



**World Health
Organization**

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

SAGE

April 2019

**Strategic Advisory Group of Experts
on Immunization
02 - 04 April 2019**

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

SAGE April 2019

This booklet contains key background documents for the
meeting of the
Strategic Advisory Group of Experts (SAGE) on Immunization
02 - 04 April 2019

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

[SAGE/meetings/2019/April](https://www.who.int/sage/meetings/2019/April)

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Draft Agenda

Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization
02 - 04 April 2019
Centre International de Conférences Genève (CICG), Geneva, Switzerland

Tuesday, 02 April 2019

Time	Session	Purpose of session, target outcomes and questions for SAGE	Duration
10:00	Welcome – introduction of participants A. CRAVIOTO. Chair of SAGE.		20 min.
10:20	Report from Director, IVB and Regional Updates - Session 1 Global report including key updates and challenges from regions. K. O'BRIEN. WHO. 30 min. Discussion: 1h	FOR INFORMATION	1h 30 min.
10:50	Coffee/Tea break	Break	30 min.
11:20	Cont. Session 1 Discussion: 1 h	FOR INFORMATION	
12:20	Report from Gavi, the Vaccine Alliance - Session 2 Report from Gavi, the Vaccine Alliance. S. BERKLEY. Gavi, the Vaccine Alliance. 15 min. Discussion: 25 min.	FOR INFORMATION	40 min.
13:00	Lunch	Break	1h 30 min.
14:30	Quality and Use of Immunization and Surveillance Data - Session 3 Introduction to the Working Group (WG), its terms of reference and work done. J. JAWAD. SAGE member. 5 min. Methods and Landscape: Current state of reporting & data, existing guidance and data quality. Data quality and use framework & SAGE WG Perspective. H. SCOBIE.	FOR DECISION The session will focus on the major WG findings for each one of its 6 terms of reference, on the proposed way forward and on the draft recommendations to be endorsed by SAGE.	2h

<p>US Centers for Disease Control and Prevention (CDC). 15 min.</p> <p>Barriers and solutions to data quality and use: Governance, health workers, & program management, data use/continuous quality improvement (CQI), tools & Innovations. N RAHIMI. Shifo and M. EDELSTEIN. Public Health England (PHE). 20 min.</p> <p>Gaps, research and way forward. M. EDELSTEIN. PHE. 5 min.</p> <p>Questions and clarifications: 40 min.</p> <p>Working Group recommendations. J. JAWAD. SAGE member. 10 min.</p> <p>Discussion: 20 min.</p>			
16:30	Coffee/tea break	Break	30 min.
17:00	Report from the Global Advisory Committee on Vaccine Safety (GACVS) meeting 5-6 December 2018– Session 4	FOR INFORMATION	30 min.
	Immunization stress-related responses. M. BALAKRISHNAN. WHO. 15 min.	Immunization stress-related responses: Presentation of findings and guidance to countries.	
	Discussion: 15 min.		
17:30	End of Day		
17:45	Cocktail		

Wednesday, 03 April 2019

9:00	Update on the development of a Post-2020 Immunization Strategy. - Session 5	FOR INFORMATION AND DISCUSSION	2h
	Lessons learned from the Global Vaccine Action Plan (GVAP) – interim findings. N. MACDONALD. SAGE member. 20 min.	SAGE will be presented with the interim results of the evaluation of the Decade of Vaccines GVAP and lessons learnt.	
	Discussion: 40 min.		
10:00	Coffee/tea break	Break	30 min.
10:30	Cont. Session 5	SAGE will further be updated on the development of a post 2020	

