine diphtérique, l'anatoxine tétanique et des antigènes coquelucheux ont été associés pour former le vaccin antidiphtérique-antitétanique-anticoquelucheux (DTC), qui est largement utilisé dans le monde entier.[7]

[20] World Health Organization. Recommendations to assure the quality, safety and efficacy of diphtheria vaccines (adsorbed). WHO Technical Report Series No. 980, Annex 4. 2014;66:211-270. Available at http://www.who.int/biologicals/vaccines/Diphtheria_Recommendations_TRS_980_Annex_4.pdf?ua=1, accessed May 2017.

[21] World Health Organization. Scheifele DW and Ochnio JJ. Immunological basis for vaccination series. Diphtheria Update 2009. Available at http://apps.who.int/iris/bitstream/10665/44094/1/9789241597869_eng.pdf, accessed April 2017.

[20] Organisation mondiale de la Santé. Recommendations to assure the quality, safety and efficacy of diphtheria vaccines (adsorbed). WHO Technical Report Series No. 980, Annex 4. 2014;66:211-270. Disponible à l'adresse: http://www.who.int/biologicals/vaccines/Diphtheria_Recommendations_TRS_980_Annex_4.pdf?ua=1; consulté en mai 2017.

[21] Organisation mondiale de la Santé. Scheifele DW and Ochnio JJ. Immunological basis for immunization series. Diphtheria Update 2009. Disponible à l'adresse: http://apps.who.int/iris/bitstream/10665/44094/1/9789241597869_eng.pdf; consulté en avril 2017.

Vaccine characteristics, content, dosage, administration, storage

Diphtheria vaccines contain inactivated toxin (toxoid) adsorbed onto an adjuvant (usually aluminum hydroxide or aluminum phosphate). Multi-dose vials have preservative added, although single-dose vials prepared without preservative are available from some manufacturers.[10] Toxoid concentration is expressed as flocculation units (Lf) and is established as the amount of toxoid that flocculates 1 unit of an international reference antitoxin. Toxoid potency is measured in international units (IU) as determined by guinea-pig challenge assay or serological assay either in guinea-pigs or mice.[20] According to WHO recommendations,[22] the higher potency of diphtheria vaccine (D), which is used for the immunization of children up to 6 years of age, should be no less than 30 IU per dose. Tetanus-diphtheria (Td, low-dose diphtheria toxoid) formulations and tetanus-diphtheria-acellular pertussis (Tdap) formulations are licensed for use from 5 years of age and 3 years of age, respectively. This reduction of diphtheria toxoid potency minimizes reactogenicity at the injection site but is still sufficient to provoke an antibody response in older children and adults.

Currently, for pediatric use, diphtheria toxoid is almost exclusively available in combination with tetanus toxoid (T) as DT, or with tetanus and pertussis antigens (DTP). The pertussis component is specified as whole-cell (wP) or acellular (aP) (DTwP and DTaP) depending on whether killed pertussis organisms or one or more highly purified individual pertussis antigens are included. DTwP or DTaP may also be combined with additional vaccine antigens, such as hepatitis B surface antigen (HBsAg) and *Haemophilus influenzae* type b (Hib) conjugates as pentavalent vaccines, and with inactivated polio vaccine (IPV) as hexavalent vaccines. For the routine immunization of infants, these combination vaccines are licensed to be used in a 3-dose vaccination series starting as soon as possible from 6 weeks of age with a minimum interval of 4 weeks between doses, then a booster dose at age 15–18 months, dependent on product.[23] A wide range of vaccination schedules are used around the world, some including >7 doses of diphtheria toxoid-containing vaccine.

Most diphtheria toxoid-containing vaccines are administered as a 0.5 mL dose, by intramuscular injection only.

Vaccines containing diphtheria toxoid should be stored at 2–8 °C. If vaccines have been frozen, they should not be used.

Propriétés, contenu, dosage, administration et stockage des vaccins

Les vaccins antidiphtériques contiennent la toxine inactivée (anatoxine), adsorbée sur un adjuvant (généralement l'hydroxyde d'aluminium ou le phosphate d'aluminium). Les flacons multidoses contiennent en outre un agent conservateur, bien que certains fabricants fournissent également des flacons monodoses préparés sans conservateur.[10] La concentration en anatoxine est exprimée en unités de floculation (Lf) et est définie comme la quantité d'anatoxine qui flocule 1 unité d'une antitoxine de référence internationale. L'activité de l'anatoxine est mesurée en unité internationale (UI) et est déterminée par une inoculation d'épreuve ou un test sérologique chez des cobayes ou des souris.[20] Selon les recommandations de l'OMS,[22] le vaccin antidiphtérique de plus forte activité (D), qui est utilisé pour vacciner les enfants jusqu'à l'âge de 6 ans, ne doit pas avoir une activité inférieure à 30 UI par dose. Des formulations à teneur réduite en anatoxine diphtérique du vaccin antitétanique-antidiphtérique (Td) et du vaccin antitétanique-antidiphtérique-anticoquelucheux acellulaire (Tdca) sont homologuées pour un usage à partir de l'âge de 5 ans et de 3 ans, respectivement. Cette réduction de l'activité de l'anatoxine diphtérique limite la réactogénicité au point d'injection tout en restant suffisante pour provoquer une réponse en anticorps chez les enfants plus âgés et les adultes.

Actuellement, pour un usage pédiatrique, l'anatoxine diphtérique est presque exclusivement disponible en association avec l'anatoxine tétanique (T) sous forme de vaccin DT, ou en association avec les antigènes tétanique et coquelucheux (DTC). La composante anticoquelucheuse est spécifiée comme étant à germes entiers (Ce) ou acellulaire (Ca) (vaccins DTCe et DTCa), selon qu'elle comporte les germes tués de la coqueluche ou un ou plusieurs antigènes coquelucheux individuels hautement purifiés. Les vaccins DTCe et DTCa peuvent également être associés à d'autres antigènes vaccinaux, comme l'antigène de surface de l'hépatite B (AgHBs) et le vaccin conjugué contre *Haemophilus influenzae* type b (Hib) pour former un vaccin pentavalent, ainsi qu'avec le vaccin antipoliomyélitique inactivé (VPI) sous forme de vaccin hexavalant. Dans le cadre de la vaccination systématique des nourrissons, ces vaccins combinés sont homologués pour une série de vaccination à 3 doses, administrées dès que possible à partir de l'âge de 6 semaines avec un intervalle de 4 semaines au minimum entre les doses, suivies d'une dose de rappel à l'âge de 15-18 mois, selon le produit.[23] De nombreux calendriers vaccinaux différents sont appliqués dans le monde, certains prévoyant >7 doses de vaccin contenant l'anatoxine diphtérique.

La dose vaccinale de la plupart des vaccins à base d'anatoxine diphtérique est de 0,5 ml, administrée exclusivement par injection intramusculaire.

Les vaccins contenant l'anatoxine diphtérique doivent être conservés à une température comprise entre 2 °C et 8 °C. S'ils ont été congelés, ils ne doivent pas être utilisés.

[22] Recommendations to assure the quality, safety and efficacy of DT-based combined vaccines. WHO Technical Report Series No. 980, Annex 6. 2014.335–406. Available at http://who.int/biologicals/vaccines/Combined_Vaccines_TRS_980_Annex_6.pdf?ua=1, accessed June 2017.

[23] World Health Organization. List of prequalified vaccines. Available at https://extranet.who.int/gavi/PQ_Web/, accessed July 2016.

[22] Recommendations to assure the quality, safety and efficacy of DT-based combined vaccines. WHO Technical Report Series No. 980, Annex 6. 2014.335–406. Disponible à l'adresse: http://who.int/biologicals/vaccines/Combined_Vaccines_TRS_980_Annex_6.pdf?ua=1; consulté en juin 2017.

[23] Organisation mondiale de la Santé. List of prequalified vaccines. Disponible à l'adresse: https://extranet.who.int/gavi/PQ_Web/; consulté en juillet 2016.

Immunogenicity, efficacy and effectiveness

Although evidence suggests that high maternal antitoxin antibody levels affect the immune response of the infant, leading to a lower immune response after the first 2 doses of diphtheria-containing vaccine, most infants develop protective levels of antibody after completion of the full 3-dose primary series. After the primary series of DTP-containing vaccine, 94–100% of children have anti-diphtheria antibody levels >0.01 IU/mL.[21] A randomized controlled trial of a 3-dose primary series of a DTwP-Hib vaccine, starting at 6–8 weeks of age with intervals of 4 weeks between doses, showed that seroprotection (≥0.1 IU/ mL) was obtained in 93.9–100% of the infants.[24]

A randomized controlled trial compared the immunogenicity of a liquid combination vaccine containing diphtheria-tetanus toxoid, 5-component acellular pertussis, IPV and Hib with that of a DTaP-IPV/Hib vaccine, administered at 3, 5, and 12 months of age. The resulting seroprotection rates to diphtheria toxoid (≥0.1 IU/mL) were 95.1% (95% CI: 92.1–97.2%) and 90.3% (95% CI: 86.7–93.2%), respectively.[25]

When comparing the diphtheria antibody responses induced by combined DTP-HepB-Hib vaccine(s) (including DTwP and DTaP vaccines) with levels obtained by separately administered DTP-Hep B and Hib vaccines, no significant differences (RR 0.91; 95% CI: 0.59–1.38) were observed.[26] Similar serological responses are achieved following a 3-dose primary vaccination series in adults aged >18 years.[27] No evidence could be retrieved on the duration of protective immunity following a 3-dose primary vaccination series in adults.

Although randomized controlled clinical trials were not conducted to assess the efficacy of diphtheria toxoid against diphtheria, there is consistent evidence from observational studies that diphtheria toxoid immunization is effective against clinical respiratory diphtheria.

Prophylactic administration of an antipyretic leads to statistically significant lowering of the antibody response, though a systematic review indicated that diphtheria antibody levels were above the protective threshold in those receiving prophylactic antipyretics.[28]

Most of the evidence on effectiveness comes from outbreak settings. During an epidemic in 1940–1941 in

Immunogénicité et efficacité

Les données semblent indiquer qu'un titre élevé d'anticorps antitoxine maternels se répercute sur la réponse immunitaire du nourrisson, se traduisant par une réponse immunitaire réduite après 2 doses de vaccin à base d'anatoxine diphtérique. Toutefois, la plupart des nourrissons obtiennent des titres protecteurs d'anticorps après la série complète de primovaccination à 3 doses. Suite à la série de primovaccination par le DTC, 94-100% des enfants présentent des taux d'anticorps antidiphtériques >0,01 UI/ml.[21] Un essai contrôlé randomisé d'une série de primovaccination par 3 doses de vaccin DTCe-Hib, administrées à partir de l'âge de 6-8 semaines et espacées de 4 semaines, a montré qu'une séroprotection (≥0,1 UI/ml) était obtenue chez 93,9-100% des nourrissons.[24]

Un essai contrôlé randomisé a comparé l'immunogénicité d'une association vaccinale liquide contenant les anatoxines diphtérique et tétanique, le vaccin anticoquelucheux acellulaire à 5 composants, le VPI et le vaccin anti-Hib à celle d'un vaccin DTCa-VPI/Hib, administrés aux âges de 3, 5 et 12 mois. Les taux de séroprotection obtenus pour l'anatoxine diphtérique (≥0,1 UI/ml) étaient de 95,1% (IC à 95%: 92,1-97,2) et 90,3% (IC à 95%: 86,7-93,2), respectivement.[25]

La comparaison entre les réponses en anticorps antidiphtériques induites par les vaccins combinés DTC-HepB-Hib (vaccins DTCe et DTCa compris) et celles obtenues par l'administration séparée des vaccins DTC-HepB et Hib ne révèle aucune différence notable (RR 0,91; IC à 95%: 0,59-1,38).[26] Des réponses sérologiques semblables sont obtenues après une série de primovaccination à 3 doses chez les adultes de >18 ans.[27] Aucune donnée n'a pu être recueillie concernant la durée de l'immunité protectrice suite à une série de primovaccination par 3 doses chez l'adulte.

Bien qu'aucun essai clinique contrôlé randomisé n'ait été mené pour évaluer l'efficacité de l'anatoxine diphtérique contre la diphtérie, des données concordantes issues d'études d'observation montrent que la vaccination par l'anatoxine diphtérique est efficace contre la diphtérie respiratoire clinique.

L'administration prophylactique d'un antipyrétique entraîne une baisse statistiquement significative de la réponse en anticorps, bien qu'une revue systématique ait indiqué que les titres d'anticorps antidiphtériques obtenus chez les personnes ayant reçu des antipyrétiques à titre prophylactique se situent au-dessus du seuil protecteur.[28]

La plupart des données sur l'efficacité proviennent des situations de flambées. Lors de l'épidémie survenue en 1940-1941 à

[24] Cherian T et al. Safety and immunogenicity of *Haemophilus influenzae* type B vaccine given in combination with DTwP at 6, 10 and 14 weeks of age. Indian Pediatr. 2002;39(5):427–436.

[25] Vesikari T et al. Randomized, Controlled, Multicenter Study of the Immunogenicity and Safety of a Fully Liquid Combination Diphtheria–Tetanus Toxoid–Five-Component Acellular Pertussis (DTaP5), Inactivated Poliovirus (IPV), and *Haemophilus influenzae* type b (Hib) Vaccine Compared with a DTaP3-IPV/Hib Vaccine Administered at 3, 5, and 12 Months of Age. Clin Vaccine Immunol. 2013;20(10):1647–1653.

[26] Bar On ES et al. Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* B (HIB) (Review). Cochrane Database of Systematic Reviews. 2012; Issue 4. Art. No.: CD005530.

[27] Myers MG et al. Primary immunization with tetanus and diphtheria toxoids: reaction rates and immunogenicity in older children and adults. JAMA.1982;248:2478–2480.

[28] Das R et al. The Effect of Prophylactic Antipyretic Administration on Post-Vaccination Adverse Reactions and Antibody Response in Children: A Systematic Review. Plose One. 2014. Available at https://doi.org/10.1371/journal.pone.0106629, accessed July 2017.

[24] Cherian T et al. Safety and immunogenicity of *Haemophilus influenzae* type B vaccine given in combination with DTwP at 6, 10 and 14 weeks of age. Indian Pediatr. 2002;39(5):427–436.

[25] Vesikari T et al. Randomized, Controlled, Multicenter Study of the Immunogenicity and Safety of a Fully Liquid Combination Diphtheria–Tetanus Toxoid–Five-Component Acellular Pertussis (DTaP5), Inactivated Poliovirus (IPV), and *Haemophilus influenzae* type b (Hib) Vaccine Compared with a DTaP3-IPV/Hib Vaccine Administered at 3, 5, and 12 Months of Age. Clin Vaccine Immunol. 2013;20(10):1647–1653.

[26] Bar On ES et al. Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* B (HIB) (Review). Cochrane Database of Systematic Reviews. 2012; Issue 4. Art. No.: CD005530.

[27] Myers MG et al. Primary immunization with tetanus and diphtheria toxoids: reaction rates and immunogenicity in older children and adults. JAMA.1982;248:2478–2480.

[28] Das R et al. The Effect of Prophylactic Antipyretic Administration on Post-Vaccination Adverse Reactions and Antibody Response in Children: A Systematic Review. Plose One. 2014. Disponible à l'adresse: https://doi.org/10.1371/journal.pone.0106629; consulté en juillet 2017.

Halifax, Canada,[29] among those vaccinated (most individuals had received 3 primary doses), the monthly incidence of diphtheria fell to 24.5 per 100 000 population, about one seventh of the rate in the unvaccinated children during that same period (168.9 per 100 000). In the United Kingdom (UK)[30] in 1943, the rate of clinical respiratory diphtheria among unimmunized persons was 3.5-fold greater than that among those immunized with diphtheria vaccine, and mortality was 25-fold greater. In an outbreak in Texas, USA, in 1970[31] only 2 of 205 fully vaccinated (having received ≥3 vaccine doses) exposed elementary schoolchildren acquired the disease; the risk of symptomatic diphtheria was 30 times greater for unvaccinated children, and 11.5 times greater for those with incomplete vaccination, compared to those fully vaccinated. During 1981–1982 in Yemen,[32] the protective effectiveness of diphtheria toxoid, assessed by the case-control method, was found to be 87% among those who had received ≥3 doses.

Most recent data on vaccine effectiveness stem from the epidemic in the 1990s in countries of the former Soviet Union. These data suggest that contributing factors to the epidemic included the accumulation of susceptible individuals among both adults and children and social factors such as large numbers of migrants. Problems related to vaccine quality, vaccine supply, or access to vaccine providers did not contribute significantly to the epidemic.[33] Case-control studies showed that ≥3 doses of diphtheria toxoid induced 95.5% (95% CI: 92.1–97.4%) protective effectiveness among children aged <15 years. Protection increased to 98.4% (95% CI: 96.5–99.3%) after ≥5 doses of this vaccine. Results from the Ukraine in 1992[34] suggest that the effectiveness of ≥3 doses was 98.2% (95% CI: 90.3–99.9%) while data from the Russian Federation in 1993[35] indicated that the effectiveness of ≥3 doses was 96.9% (95% CI: 94.3–98.4%), increasing to 99.0% for ≥5 doses (95% CI: 97.7–99.6%).

A systematic review of evidence indicates that 2 primary doses result in substantially lower antitoxin titres than 3 doses in the primary series. However, this difference does not persist during the second year of life and after boosting, nor does it appear to impact clinical protection. The review also found that booster vaccination during the second year of life after a 2-dose or 3-dose primary series substantially increases antitoxin titres.[36] With regard to the effect of the length of the interval

[29] Wheeler SM et al. Epidemiological observations in the Halifax epidemic. Am J Public Health. 1942;32:947–956.

[30] Stuart G. A note on diphtheria incidence in certain European countries. Br Med J. 1945;2:613–615.

[31] Miller LW et al. Diphtheria immunization: effect on carriers and the control of outbreaks. Am J Dis Child. 1972;123:197–199.

[32] Jones EE et al. Diphtheria: a possible foodborne outbreak in Hodeida, Yemen Arab Republic. Bull World Health Organ. 1985;63:287–293.

[33] Markina SS et al. Diphtheria in the Russian Federation in the 1990s. J Infect Dis. 2000;181(Suppl. 1):S27-S34.

[34] Chen RT et al. Ukraine, 1992: first assessment of diphtheria vaccine effectiveness during the recent resurgence of diphtheria in the former Soviet Union. J Infect Dis. 2000;181(Suppl.1):178–183.

[35] Bisgard KM et al. Diphtheria toxoid vaccine effectiveness: a case-control study in Russia. J Infect Dis. 2000;181(Suppl.1):184–187.

[36] World Health Organization. Comparative efficacy/effectiveness of schedules in infant immunisation against pertussis, diphtheria and tetanus: Systematic review and meta-analysis. Available at http://www.who.int/immunization/sage/meetings/2015/april/5_Report_D_T_140812.pdf?ua=1, accessed April 2017.

Halifax (Canada),[29] l'incidence mensuelle de la diphtérie parmi les personnes vaccinées (par 3 doses de primovaccination dans la plupart des cas) avait été réduite à 24,5 cas pour 100 000 habitants, soit environ un septième du taux relevé chez les enfants non vaccinés durant la même période (168,9 pour 100 000). Au Royaume-Uni[30] en 1943, le taux de diphtérie respiratoire clinique chez les sujets non vaccinés était 3,5 fois supérieur à celui des personnes vaccinées contre la diphtérie, avec un taux de mortalité 25 fois supérieur. Lors d'une flambée qui a touché le Texas (États-Unis d'Amérique) en 1970,[31] on a observé que sur 205 écoliers du primaire entièrement vaccinés (par ≥3 doses) qui avaient été exposés à la diphtérie, seuls 2 ont contracté la maladie; le risque de diphtérie symptomatique était 30 fois supérieur chez les enfants non vaccinés, et 11,5 fois supérieur parmi les enfants partiellement vaccinés par rapport à celui des enfants pleinement vaccinés. En 1981-1982 au Yémen,[32] l'efficacité protectrice de l'anatoxine diphtérique, évaluée par une étude cas-témoin, était de 87% parmi les sujets ayant reçu ≥3 doses de vaccin.

La plupart des données récentes sur l'efficacité vaccinale sont issues de l'épidémie qui a sévi dans les années 1990 dans les pays de l'ancienne Union soviétique. Ces données révèlent que l'accumulation de sujets sensibles, tant parmi les adultes que parmi les enfants, ainsi que certains facteurs sociaux, comme une forte population de migrants, comptaient parmi les facteurs contributeurs de l'épidémie. Les problèmes liés à la qualité des vaccins, à l'approvisionnement en vaccins ou à l'accès aux fournisseurs de vaccins n'avaient pas contribué de manière significative à l'épidémie.[33] Des études cas-témoins ont montré que ≥3 doses d'anatoxine diphtérique induisaient une efficacité protectrice de 95,5% (IC à 95%: 92,1-97,4%) chez les enfants âgés de <15 ans. La protection passait à 98,4% (IC à 95%: 96,5-99,3%) après ≥5 doses de vaccin. Les résultats obtenus en Ukraine en 1992[34] donnent une efficacité de 98,2% (IC à 95%: 90,3-99,9%) pour ≥3 doses, tandis que les données recueillies en Fédération de Russie en 1993[35] indiquent que l'efficacité pour ≥3 doses était de 96,9% (IC à 95%: 94,3-98,4%), atteignant 99,0% pour ≥5 doses (IC à 95%: 97,7-99,6%).