Update on the development and emerging priorities for the post 2020 immunization strategy. P. LYDON. WHO. 15 min.		immunization strategy.	
11:30	<p>Discussion: 45 min.</p> <p>Session Immunization Partners - Session 6</p> <p>Report from the Coalition for Epidemic Preparedness Innovations (CEPI). R. HATCHETT. CEPI. 20 min.</p> <p>Discussion: 20 min.</p>	FOR INFORMATION	40 min.
12:10	Lunch	Break	1h
13:10	<p>Malaria Vaccine - Session 7</p> <p>Introduction to the session.</p> <p>F. WERE. Member of SAGE and of the Programme Advisory Group for the Malaria Vaccine Implementation Programme (MVIP). 5 min.</p> <p>Brief update on the Malaria Vaccine Implementation Programme (MVIP) and review of data informing the Framework for Policy Decision on RTS,S/AS01.</p> <p>M. HAMEL. WHO. 20 min.</p> <p>Recommendations of the SAGE/Malaria Programme Advisory Committee (MPAC) Working Group on the Framework for Policy Decision on RTS,S/AS01.</p> <p>P. SMITH. Chair of the SAGE/MPAC Framework WG. 20 min.</p> <p>Discussion: 75 min.</p>	<p>FOR INFORMATION AND DECISION</p> <p>For information:</p> <ul style="list-style-type: none"> Update on the Malaria Vaccine Implementation Programme Overview of new data on RTS,S/AS01 that informed the framework development <p>For decision:</p> <ul style="list-style-type: none"> Present SAGE and MPAC with the recommendations by the SAGE/MPAC Working Group on the Framework for Policy Decision on RTS,S/AS01 and request SAGE/MPAC's consideration of the proposed Framework. 	2h
15:10	Coffee/tea break	Break	30 min.
15:40	<p>Polio the last mile - Session 8</p> <p>Update from the Global Polio Eradication Initiative including presentation of "Polio Eradication, Certification, and Integration: The Endgame Strategy 2019-2023." M. ZAFFRAN. WHO. 30 min.</p> <p>Presentation of draft "Guidelines for surveillance of vaccine-derived polioviruses excreted by persons with primary immunodeficiency diseases". O. MACH. WHO. 10 min.</p> <p>Report from SAGE Polio Working Group including presentation of the "Poliovirus Containment Breach Protocol". P. FIGUEROA. SAGE Polio Working Group Member. 20 min.</p> <p>Discussion: 60 min.</p>	<p>FOR INFORMATION AND DECISION</p> <p>SAGE will be informed on the current status of the polio eradication program; "Polio Eradication, Certification, and Integration: The Endgame Strategy 2019-2023".</p> <p>SAGE will be asked to recommend on and endorse:</p> <ul style="list-style-type: none"> Guidelines for surveillance of vaccine-derived polioviruses excreted by persons with primary immunodeficiency diseases; Poliovirus Containment Breach Protocol. 	2h
17:40	End of day		

Thursday, 04 April 2019

09:00	Meningococcal vaccines: Global Strategy - Session 9 Presentation on the Defeating Meningitis by 2030 strategy. Overview and process. M-P. PREZIOSI. WHO. 15 min. Discussion: 45 min.	FOR INFORMATION	1h
10:00	Coffee/tea break	Break	30 min.
10:30	Ebola vaccines – Session 10 Update on Ebola vaccine interim recommendations and on the ongoing response to the outbreak. A.-M. HENAO-RESTREPO. WHO. 15 min. Questions: 15 min. Review of evidence on risks and benefits of vaccination of children below one year of age and of lactating women. TBD. 30 min. Discussion: 1h.	FOR INFORMATION AND DECISION For information: current vaccine recommendations and ongoing response. For decision: Assessment of benefit-risk profiles of vaccinating children below one year of age and lactating women.	2h
12:30	Update on the SAGE Evaluation –Session 11 Rational. J. HOMBACH. WHO. 5 min. Process. C. MANTEL. MMGH Consulting. 10 min. Findings and preliminary recommendations. H. NOHYNEK. National Institute for Health and Welfare (THL) Finland. 15 min. Discussion: 15 min.	FOR INFORMATION Presentation of process and findings from the evaluation of SAGE.	45 min.
13:15	Closing		20 min.
13:35	End of meeting		