Selon une revue systématique des données, les titres d'antitoxine obtenus après 2 doses de primovaccination sont considérablement plus faibles qu'après 3 doses de primovaccination. Toutefois, cette différence s'estompe durant la deuxième année de vie et après les doses de rappel et ne semble pas avoir d'impact sur la protection clinique. Cette revue a également montré que l'administration d'une dose de rappel dans la deuxième année de vie, après 2 ou 3 doses de primovaccination, accroît notablement les titres d'antitoxine.[36] S'agissant de l'intervalle

[29] Wheeler SM et al. Epidemiological observations in the Halifax epidemic. Am J Public Health. 1942;32:947–956.

[30] Stuart G. A note on diphtheria incidence in certain European countries. Br Med J 1945;2:613–615.

[31] Miller LW et al. Diphtheria immunization: effect on carriers and the control of outbreaks. Am J Dis Child. 1972;123:197–199.

[32] Jones EE et al. Diphtheria: a possible foodborne outbreak in Hodeida, Yemen Arab Republic. Bull World Health Organ. 1985;63:287–293.

[33] Markina SS et al. Diphtheria in the Russian Federation in the 1990s. J Infect Dis. 2000;181(Suppl. 1): S27-S34.

[34] Chen RT et al. Ukraine, 1992: first assessment of diphtheria vaccine effectiveness during the recent resurgence of diphtheria in the former Soviet Union. J Infect Dis. 2000;181(Suppl.1): 178–183.

[35] Bisgard KM et al. Diphtheria toxoid vaccine effectiveness: a case-control study in Russia. J Infect Dis. 2000; 181(Suppl.1): 184–187.

[36] World Health Organization. Comparative efficacy/effectiveness of schedules in infant immunisation against pertussis, diphtheria and tetanus: Systematic review and meta-analysis. Disponible à l'adresse: http://www.who.int/immunization/sage/meetings/2015/april/5_Report_D_T_140812.pdf?ua=1; consulté en avril 2017.

between primary doses, evidence suggests that an accelerated schedule (2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) results in 2-fold lower antibody titres when measured after the third dose or during the second year of life, as compared to a longer schedule (with an interval of around 6 months between the second and third doses).[36] On immunological grounds, an interval of 6 months between the second priming dose and the third dose (2p+1) results in more durable protection than 3 doses administered at 1 month intervals (3p+0).[21] However, the purpose of early vaccination of infants with 3 doses of DTP-containing vaccine at intervals of 4–8 weeks is to ensure early protection against pertussis, as severe disease and mortality from pertussis are almost entirely limited to the first weeks and months of life.[4]

Vaccination has led to significant decreases in diphtheria incidence worldwide, and is also responsible for the development of herd protection. At the population level, it is believed that vaccine coverage of 80–85% must be maintained in order to maintain herd protection/community protection and reduce the threat of an outbreak.[7] As non-immune individuals living in highly vaccinated populations can develop respiratory diphtheria, every person should be adequately protected by vaccination.

Duration of protection and booster requirements in children

In the absence of natural boosting, data indicate that immunity following a 3-dose primary vaccination schedule wanes over time.[7, 8] Therefore, booster doses are needed to ensure continuing protection. However, the optimal number of required booster doses and interval between doses remain uncertain. A systematic review revealed that only limited data were available on the duration of protective effectiveness and/or immunogenicity of a 3-dose primary plus 3-dose booster schedule until adulthood.[37] Data on the duration of seroprotection from 2 large representative population studies from the Netherlands,[38] using a complete 3-dose primary series plus 3-dose booster series prior to adolescence, indicate that this schedule results in very high seroprevalence above the threshold for basic protection (≥0.01 IU/mL) up to 39 years of age and potentially longer. The first 4 doses in the series had a potency of >60 IU, while the final 2 doses had a potency of >5 IU. A seroprevalence of 94.6% (95% CI: 87.3–100%) for basic protection was observed even in the age group 35–39 years. A seroprevalence of 37.8% (95% CI: 22.2–53.5%) above the threshold for full protection (0.1 IU/mL) was observed in the age group 35–39 years. Given the low number of reported cases of diphtheria in the Netherlands and the high vaccination coverage in the past years, it can be assumed that there has been little chance of exposure to

[37] World Health Organization. Diphtheria vaccine. Review of evidence on vaccine effectiveness and immunogenicity to assess the duration of protection ≥10 years after the last booster dose. Available at http://www.who.int/immunization/sage/meetings/2017/april/2_Review_Diphtheria_results_April2017_final_clean.pdf?ua=1, accessed April 2017.

[38] Swart EM et al. Long-Term Protection against Diphtheria in the Netherlands after 50 Years of Vaccination: Results from a Seroepidemiological Study. PLoS ONE 11(2):e0148605.

entre les doses de primovaccination, les données indiquent que les titres d'anticorps obtenus, tels que mesurés après la troisième dose ou durant la deuxième année de vie, sont 2 fois plus faibles avec un schéma d'administration accéléré (2, 3, 4 mois; 3, 4, 5 mois; 2, 4, 6 mois) qu'avec un schéma de plus longue durée (prévoyant un écart d'environ 6 mois entre la deuxième dose et la troisième dose).[36] Sur le plan immunologique, un intervalle de 6 mois entre la deuxième dose de primovaccination et la troisième dose (2p+1) confère une protection plus durable que 3 doses administrées à 1 mois d'écart (3p+0).[21] Toutefois, l'objectif de la vaccination précoce des nourrissons par 3 doses de vaccin DTC espacées de 4-8 semaines est de garantir une protection précoce contre la coqueluche car les cas graves et les décès dus à la coqueluche se produisent presque exclusivement durant les premières semaines et les premiers mois de la vie.[4]

La vaccination a entraîné une baisse considérable de l'incidence de la diphtérie dans le monde et a permis le développement d'une protection collective. Au niveau de la population, on estime qu'il faut maintenir une couverture vaccinale de 80-85% pour préserver la protection collective/communautaire et réduire le risque de flambée.[7] Les sujets non immunisés qui vivent au sein de populations fortement vaccinées peuvent contracter une diphtérie respiratoire et il est donc important que toutes les personnes soient convenablement protégées par la vaccination.

Durée de la protection et nécessité des rappels chez l'enfant

En l'absence de rappel naturel, les données indiquent que l'immunité acquise après 3 doses de primovaccination s'estompe avec le temps.[7, 8] L'administration de doses de rappel est donc nécessaire pour pérenniser la protection. Cependant, le nombre optimal de doses de rappel, ainsi que l'intervalle entre ces doses, n'ont pas été clairement établis. Une revue systématique a montré qu'on ne dispose que de données limitées sur la durée de l'efficacité protectrice et/ou l'immunogénicité résultant d'un calendrier à 3 doses de primovaccination suivies de 3 doses de rappel jusqu'à l'âge adulte.[37] Des données sur la durée de la séroprotection tirées de 2 grandes études représentatives de la population aux Pays-Bas,[38] portant sur une série complète de 3 doses de primovaccination suivies d'une série de 3 doses de rappel avant l'adolescence, indiquent que ce calendrier induit une très forte séroprévalence, supérieure au seuil de protection de base (≥0,01 UI/ml), jusqu'à l'âge de 39 ans, voire plus. Les 4 premières doses de la série avaient une activité >60 UI, contre >5 UI pour les 2 dernières doses. Pour le niveau de protection de base, la séroprévalence était de 94,6% (IC à 95%: 87,3-100), même dans la tranche d'âge de 35-39 ans. Pour les titres supérieurs au seuil de protection complète (0,1 UI/ml), une séroprévalence de 37,8% (IC à 95%: 22,2-53,5) a été observée dans la classe d'âge de 35-39 ans. Compte tenu du faible nombre de cas de diphtérie notifiés aux Pays-Bas et de la forte couverture vaccinale enregistrée ces dernières années, la probabilité d'une exposition à l'infection, servant de rappel naturel, est vraisem-

[37] Organisation mondiale de la Santé. Diphtheria vaccine. Review of evidence on vaccine effectiveness and immunogenicity to assess the duration of protection ≥10 years after the last booster dose. Disponible à l'adresse: http://www.who.int/immunization/sage/meetings/2017/april/2_Review_Diphtheria_results_April2017_final_clean.pdf?ua=1; consulté en avril 2017.

[38] Swart EM et al. Long-Term Protection against Diphtheria in the Netherlands after 50 Years of Vaccination: Results from a Seroepidemiological Study. PLoS ONE 11(2):e0148605.

infection that would provide natural boosting. The observed high levels of protective immunity are therefore likely to be attributable to the 6-dose vaccination schedule used in the country. These data indicate that following a 3-dose primary plus 3-dose booster schedule, administration of decennial booster doses may not be necessary through middle age.[39]

Among women who had received a complete DTP-containing primary series (3 doses) in Portugal during childhood and at least one booster (n=22), none were found to be susceptible before 25 years had elapsed since the last dose. All those who had received at least 6 doses (n=17) had anti-diphtheria antibody levels above the threshold for full protection up to 38 years since the last dose.[40] A cross-sectional seroprevalance study in one State in the USA modelled a half-life for diphtheria-specific immunity (>0.01 IU/mL) of 27 years (95% CI: 18–51 years).[41] Data from the UK indicate good antibody levels in individuals aged 16–34 years in 2009, of whom most had received the currently recommended 5 doses of diphtheria toxoid with the last dose during adolescence (geometric mean concentration 0.15 IU/mL).[42] Similarly data from Singapore indicate a seroprevalence of 96% for diphtheria for individuals aged 6 to >40 years.[43]

Serological studies indicate that in some settings, a high proportion of adults are susceptible to diphtheria. However, different childhood immunization schedules, booster immunization during military service, impact of natural exposure to toxigenic *C. diphtheriae*, as well as differences in serological methods, complicate the international comparison of such data.

Vaccine safety

Diphtheria toxoid is one of the safest vaccines available. Severe reactions are rare, and to date no anaphylactic reactions attributable to the diphtheria component have been described. However, local reactions at the site of injection are common, although reported rates differ widely (<10 to >50%). The frequency of adverse events varies with factors such as vaccination history, pre-vaccination level of diphtheria antitoxin antibody, combination vaccines including diphtheria toxoid, and the administered dose of toxoid. Local reactions and pain at the injection site occur more frequently with increasing number of doses, and when combined

blablement faible. Les taux élevés d'immunité protectrice qui ont été observés sont donc probablement imputables au calendrier vaccinal à 6 doses utilisé dans le pays. Ces données indiquent qu'après une vaccination selon un schéma à 3 doses de primovaccination suivies de 3 doses de rappel, l'administration de doses de rappel tous les 10 ans jusqu'en milieu de vie pourrait s'avérer inutile.[39]

Au Portugal, parmi des femmes qui avaient reçu la série complète de vaccination DTC (3 doses) durant l'enfance et au moins une dose de rappel (n=22), aucune n'a manifesté de sensibilité dans les 25 années qui ont suivi la dernière dose. Toutes celles qui avaient bénéficié d'au moins 6 doses (n=17) présentaient des titres d'anticorps antidiphtériques supérieurs au seuil de protection complète jusqu'à 38 ans après la dernière dose.[40] Dans le cadre d'une étude transversale de la séroprévalence dans un État des États-Unis d'Amérique, la modélisation a estimé à 27 ans (IC à 95%: 18-51 ans) la demi-vie de l'immunité spécifique contre la diphtérie (>0,01 UI/ml).[41] Au Royaume-Uni, les données révèlent des titres favorables d'anticorps (moyenne géométrique de 0,15 UI/ml) chez les sujets âgés de 16-34 ans en 2009, dont la plupart avaient reçu les 5 doses actuellement recommandées d'anatoxine diphtérique, la dernière étant administrée à l'adolescence.[42] De même, des données recueillies à Singapour indiquent une séroprévalence de 96% pour la diphtérie chez les personnes âgées de 6 ans à >40 ans.[43]

Des études sérologiques montrent que dans certains milieux, une forte proportion d'adultes est sensible à la diphtérie. Cependant, l'utilisation de différents calendriers de vaccination de l'enfant, l'administration de doses de rappel pendant le service militaire, l'impact de l'exposition naturelle à la bactérie *C. diphtheriae* toxinogène, ainsi que les différences entre les méthodes d'analyse sérologique, rendent la comparaison internationale de ces données difficile.

Innocuité du vaccin

Le vaccin à base d'anatoxine diphtérique est l'un des plus sûrs dont on dispose. Les réactions graves sont rares et, à ce jour, aucune réaction anaphylactique imputable à la composante antidiphtérique n'a été constatée. Cependant, les réactions locales au point d'injection sont courantes, même si leur fréquence varie considérablement selon les données communiquées (de <10% à >50%). Divers facteurs, tels que les antécédents vaccinaux, le titre d'anticorps contre la toxine diphtérique avant la vaccination, l'utilisation de vaccins combinés contenant l'anatoxine diphtérique et la dose d'anatoxine administrée, influent sur la fréquence des manifestations indésirables. Les réactions locales et la douleur au point d'injection sont plus

[39] GRADE table. Duration of protection. Grading of scientific evidence: Duration of protection – Available at http://www.who.int/immunization/policy/position_papers/diphtheria_GRAD_duration.pdf

[40] Goncalves G et al. Levels of diphtheria and tetanus specific IgG of Portuguese adult women, before and after vaccination with adult type Td. Duration of immunity following vaccination. BMC Public Health. 2007;7:109.

[41] Hammarlund E et al. Durability of Vaccine-Induced Immunity Against Tetanus and Diphtheria Toxins: A Crosssectional Analysis. Clinical Infectious Diseases. 2016;62:1111–1118.

[42] Wagner K et al. Immunity to tetanus and diphtheria in the UK in 2009. Vaccine. 2012;30:7111–7117.

[43] Oh HML et al. Seroprevalence of pertussis, and diphtheria and poliovirus antibodies among healthcare personnel in Singapore. Poster presented at: 10th Healthcare Infection Society International Conference Edinburgh, Scotland, 2016.

[39] Tableau GRADE. Durée de la protection. Disponible à l'adresse: http://www.who.int/immunization/policy/position_papers/diphtheria_GRAD_duration.pdf

[40] Goncalves G et al. Levels of diphtheria and tetanus specific IgG of Portuguese adult women, before and after vaccination with adult type Td. Duration of immunity following vaccination. BMC Public Health. 2007;7:109.

[41] Hammarlund E et al. Durability of Vaccine-Induced Immunity Against Tetanus and Diphtheria Toxins: A Crosssectional Analysis. Clinical Infectious Diseases. 2016;62:1111–1118.

[42] Wagner K et al. Immunity to tetanus and diphtheria in the UK in 2009. Vaccine. 2012;30:7111–7117.

[43] Oh HML et al. Seroprevalence of pertussis, and diphtheria and poliovirus antibodies among healthcare personnel in Singapore. Affiche présentée à la 10e conférence internationale de la Healthcare Infection Society, Édimbourg (Écosse), 2016.

with tetanus toxoid, or with tetanus toxoid and pertussis antigens.[44]

Mild adverse events following DTwP when administered for both primary and booster doses in infants and children consist of local reactions (50%) and systemic reactions such as fever >38 °C and irritability (40–75%), drowsiness (33–62%), loss of appetite (20–35%), and vomiting (6–13%). Mild adverse events are similar but less frequent following administration of vaccines containing acellular pertussis antigens compared to vaccines containing whole-cell pertussis antigens. More severe adverse events are rare and may consist of temperature in excess of 40.5 °C (0.3% of vaccine recipients), febrile seizures (8 per 100 000 doses) or hypotonic–hyporesponsive episodes (0–291 per 100 000 doses). During primary immunization, severe adverse events occurring after DTaP are similar to those experienced after DTwP but occur less frequently. Seizures, persistent crying, hypotonic–hyporesponsive episodes, and fever in excess of 40 °C have been uncommonly reported with DTaP.[45] No causal relationship has been established between DTwP and acute encephalopathy.

In adults, rates of local reactions are more frequent with booster doses containing 12 Lf compared with 5 or 2 Lf of diphtheria toxoid.[46] Such observations have resulted in the recommendation to provide low-dose diphtheria toxoid (Td) for immunization of individuals aged ≥7 years. Clinical trials have shown that DT and DTaP are comparable in terms of both local and systemic reactogenicity when used for primary vaccination of infants. Large local reactions are observed in 1–2% of recipients after the DTaP booster vaccination. Available data suggest that both tetanus and diphtheria toxoid contribute to the reactogenicity of Td and DT.[45]

Special risk groups

Pregnant women: Vaccination during pregnancy is not necessary to protect neonatal infants against diphtheria, but diphtheria-containg vaccines combined with pertussis and tetanus can be used to protect young infants against tetanus and pertussis. For all 3 antigens, vaccination during pregnancy also serves to boost immunity and increase the duration of protection in those who had not received the full set of recommended booster doses.

A systematic review[47] showed that pain at the injection site was reported more frequently among pregnant women who received Tdap than placebo (RR 5.68, 95% CI: 1.54–20.94%). However, the occurrence of other local

[44] World Health Organization. Safety from randomized controlled trials and observational studies of pertussis vaccines. Available at http://www.who.int/immunization/sage/meetings/2015/april/8_Safety_DTP_RCTs_obs_studies_draft.pdf?ua=1, accessed April 2017.

[45] World Health Organization. Information sheet. Diphtheria, Pertussis, Tetanus Vaccines. Available at http://www.who.int/vaccine_safety/initiative/tools/DTP_vaccine_rates_information_sheet.pdf?ua=1, accessed May 2017.

[46] O Simonsen et al. Revaccination of adults against diphtheria. I: Responses and reactions to different doses of diphtheria toxoid in 30-70-year-old persons with low serum antitoxin levels. Acta Pathol Microbiol Immunol Scand [C]. 1986;94:213–218.

[47] Demicheli V et al. Vaccines for women for preventing neonatal tetanus. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD002959.

fréquentes lorsque le nombre de doses augmente et lorsque le vaccin est associé à l'anatoxine tétanique ou à une combinaison d'anatoxine tétanique et d'antigènes coquelucheux.[44]

Les manifestations indésirables bénignes observées après la vaccination par le DTCe, lorsqu'il est administré à la fois pour la primovaccination et les rappels chez les nourrissons et les enfants, sont des réactions locales (50%) et des réactions systémiques, telles que fièvre >38 °C et irritabilité (40-75%), somnolence (33-62%), perte d'appétit (20-35%) et vomissements (6-13%). Les manifestations indésirables bénignes associées aux vaccins contenant des antigènes coquelucheux acellulaires sont comparables à celles des vaccins à germes entiers, mais sont moins fréquentes. Les réactions indésirables plus graves sont rares; il peut s'agir d'une fièvre supérieure à 40,5 °C (0,3% des personnes vaccinées), de convulsions fébriles (8 pour 100 000 doses) ou d'épisodes hypotoniques-hyporéactifs (0-291 pour 100 000 doses). Au cours de la primovaccination, les manifestations indésirables graves survenant après l'administration de DTCa sont semblables à celles observées avec le DTCe, mais moins fréquentes. Peu de réactions de convulsions, de pleurs persistants, d'épisodes hypotoniques-hyporéactifs et de fièvre supérieure à 40 °C ont été signalées avec le DTCa.[45] Aucun lien de causalité n'a été établi entre le DTCe et l'encéphalopathie aiguë.

Chez les adultes, les réactions locales sont plus fréquentes avec les doses de rappel contenant 12 Lf d'anatoxine diphtérique qu'avec celles de 5 ou 2 Lf.[46] C'est pourquoi il est recommandé d'utiliser l'anatoxine diphtérique faiblement dosée (Td) pour la vaccination des sujets âgés de ≥7 ans. Des essais cliniques ont montré que le DT et le DTCa sont comparables en termes de réactogénicité locale et systémique lorsqu'ils sont utilisés pour la primovaccination du nourrisson. Des réactions locales étendues sont observées chez 1-2% des personnes ayant reçu une dose de rappel de DTCa. Les données disponibles semblent indiquer que les anatoxines tétanique et diphtérique contribuent toutes deux à la réactogénicité des vaccins Td et DT.[45]

Groupes à risque particuliers

Femmes enceintes: La protection des nouveau-nés contre la diphtérie n'exige pas de vaccination de la femme enceinte, mais les vaccins combinés contre la diphtérie, la coqueluche et le tétanos peuvent être employés pendant la grossesse pour conférer aux jeunes nourrissons une protection contre le tétanos et la coqueluche. Pour les 3 antigènes, la vaccination pendant la grossesse permet également de stimuler l'immunité et d'accroître la durée de protection des femmes qui n'ont pas reçu la série complète de doses de rappel recommandées.

Une revue systématique[47] a montré que les femmes enceintes recevant le Tdca signalaient plus souvent une douleur au point d'injection que celles qui recevaient un placebo (RR=5,68; IC à 95%: 1,54-20,94). Toutefois, aucune différence statistiquement significative n'a

[44] Organisation mondiale de la Santé. Safety from randomized controlled trials and observational studies of pertussis vaccines. Disponible à l'adresse: http://www.who.int/immunization/sage/meetings/2015/april/8_Safety_DTP_RCTs_obs_studies_draft.pdf?ua=1; consulté en avril 2017.

[45] Organisation mondiale de la Santé. Fiche d'information. Vaccin contre la diphtérie, la coqueluche et le tétanos. Disponible à l'adresse: http://www.who.int/vaccine_safety/initiative/tools/May_2014_DTP_final_FR.pdf?ua=1; consulté en mai 2017.

[46] O Simonsen et al. Revaccination of adults against diphtheria. I: Responses and reactions to different doses of diphtheria toxoid in 30-70-year-old persons with low serum antitoxin levels. Acta Pathol Microbiol Immunol Scand [C]. 1986; 94:213–218.

[47] Demicheli V et al. Vaccines for women for preventing neonatal tetanus. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD002959.

(erythema, induration) and systemic (fever, headache, malaise, myalgia) reactions within 7 days after vaccination was not statistically different in vaccine and placebo recipients. Reported local and systemic reactions were mainly of mild or moderate intensity. None of the serious adverse events observed in mothers and newborn infants was judged to be attributable to the effect of vaccination. Gestational age, birth weight, Apgar score, and neonatal complications did not differ significantly in infants born to vaccinated or unvaccinated mothers. Evidence from another systematic review suggests that antenatal combined Tdap administered during the second or third trimester of pregnancy, based on the recommendations for pertussis vaccination during pregnancy,[4] is not associated with clinically significant harm to the fetus or neonatal infant. Medically attended events in pregnant women are similar in vaccinated and unvaccinated groups.[48]

HIV-infected persons: Among children infected with HIV type 1 (HIV-1), 70.8% developed protective antibody titres following diphtheria toxoid administered at 6, 10, and 14 weeks compared with 98.5% among HIV-1 negative children ($P < 0.05$). Geometric mean antibody titres to diphtheria were significantly lower in children with HIV-1 infection than in uninfected children. Vaccine-associated side effects were similarly low in all children.[49] Multiple linear regression analysis showed lower diphtheria antibody levels, independent of the interval between last booster and antibody assessment, in HIV-1 infected women than in uninfected women. Following a booster dose the mean diphtheria antibody levels were higher in uninfected than in HIV-infected women.[50]

Vaccine co-administration

Concomitant administration of vaccines containing DTaP or DTwP and other childhood vaccines does not interfere with the antibody response to any of the involved antigens. This applies to primary immunization and to subsequent vaccine doses.

Co-administration of diphtheria toxoid-containing vaccines with BCG, conjugate pneumococcal vaccine (PCV), IPV and oral polio vaccine (OPV) and measles, measles and rubella, and measles, mumps and rubella vaccine, conjugate meningococcal meningitis vaccine, hepatitis B vaccine, rotavirus vaccine, varicella vaccine and Hib vaccine is safe and does not result in decreased immunogenicity.[51, 52] Also, Tdap alone or Tdap in combi-

été relevée entre le groupe vacciné et le groupe placebo en ce qui concerne la fréquence des autres réactions locales (érythème, induration) et systémiques (fièvre, céphalées, malaise, myalgie) dans les 7 jours suivant la vaccination. La plupart des réactions locales et systémiques signalées étaient d'intensité légère à modérée. Il a été déterminé qu'aucune des manifestations indésirables graves observées chez les mères et les nouveau-nés n'était imputable à la vaccination. Aucune différence sensible de l'âge gestationnel, du poids de naissance, du score d'Apgar et des complications néonatales n'a été constatée entre les nourrissons nés de mères vaccinées et non vaccinées. Selon les données d'une autre revue systématique, l'administration prénatale du vaccin combiné Tdca au deuxième ou troisième trimestre de la grossesse, conformément aux recommandations relatives à la vaccination anticoquelucheuse durant la grossesse,[4] n'est pas associée à un préjudice cliniquement significatif pour le fœtus ou le nouveau-né. Les événements nécessitant une assistance médicale sont comparables chez les femmes enceintes vaccinées et non vaccinées.[48]

Personnes infectées par le VIH: Parmi les enfants infectés par le VIH de type 1 (VIH-1), la proportion de sujets obtenant des titres protecteurs d'anticorps après l'administration d'anatoxine diphtérique à 6, 10 et 14 semaines était de 70,8%, contre 98,5% parmi les enfants négatifs pour le VIH-1 ($P<0,05$). Les titres moyens géométriques d'anticorps antidiphtériques étaient sensiblement plus faibles chez les enfants présentant une infection à VIH-1 que chez les enfants non infectés. Les effets secondaires associés à la vaccination étaient rares chez tous les enfants.[49] Une analyse à régression linéaire multiple a montré que les femmes infectées par le VIH-1 présentaient des taux d'anticorps antidiphtériques plus faibles que les femmes non infectées, quel que soit l'intervalle écoulé entre la dernière dose de rappel et la mesure des anticorps. Suite à l'administration d'une dose de rappel, les titres moyens d'anticorps antidiphtériques obtenus étaient plus élevés chez les femmes non infectées que chez les femmes infectées par le VIH.[50]

Coadministration avec d'autres vaccins

L'administration concomitante des vaccins contenant le DTCa ou DTCe avec d'autres vaccins administrés pendant l'enfance n'interfère pas avec la réponse en anticorps à l'un quelconque des antigènes impliqués. Cela vaut aussi bien pour la primovaccination que pour les doses ultérieures.

La coadministration des vaccins contenant l'anatoxine diphtérique avec le vaccin BCG, le vaccin antipneumococcique conjugué (VPC), le VPI, le vaccin antipoliomyélitique oral (VPO), le vaccin antirougeoleux, antirougeoleux-antirubéoleux ou antirougeoleux-antiourlien-antirubéoleux, le vaccin antiméningococcique conjugué, le vaccin anti-hépatite B, le vaccin antirotavirus, le vaccin contre la varicelle et le vaccin anti-Hib ne présente pas de danger et n'entraîne pas de baisse de l'immunogénicité.[51, 52]

[48] McMillan M et al. Safety of Tetanus, Diphtheria, and Pertussis Vaccination During Pregnancy: A Systematic Review. Obstet Gynecol. 2017;129:560–573.

[49] Ryder RW et al. Safety and immunogenicity of bacille Calmette-Guérin, diphtheria-tetanus-pertussis, and oral polio vaccines in newborn children in Zaire infected with human immunodeficiency virus type 1. J Pediatr. 1993;122(5Pt1):697–702.

[50] Bonetti T et al. Tetanus and diphtheria antibodies and response to a booster dose in Brazilian HIV-1-infected women. Vaccine. 2004;22(27–28):3707–3712.

[51] King GE et al. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. Pediatr Infect Dis J. 1994;13:394–407.

[52] Dolan S et al. Summary of evidence on the administration of multiple injectable vaccines in infants during a single visit: safety, immunogenicity, and vaccine administration practices (prepared for the April 2015 SAGE meeting. Available at http://www.who.int/immunization/sage/meetings/2015/april/5_Summary_of_Evidence_3-25-2015.pdf, accessed April 2017.

[48] McMillan M et al. Safety of Tetanus, Diphtheria, and Pertussis Vaccination During Pregnancy: A Systematic Review. Obstet Gynecol. 2017;129:560–573.

[49] Ryder RW et al. Safety and immunogenicity of bacille Calmette-Guérin, diphtheria-tetanus-pertussis, and oral polio vaccines in newborn children in Zaire infected with human immunodeficiency virus type 1. J Pediatr. 1993;122(5Pt1):697–702.

[50] Bonetti T et al. Tetanus and diphtheria antibodies and response to a booster dose in Brazilian HIV-1-infected women. Vaccine. 2004;22(27–28):3707–3712.

[51] King GE et al. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. Pediatr Infect Dis J. 1994;13:394–407.

[52] Dolan S et al. Summary of evidence on the administration of multiple injectable vaccines in infants during a single visit: safety, immunogenicity, and vaccine administration practices (préparé pour la réunion du SAGE d'avril 2015). Disponible à l'adresse: http://www.who.int/immunization/sage/meetings/2015/april/5_Summary_of_Evidence_3-25-2015.pdf; consulté en avril 2017.

nation with IPV may be administered concomitantly without causing clinically relevant immunological interference between any of the included antigens. Human papilloma virus (HPV) vaccines can be co-administered with diphtheria-containing vaccines.[53, 54, 55] Adult diphtheria vaccine booster formulations could be administered concomitantly with trivalent inactivated influenza vaccine.[56]

Conjugate vaccines that contain diphtheria toxoid or diphtheria toxin cross-reactive materials (CRM) as a protein carrier may induce a booster response to diphtheria in persons previously immunized against diphtheria. Animal studies have demonstrated that CRM protein carriers do not induce sufficient diphtheria-protective antibody levels in naive recipients. Simultaneous administration of diphtheria toxoid with CRM protein carrier-containing vaccines does not seem to impact negatively on the immunogenicity of either vaccine.[7] Concomitant administration of CRM-conjugated vaccines can in fact increase the immune response to diphtheria and its persistence after diphtheria vaccination.[57] For example, vaccination with meningococcal polysaccharide conjugate vaccines (with CRM as the carrier protein), administered jointly with the adult formulation of Td vaccine, resulted in higher geometric mean diphtheria antitoxin antibody concentrations (120.0 IU/mL versus 8.4 IU/mL) than obtained with Td alone. Boosting of diphtheria responses were observed in UK children, following immunization with a CRM-containing pneumococcal conjugate vaccine (PCV7). Administration of CRM-conjugated vaccines before Tdap can induce significantly higher and more persistent anti-diphtheria responses than when administered after Tdap.[58] Tdap vaccination before administration of PCV13 significantly reduced the response to 7 of the 13 pneumococcal serotypes in adults.[59] This has been attributed to carrier-induced epitope suppression, i.e. the presence of pre-existing antibody to a carrier protein has the potential to suppress the subsequent immune response to an antigen conjugated to the same carrier.[60]

Le Tdca, seul ou en association avec le VPI, peut également être coadministré avec d'autres vaccins sans produire d'interférence immunologique cliniquement pertinente entre les différents antigènes. Les vaccins contre le papillomavirus humain (VPH) peuvent être administrés en même temps que les vaccins antidiphtériques.[53, 54, 55] Les doses de rappel du vaccin antidiphtérique destinées aux adultes peuvent être coadministrées avec le vaccin antigrippal trivalent inactivé.[56]

Les vaccins conjugués contenant l'anatoxine diphtérique ou une substance à réactivité croisée (CRM) de la toxine diphtérique servant de protéine porteuse peuvent induire une réponse de rappel à la diphtérie chez les personnes préalablement vaccinées contre la diphtérie. Des études chez l'animal ont montré que les protéines porteuses CRM n'induisent pas une concentration en anticorps antidiphtériques suffisante pour être protectrice chez les sujets non préalablement vaccinés. L'administration simultanée d'anatoxine diphtérique avec un vaccin contenant une protéine porteuse CRM ne semble pas compromettre l'immunogénicité de l'un ou l'autre des deux vaccins.[7] L'administration concomitante de vaccins conjugués à la protéine CRM peut en fait accroître la réponse immunitaire à la diphtérie, ainsi que sa persistance après la vaccination antidiphtérique.[57] Par exemple, on a observé que l'administration simultanée d'un vaccin antiméningococcique polyosidique conjugué (contenant la protéine porteuse CRM) et d'un vaccin Td de formulation adulte produisait un titre moyen géométrique plus élevé d'anticorps contre la toxine diphtérique (120,0 UI/ml) que le vaccin Td utilisé seul (8,4 UI/ml). Au Royaume-Uni, on a constaté une stimulation de la réponse immunitaire contre la diphtérie chez les enfants ayant été vaccinés par un vaccin antipneumococcique conjugué contenant la protéine CRM (VPC7). L'administration d'un vaccin conjugué à la protéine CRM avant le vaccin Tdca peut induire des réponses antidiphtériques plus fortes et plus durables que lorsque ce vaccin est administré après le Tdca.[58] La vaccination par le Tdca avant le VPC13 affaiblit considérablement la réponse à 7 des 13 sérotypes pneumococciques chez l'adulte.[59] Cela s'explique par la suppression épitopique induite par le vecteur, un phénomène dans lequel la présence d'anticorps préexistants contre la protéine porteuse est susceptible de supprimer la réponse immunitaire ultérieure à un antigène conjugué à ce même vecteur.[60]

[53] GlaxoSmithKline Biologicals SA Cervarix. Summary of Product Characteristics. Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=179, accessed May 2017.

[54] Merck. Gardasil. Summary of Product Characteristics. Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=178, accessed May 2017.

[55] Merck. Gardasil 9. Summary of Product Characteristics. European Medicines Agency. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003852/WC500189111.pdf, accessed May 2017.

[56] Adacel, package insert. Toronto, Ontario, Canada: Sanofi Pasteur Limited; Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=315, accessed July 2017.

[57] Bröker M. Potential protective immunogenicity of tetanus toxoid, diphtheria toxoid and Cross Reacting Material 197 (CRM197) when used as carrier proteins in glycoconjugates. Human Vaccines & Immunotherapeutics 2016;12:664–667.

[58] Bröker M et al. Polysaccharide conjugate vaccine protein carriers as a "neglected valency" – Potential and limitations. Vaccine. 2017;35:3286–3294.

[59] Tashani M et al. Tetanus–diphtheria–pertussis vaccine may suppress the immune response to subsequent immunization with pneumococcal CRM197-conjugate vaccine (coadministered with quadrivalent meningococcal TT-conjugate vaccine): a randomized, controlled trial. Journal of Travel Medicine. 2017;24(4). Available at https://doi.org/10.1093/jtm/tax006, accessed July 2017.

[60] Findlow H and Borrow R. Interactions of conjugate vaccines and co-administered vaccines . Human Vaccines & Immunotherapeutics 2016; 12: 226–230.

[53] GlaxoSmithKline Biologicals SA Cervarix. Summary of Product Characteristics. Disponible à l'adresse: https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=179; consulté en mai 2017

[54] Merck. Gardasil. Summary of Product Characteristics. Disponible à l'adresse: https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=178; consulté en mai 2017

[55] Merck. Gardasil 9. Summary of Product Characteristics. European Medicines Agency. Disponible à l'adresse: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003852/WC500189111.pdf; consulté en mai 2017

[56] Adacel, package insert. Toronto, Ontario, Canada: Sanofi Pasteur Limited; Disponible à l'adresse: https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=315; consulté en juillet 2017

[57] Bröker M. Potential protective immunogenicity of tetanus toxoid, diphtheria toxoid and Cross Reacting Material 197 (CRM197) when used as carrier proteins in glycoconjugates. Human Vaccines & Immunotherapeutics 2016;12:664–667.

[58] Bröker M et al. Polysaccharide conjugate vaccine protein carriers as a "neglected valency" – Potential and limitations. Vaccine. 2017;35:3286–3294.

[59] Tashani M et al. Tetanus–diphtheria–pertussis vaccine may suppress the immune response to subsequent immunization with pneumococcal CRM197-conjugate vaccine (coadministered with quadrivalent meningococcal TT-conjugate vaccine): a randomized, controlled trial. Journal of Travel Medicine. 2017;24(4). Disponible à l'adresse: https://doi.org/10.1093/jtm/tax006, consulté en juillet 2017.

[60] Findlow H and Borrow R. Interactions of conjugate vaccines and co-administered vaccines . Human Vaccines & Immunotherapeutics 2016; 12: 226–230.

Cost-effectiveness

The cost-effectiveness of diphtheria toxoid given as combination diphtheria-tetanus-pertussis vaccine has been evaluated in the USA. It was estimated that in 1997, vaccination prevented 276 750 cases and 27 675 deaths from diphtheria.[61] DTwP and DTaP were found to be cost-saving from both societal and health-care system perspectives. Furthermore, an analysis of DTaP as part of the overall routine vaccination schedule in the USA in 2001 estimated savings of more than US$ 2 billion in direct costs and US$ 24 billion in total costs for cases of diphtheria prevented.[7, 62]

WHO position

All children worldwide should be immunized against diphtheria. Recent diphtheria outbreaks in several countries reflect inadequate vaccination coverage and have demonstrated the importance of sustaining high levels of coverage in childhood immunization programmes. Every country should seek to achieve timely vaccination with a complete primary series plus booster doses. Those who are unimmunized are at risk regardless of the setting.

Primary vaccination for infants

As diphtheria toxoid is almost exclusively available in fixed combinations with other antigens, immunization programmes need to harmonize immunization schedules between diphtheria, tetanus and pertussis. For vaccination of infants, DTP-containing vaccine often includes other antigens scheduled at the same time, such as Hib, IPV, and hep B, in order to reduce the number of injections.

A primary series of 3 doses of diphtheria toxoid-containing vaccine is recommended, with the first dose administered as early as 6 weeks of age. Subsequent doses should be given with an interval of at least 4 weeks between doses. The third dose of the primary series should be completed by 6 months of age if possible. If either the start or the completion of the primary series has been delayed, the missing doses should be given at the earliest opportunity with an interval of at least 4 weeks between doses.

The need for early infant vaccination with DTP-containing vaccine is principally to ensure rapid protection against pertussis, because severe disease and death from pertussis is almost entirely limited to the first weeks and months of life.

The 3-dose primary series is the foundation for building lifelong immunity to diphtheria. In view of the historical low coverage in many countries, providing the

[61] Ekwueme DU et al. Economic evaluation of use of diphtheria, tetanus, and acellular pertussis vaccine or diphtheria, tetanus, and whole-cell pertussis vaccine in the United States, 1997. Arch Pediatr Adolesc Med. 2000;154(8):797–803.

[62] Zhou F et al. Economic evaluation of the 7-vaccine routine childhood immunization schedule in the United States, 2001. Arch Pediatr Adolesc Med. 2005;159(12):1136–1144.

Rapport coût/efficacité

Une analyse a été effectuée aux États-Unis d'Amérique pour évaluer le rapport coût/efficacité de l'anatoxine diphtérique lorsqu'elle est administrée sous forme de vaccin antidiphtérique-antitétanique-anticoquelucheux combiné. On estime qu'en 1997, 276 750 cas de diphtérie et 27 675 décès ont pu être prévenus grâce à la vaccination.[61] Il a été déterminé que la vaccination par le DTCe et le DTCa permettait de réaliser des économies, tant sur le plan sociétal qu'au niveau des systèmes de santé. Une analyse réalisée aux États-Unis d'Amérique en 2001 a en outre estimé que l'administration de DTCa dans le cadre du calendrier général de vaccination systématique génère des économies de plus de US$ 2 milliards sur les coûts directs et de US$ 24 milliards sur les dépenses totales du fait des cas de diphtérie évités.[7, 62]

Position de l'OMS

Tous les enfants, dans le monde entier, devraient être vaccinés contre la diphtérie. Les récentes flambées de diphtérie apparues dans plusieurs pays sont le signe d'une couverture vaccinale insuffisante, montrant à quel point il est important de maintenir un haut niveau de couverture dans le cadre des programmes de vaccination infantile. Tous les pays doivent s'employer à assurer une vaccination en temps utile contre la diphtérie, avec une série complète de primovaccination suivie de doses de rappel. Les personnes non vaccinées sont exposées à un risque, quel que soit le milieu dans lequel elles vivent.

Primovaccination des nourrissons

Étant donné que l'anatoxine diphtérique est presque exclusivement disponible en association fixe avec d'autres antigènes il est nécessaire que les programmes de vaccination harmonisent leurs calendriers de vaccination contre la diphtérie, le tétanos et la coqueluche. Le vaccin à valence DTC destiné aux nourrissons comprend souvent d'autres antigènes dont l'administration est prévue au même moment, comme ceux du Hib, du VPI et de l'hépatite B, afin de réduire le nombre d'injections.

Il est recommandé d'effectuer une série de primovaccination par 3 doses de vaccin contenant l'anatoxine diphtérique, dont la première est administrée dès l'âge de 6 semaines. Les doses suivantes doivent être administrées avec un intervalle minimal de 4 semaines entre les doses. La troisième dose de la série de primovaccination devrait si possible être administrée au plus tard à l'âge de 6 mois. Si le début ou la fin de la série de primovaccination a été retardé, les doses manquantes doivent être administrées dans les meilleurs délais, avec un écart minimal de 4 semaines entre les doses.

La vaccination précoce des nourrissons par le vaccin à valence DTC vise essentiellement à garantir une protection rapide contre la coqueluche, car les cas graves et les décès dus à la coqueluche se produisent presque exclusivement durant les premières semaines et les premiers mois de la vie.

Les 3 doses de primovaccination servent de base à l'acquisition d'une immunité à vie contre la diphtérie. Compte tenu des taux traditionnellement faibles de la couverture vaccinale dans de

[61] Ekwueme DU et al. Economic evaluation of use of diphtheria, tetanus, and acellular pertussis vaccine or diphtheria, tetanus, and whole-cell pertussis vaccine in the United States, 1997. Arch Pediatr Adolesc Med. 2000;154(8):797–803.

[62] Zhou F et al. Economic evaluation of the 7-vaccine routine childhood immunization schedule in the United States, 2001. Arch Pediatr Adolesc Med. 2005;159(12):1136–1144.

primary series to persons who missed these doses in infancy is important. At any age those who are unvaccinated or incompletely vaccinated against diphtheria should receive the doses necessary to complete their vaccination.

Booster doses

Immunization programmes should ensure that 3 booster doses of diphtheria toxoid-containing vaccine are provided during childhood and adolescence. This series will provide protection throughout adolescence and adulthood. The diphtheria booster doses should be given in combination with tetanus toxoid using the same schedule, i.e at 12–23 months of age, 4–7 years of age, and 9–15 years of age, using age-appropriate vaccine formulations. Given the increasing life expectancy worldwide, it remains to be determined whether a booster dose later in life may be necessary to ensure life-long protection.[63]

National vaccination schedules can be adjusted within the age limits specified above to enable programmes to tailor their schedules based on local epidemiology, the timing of vaccination doses and other scheduled interventions, and on any other programmatic issues.

With an increasing proportion of children attending school worldwide, immunization programmes targeting school-age children are increasingly important. This is particularly relevant for the booster doses of diphtheria toxoid-containing vaccine. A second booster dose could be provided around the age of primary school entry and a third booster dose on completion of primary school or start of secondary school. Screening of vaccination status at school entry can also provide an effective opportunity to catch up on any missed vaccinations and reduce the risk of vaccine-preventable disease outbreaks in schools. A school-based immunization approach may be linked to other important health interventions for children and adolescents.

Catch-up schedule in children aged ≥1 year, adolescents and adults

Opportunities should be taken to provide or complete the 3-dose diphtheria toxoid-containing vaccine series for those who were not vaccinated, or incompletely vaccinated, during infancy. For previously unimmunized children aged 1–7 years, the recommended primary schedule is 3 doses with a minimum interval of 4 weeks between the first and the second dose, and an interval of at least 6 months between the second and third dose, using DTP-containing vaccine. Using Td or Tdap combination vaccine, the recommended schedule for primary immunization of older children (>7 years), adolescents and adults is 3 doses with a minimum interval of 4 weeks between the first and the second dose, and an interval of at least 6 months

nombreux pays, il est important d'administrer les doses de primovaccination aux sujets qui n'en ont pas bénéficié lorsqu'ils étaient nourrissons. Quel que soit leur âge, les personnes non vaccinées ou partiellement vaccinées contre la diphtérie devront recevoir les doses nécessaires pour achever la série de vaccination.

Doses de rappel

Les programmes de vaccination doivent veiller à ce que 3 doses de rappel d'anatoxine diphtérique soient administrées au cours de l'enfance et de l'adolescence, conférant une protection durant l'adolescence et l'âge adulte. Il convient d'administrer ces doses de rappel en association avec l'anatoxine tétanique selon un calendrier harmonisé, c'est-à-dire à l'âge de 12-23 mois, 4-7 ans et 9-15 ans, au moyen de vaccins dont la formulation est adaptée à l'âge des sujets. Compte tenu de l'allongement de l'espérance de vie à l'échelle mondiale, il reste à déterminer si l'administration d'une dose de rappel à un stade ultérieur de la vie est nécessaire pour garantir une protection à vie.[63]

Les calendriers nationaux de vaccination peuvent être ajustés dans les limites d'âge énoncées ci-dessus pour permettre aux programmes d'adapter leurs calendriers à l'épidémiologie locale, à la chronologie des doses vaccinales et d'autres interventions prévues, ainsi qu'à tout autre enjeu programmatique particulier.

Compte tenu de la proportion croissante d'enfants qui sont scolarisés dans le monde, les programmes de vaccination ciblant les enfants d'âge scolaire revêtent une importance grandissante. Cela vaut particulièrement pour les doses de rappel de vaccin contenant l'anatoxine diphtérique, la deuxième dose de rappel pouvant être administrée à un âge correspondant plus ou moins à l'entrée en école primaire et la troisième coïncidant avec la fin de l'école primaire ou le début de l'école secondaire. La vérification du statut vaccinal des enfants au début de la scolarité peut également être une occasion opportune d'assurer une vaccination de rattrapage en cas de doses omises et de réduire le risque de flambée de maladies à prévention vaccinale en milieu scolaire. La vaccination en milieu scolaire peut être associée à d'autres interventions sanitaires importantes pour l'enfant et l'adolescent.

Calendrier de rattrapage chez les enfants de ≥1 an, les adolescents et les adultes

Chez les sujets qui n'ont pas été vaccinés ou qui n'ont été que partiellement vaccinés contre la diphtérie lorsqu'ils étaient nourrissons, il convient de saisir toutes les occasions pour administrer ou compléter la série de 3 doses d'anatoxine diphtérique. Pour les enfants de 1-7 ans non préalablement vaccinés, le calendrier de primovaccination recommandé est de 3 doses, avec un intervalle minimal de 4 semaines entre la première et la deuxième dose et d'au moins 6 mois entre la deuxième et la troisième dose, au moyen d'un vaccin à valence DTC. Pour la primovaccination des enfants plus âgés (>7 ans), des adolescents et des adultes par le vaccin combiné Td ou Tdca, le calendrier recommandé est de 3 doses, avec un intervalle minimal de 4 semaines entre la première et la deuxième dose et d'au moins 6 mois entre la deuxième et la troisième dose. L'admi-

[63] Evidence to recommendation table. Evidence to recommendation table – Available at http://www.who.int/immunization/policy/position_papers/diphtheria_evidence_recommendation_table.pdf

[63] Evidence to recommendation table. Disponible à l'adresse: http://www.who.int/immunization/policy/position_papers/diphtheria_evidence_recommendation_table.pdf

between the second and a third dose. Two subsequent booster doses using Td or Tdap combination vaccines are needed with an interval of at least 1 year between doses (see Tetanus vaccines: WHO position paper).[64]

As responses to booster vaccination can still be elicited after intervals of 25–30 years, it is not necessary to repeat a primary vaccination series when booster doses have been delayed.

To further promote immunity against diphtheria, the use of Td rather than TT is recommended during pregnancy to protect against maternal and neonatal tetanus in the context of prenatal care, and when tetanus prophylaxis is needed following injuries. Opportunities for catch-up vaccination could include the delivery of diphtheria toxoid-containing vaccine with other vaccinations such as HPV vaccination for adolescents, or during routine vaccination on entry into military services or other institutions with similar requirements.

Special risk groups

Diphtheria toxoid-containing vaccines can be used in immunocompromised persons including HIV-infected individuals, though the immune response may be inferior to that in fully immunocompetent persons. All HIV-infected children should be vaccinated against diphtheria following the vaccine recommendations for the general population. A need for additional booster doses for HIV-infected persons or those with other congenital or acquired immunodeficiency has not been established.

Vaccine co-administration

Administration of the first 3 doses of diphtheria toxoid-containing vaccine together with other childhood vaccines does not interfere with the response to any of these other antigens following either primary or booster vaccination. All vaccines that are consistent with the child's prior immunization history can be administered during the same visit. In particular, diphtheria toxoid-containing vaccine can be co-administered with BCG, HPV, IPV, OPV, PCV, rotavirus, measles, mumps and rubella vaccine and meningococcal conjugate vaccines. CRM-conjugate vaccines (such as Hib, pneumococcal and meningococcal vaccines) can be administered with or before, but not after, diphtheria toxoid-containing vaccine in the routine vaccination programme.

When 2 vaccines are given during the same visit, they should be injected in different limbs. When 3 vaccines are given, 2 can be injected in the same limb and the third should be injected in the other limb. Injections in the same limb should be at least 2.5 cm apart so that local reactions can be differentiated. There are effective recommended methods to mitigate pain at the time of vaccination.[65]

nistration ultérieure de 2 doses de rappel de vaccin combiné Td ou Tdca est nécessaire, avec un intervalle d'au moins 1 an entre les doses (voir Note de synthèse: position de l'OMS sur les vaccins antitétaniques).[64]

Comme une réponse à la vaccination de rappel peut encore être obtenue au bout de 25 à 30 ans, il n'est pas nécessaire de répéter la série de primovaccination en cas de retard des rappels.

Pour renforcer encore l'immunité contre la diphtérie, il est recommandé d'utiliser le Td plutôt que le TT lorsqu'une vaccination antitétanique est administrée durant la grossesse à des fins de protection contre le tétanos maternel et néonatal, ainsi que lorsqu'une prophylaxie antitétanique est nécessaire à la suite de blessures. La vaccination de rattrapage par l'anatoxine diphtérique peut être assurée à l'occasion d'autres vaccinations, notamment la vaccination anti-PVH chez l'adolescent ou la vaccination systématique requise au début du service militaire ou exigée par d'autres institutions.

Groupes à risque particuliers

Les vaccins contenant l'anatoxine diphtérique peuvent être administrés aux personnes immunodéprimées, y compris celles qui sont infectées par le VIH, mais la réponse immunitaire suscitée peut être plus faible que chez les sujets pleinement immunocompétents. Tous les enfants présentant une infection à VIH doivent être vaccinés contre la diphtérie conformément aux recommandations vaccinales applicables à la population générale. La nécessité de doses de rappel supplémentaires chez les personnes infectées par le VIH ou présentant une immunodéficience congénitale ou acquise n'a pas été établie.

Coadministration avec d'autres vaccins

L'administration simultanée des 3 premières doses d'anatoxine diphtérique avec d'autres vaccins administrés pendant l'enfance n'interfère pas avec la réponse immunitaire à l'un quelconque de ces autres antigènes, que ce soit après la primovaccination ou la vaccination de rappel. Tous les vaccins compatibles avec les antécédents vaccinaux de l'enfant peuvent être administrés lors de la même visite. En particulier, le vaccin à base d'anatoxine diphtérique peut être coadministré avec les vaccins BCG, anti-PVH, VPI, VPO, VPC, antirotavirus, antirougeoleux-antiourlien-antirubéoleux et antiméningococcique conjugué. Dans le programme de vaccination systématique, les vaccins conjugués à la protéine CRM (comme les vaccins anti-Hib, antipneumococcique et antiméningococcique) peuvent être administrés soit avant, soit en même temps que le vaccin contenant l'anatoxine diphtérique, mais pas après.

Lorsque 2 vaccins sont administrés au cours d'une même visite, ils doivent être injectés dans des membres différents. Si 3 vaccins sont administrés, 2 peuvent être injectés dans un même membre, le troisième devant alors être injecté dans l'autre membre. Les injections pratiquées sur le même membre doivent être espacées d'au moins 2,5 cm pour pouvoir distinguer les réactions locales. Il existe des méthodes efficaces recommandées pour atténuer la douleur au moment de la vaccination.[65]

[64] See No. 6, 2017, pp. 53–76.

[65] See No. 39, 2015, pp. 505–510.

[64] Voir N° 6, 2017, pp. 53-76.

[65] Voir N° 39, 2015, pp. 505-510.

Health-care workers

In endemic settings and outbreaks, health-care workers may be at greater risk of diphtheria than the general population. Therefore, special attention should be paid to immunizing health-care workers who may have occupational exposure to *C. diphtheriae*. All health-care workers should up to date with immunization as recommended in their national immunization schedules.

Travellers

Travellers are generally not at special risk of diphtheria, unless they travel to an endemic country or outbreak setting. They should follow the vaccine recommendations for the general population and ensure they are up to date with their diphtheria vaccinations before travelling.

Surveillance

Efficient national surveillance and reporting systems, with district-level data analysis, are essential in all countries. Countries should report all available data on diphtheria cases, including data from their integrated disease surveillance and response databases. Cases of diphtheria caused by *C. diphtheriae* (and *C. ulcerans*, where laboratory capacity is available) should be reported for countries with established capability for laboratory confirmation.

Epidemiological surveillance ensuring early detection of diphtheria outbreaks should be in place in all countries. All countries should have access to laboratory facilities for reliable identification of toxigenic *C. diphtheriae*. Laboratory capacity should be strengthened where necessary.

Research

Immunity gaps may occur in older age groups due to waning immunity, but available data are insufficient to warrant global recommendations on diphtheria vaccination in these groups. Further studies, including serosurveys, are required to generate information on the duration of protection and the possible need for booster doses in older age groups.

The impact of maternal Td or Tdap vaccination on infant immune responses to conjugate vaccines containing diphtheria toxoid or CRM has not been adequately studied. ■

Agents de santé

Dans les situations d'endémie et de flambée, les agents de santé peuvent être exposés à un risque de diphtérie plus important que la population générale. Il convient donc de porter une attention particulière à la vaccination des agents de santé susceptibles de subir une exposition professionnelle à *C. diphtheriae*. Tous les agents de santé doivent être à jour dans leurs vaccinations, conformément au calendrier national de vaccination.

Voyageurs

Les voyageurs ne sont généralement pas exposés à un risque particulier de diphtérie, sauf s'ils se rendent dans un pays d'endémie ou une zone de flambée. Ils doivent respecter les recommandations vaccinales applicables à la population générale et vérifier que leur vaccination antidiphtérique est à jour avant de voyager.

Surveillance

Il est essentiel que tous les pays disposent de systèmes nationaux efficaces de surveillance et de notification, permettant l'analyse des données à l'échelon des districts. Les pays doivent communiquer toutes les données dont ils disposent sur les cas de diphtérie, y compris celles provenant de leurs bases de données de surveillance intégrée des maladies et de riposte. Dans les pays possédant des capacités établies de confirmation en laboratoire, les cas de diphtérie dus à *C. diphtheriae* (et *C. ulcerans*, si les moyens de laboratoire le permettent) doivent être notifiés.

Un système de surveillance épidémiologique, garantissant une détection précoce des flambées de diphtérie, doit être en place dans tous les pays. Il importe que tous les pays aient accès à des installations de laboratoire permettant une identification fiable de la bactérie *C. diphtheriae* toxinogène. Les moyens de laboratoire seront renforcés si nécessaire.

Recherche

Il est possible que des lacunes immunitaires se manifestent dans les tranches d'âge plus avancées en raison d'un déclin de l'immunité. Toutefois, les données disponibles ne sont pas suffisantes pour justifier une recommandation mondiale sur la vaccination antidiphtérique dans ces classes d'âge. Des études supplémentaires, dont des enquêtes sérologiques, sont nécessaires pour recueillir des informations sur la durée de la protection et sur le besoin éventuel d'administrer des doses de rappel aux groupes plus âgés.

Les effets de la vaccination maternelle par le Td ou le Tdca sur la réponse immunitaire du nourrisson aux vaccins conjugués contenant l'anatoxine diphtérique ou la protéine CRM n'ont pas été suffisamment étudiés. ■

WHO African Region Immunization Technical Advisory Group: Call for nominations

The WHO Regional Office for Africa is soliciting proposals for nominations for current vacancies on its Regional Immunization Technical Advisory Group (RITAG). Nominations are required to be submitted no later than 4 September 2017. Nominations will be carefully reviewed by the RITAG membership selection panel

Groupe de travail technique sur la vaccination dans la Région africaine de l'OMS: Appel à candidatures

Le Bureau régional de l'OMS pour l'Afrique lance un appel à proposition de candidatures en vue de pourvoir aux vacances actuelles au sein de son Groupe consultatif technique régional sur la vaccination (RITAG). Les propositions de candidatures doivent être soumises au plus tard le 4 septembre 2017. Les candidatures seront examinées attentivement par le panel de

which will propose the selection of nominees for appointment to the WHO Regional Director for Africa.

RITAG serves as the principal advisory group to the WHO Regional Office for Africa for strategic guidance on vaccines and immunization. RITAG reports directly to the WHO Regional Director for Africa and advises the Regional Director on overall regional policies and strategies, ranging from vaccine and technology research and development, to delivery of immunization services and linkages between immunization and other health interventions. Its remit is not restricted to childhood immunization but extends to all vaccine-preventable diseases as well as all age groups.

All members are acknowledged experts with an outstanding record of achievement in their own field and an understanding of the immunization issues covered by the RITAG. They have a responsibility to provide WHO with high quality, well-considered advice and recommendations on matters described in the attached terms of reference.

RITAG members will represent a range of professional affiliations (i.e. academia, medical profession, clinical practice, research institutes, and governmental bodies including national immunization programmes, public health departments and regulatory authorities); and major areas of expertise (e.g. influenza control, diarrhoeal diseases, respiratory diseases, research, biologics, and safety).

Members will be selected on the basis of their qualifications, experience and ability to contribute to the accomplishment of the RITAG objectives. Appointment of RITAG members will be made by the WHO Regional Director for Africa upon the proposal of the selection panel. Members of the RITAG are appointed to serve for an initial term of 3 years, renewable once. Consideration is given to ensuring appropriate geographical representation and gender balance.

RITAG normally meets twice a year rotating between the WHO Regional Office in Brazzaville (Congo) and a country in the region. In addition, members may be asked to contribute to RITAG working groups, and will be fully engaged in the preparation of each meeting.

Please submit your nominations along with a letter of support by e-mail to ritag@who.int. Self-nominations as well as nominations suggested by third party individuals or organizations will be accepted. Nominees will be asked to confirm their interest, availability and commitment to serve on RITAG, to provide a curriculum vitae, a letter of motivation highlighting what their contribution to RITAG could be, and a completed declaration of interests form before their nomination will be considered by the selection panel.

Please share this request with anyone who may be interested in nominating an individual to serve as a member of this Group. ■

sélection des membres du RITAG, qui soumettra la liste des candidats retenus à la Directrice régionale de l'OMS pour l'Afrique.

Le RITAG fait office de principal groupe consultatif du Bureau régional de l'OMS pour l'Afrique chargé de formuler des orientations stratégiques dans le domaine des vaccins et de la vaccination. Le RITAG rend compte directement à la Directrice régionale et lui adresse des conseils relatifs aux politiques et stratégies régionales globales de vaccination, allant de la recherche-développement sur les vaccins et la technologie à la prestation des services de vaccination, sans oublier les liens entre la vaccination et d'autres interventions sanitaires. Le mandat de ce groupe de travail ne se limite pas à la vaccination des enfants, mais concerne toutes les maladies à prévention vaccinale et tous les groupes d'âge.

Le groupe de travail se compose d'experts de renom qui se sont distingués par des réalisations notables dans leurs domaines de compétence respectifs et qui ont une parfaite connaissance des questions de vaccination couvertes par le RITAG. Ces experts sont chargés de prodiguer des conseils à l'OMS et d'émettre des recommandations de qualité et mûrement réfléchies sur les questions décrites dans les termes de référence ci-joints.

Les membres du RITAG représentent un éventail d'affiliations professionnelles (universitaires, professions médicales, spécialistes de la pratique clinique, instituts de recherche et organismes publics englobant des programmes de vaccination, des ministères de la santé publique et des autorités de réglementation) et sont spécialisés dans de grands domaines d'expertise (lutte contre la grippe, maladies diarrhéiques, affections respiratoires, recherche, biologie, innocuité des vaccins, etc.).

Les membres du RITAG sont choisis sur la base de leurs qualifications, de leur expérience et de leur capacité à œuvrer à l'atteinte des objectifs du groupe de travail. La Directrice régionale de l'OMS pour l'Afrique nomme les membres du RITAG sur proposition du panel de sélection. Les membres du RITAG sont nommés pour un mandat de 3 ans, renouvelable une seule fois. Le choix de ces membres doit respecter les principes de la représentation géographique équitable et de la parité homme-femme.

Le RITAG se réunit normalement 2 fois par an, de façon tournante entre le siège du Bureau régional, à Brazzaville (Congo), et un pays de la Région. Ses membres sont tenus de contribuer aux groupes de travail et de participer activement aux préparatifs de chaque réunion.

Les candidatures des personnes nominées, accompagnées d'une lettre de soutien, doivent être envoyées par courriel à l'adresse ritag@who.int. Les candidatures présentées par le candidat lui-même et les candidatures proposées par de tierces personnes ou par des organisations sont acceptées. Les candidats retenus devront confirmer leur intérêt, leur disponibilité et leur engagement à servir au sein du RITAG. Ils devront aussi soumettre leur curriculum vitae, une lettre de motivation faisant ressortir leur contribution éventuelle au RITAG et un formulaire de déclaration d'intérêt dûment renseigné avant que leur désignation ne puisse être examinée par le panel de sélection.

Vous voudrez bien diffuser le présent appel à candidatures auprès de toutes les personnes qui pourraient souhaiter désigner un individu pour servir au sein du RITAG. ■

Vaccination in Acute Humanitarian Emergencies

A FRAMEWORK FOR DECISION MAKING

World Health Organization

EXECUTIVE SUMMARY

Humanitarian emergencies, regardless of type and cause, have a number of common risk factors for communicable diseases inextricably linked to excess risk of morbidity and mortality which can come from vaccine–preventable diseases (VPDs). The reduction of VPDs is a significant aim of public-health interventions during crises.

The WHO Strategic Advisory Group of Experts (SAGE) on Immunization carried out a comprehensive review of evidence on vaccination decision-making processes and considerations in humanitarian emergencies. This review resulted with decision-making framework which provides a transparent, evidence-based, and rigorous methodology for deciding on vaccination options in acute humanitarian emergencies. It consists of three essential steps: 1) assessing the local epidemiological risks of VPDs among the affected population, 2) vaccine selection and characteristics to consider, and 3) local contextual constraints that further assist in effective and timely decisions. The diagram below provides a schematic representation of this three-step approach in decision-making process.

This framework is intended to guide decision making on vaccination interventions immediately after the onset or during planning in anticipation of a possible or likely acute emergency. It may be applied in emerging humanitarian emergencies, or crisis of short duration, and in long-standing crisis and conflicts resulting in protracted humanitarian emergencies. The concept of "acute" emergency does not imply that the emergency in itself is short-lived, as in a protracted crisis situations can emerge and be considered as "acute". An acute emergency signifies a situation meeting one or more of the following conditions: sudden unplanned displacement of a large proportion of the population, direct exposure of the civilian population to new or exacerbated and sustained episodes of armed conflict, impending or already occurred sudden deterioration of nutritional status, natural or industrial disasters, and/or sudden breakdown of critical administrative and management functions which result in large-scale disruption of public health and related services.

This decision-making framework is intended for senior-level government and partner organization officials who are expected to work together to reach a decision regarding the need of vaccine antigen(s) in a given humanitarian emergency. It makes part of a package which also includes "Vaccination in Humanitarian Emergencies Implementation Guide". Both documents are supported with electronic versions to ensure that the most up-to-date vaccine and disease-specific data, and references to additional information and guidance are provided.