Current SAGE Members

Aggarwal, Prof Rakesh Professor Department of Gastroenterology Lucknow India
Cravioto, Prof Alejandro (SAGE chair) Professor Facultad de Medicina Universidad Nacional Autónoma de México Puerto Vallarta Mexico
Jani, Dr Ilesh Director General Instituto Nacional de Saúde Maputo Mozambique
Jawad, Dr Jaleela Head of immunization group Public Health Directorate, Ministry of Health Manama Bahrain
Jee, Dr Youngmee Director General Center for Infectious Disease Research Cheongju Republic of Korea
Johansen, Dr Kari (SAGE vice-chair) Expert in Vaccinology European Centre for Disease Prevention and Control Solna Sweden
MacDonald, Prof Noni Professor of Pediatrics Division of Pediatric Infectious Diseases, Dalhousie University Halifax, Nova Scotia Canada
Madhi, Prof Shabir Professor of Vaccinology University of the Witwatersrand Johannesburg South Africa
McIntyre, Prof Peter Professor in the Discipline of Child and Adolescent Health and the School of Public Health University of Sydney Australia
Mohsni, Dr Ezzeddine Senior Technical Adviser Global Health Development (GHD) The Eastern Mediterranean Public Health Network (EMPHNET) Amman Jordan

Neuzil, Prof Kathleen

Director
Center for Vaccine Development and Global Health
University of Maryland School of Medicine
Baltimore, Maryland
USA

Pollard, Prof Andrew J.

Professor
Department of Paediatrics, University of Oxford
Oxford
United Kingdom

Qadri, Dr Firdausi

Senior Director
Infectious Diseases Division
Dhaka
Bangladesh

Turner, Dr Nikki

Associate Professor
General Practice and Primary Care
Wellington
New Zealand

Were, Prof Fredrick

Dean
School of Medicine
Nairobi
Kenya

Strategic Advisory Group of Experts (SAGE)

Terms of reference

Functions

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

SAGE advises the WHO Director-General specifically on the:

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

Membership

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

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

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

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

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

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

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

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

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

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

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

1. failure to attend two consecutive SAGE meetings;

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

Meetings and operational procedures

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

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

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

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

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

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

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

Roles and responsibilities of SAGE members

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

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

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

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

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

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

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

SAGE Working Groups are established as resources intended to increase the effectiveness of SAGE deliberations by reviewing and providing evidence-based information and options for recommendations together with implications of the various options to be discussed by SAGE during one of its biannual meetings. These Working Groups are normally established on a time-limited basis to help address specific questions identified by SAGE when the issue is particularly

complicated or time-consuming and could not be addressed by an existing standing WHO advisory committee. The need and charge for a Working Group is discussed and agreed during SAGE meetings. The purpose, structure and functioning of the Working Groups is described in detail in Annex 3 (Purpose, structure and functioning of the Strategic Advisory Group of Experts on Immunization (SAGE) Working Groups).

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

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

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

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

DECLARATION OF INTERESTS FOR WHO EXPERTS

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

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

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

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

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

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

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

Name: Institution: Email:

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

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

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

EMPLOYMENT AND CONSULTING

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

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

RESEARCH SUPPORT

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

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

INVESTMENT INTERESTS

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

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

INTELLECTUAL PROPERTY

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

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

PUBLIC STATEMENTS AND POSITIONS (during the past 4 years)

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

ADDITIONAL INFORMATION

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

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

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

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

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

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

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

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

Date: _____

Signature_____



CONFIDENTIALITY UNDERTAKING

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

Signed:

Signature.....

Name.....
(print or type)

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

Purpose and decision to establish a SAGE Working Group

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

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

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

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

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

Working Group composition and selection of membership

Each Working Group should include two or more SAGE members (one of whom functions as Chair), and additional subject matter experts serving in their own individual capacity and with a view to meet the identified needed expertise for the group. SAGE members and other experts who have identified conflicts of interest cannot serve on the Working Group charged with responsibility in the identified areas of conflict. WHO staff (one of whom functions as the Working Group technical lead serve as secretariat to the Working Group. In some instances other UN or non UN agencies can be co-opted as part of the secretariat.

For the selection of experts to serve on a Working Group, a public call for nomination for Working Group members will be posted on the SAGE website together with the relevant TORs of the Working Group and indication of the desirable expertise. SAGE members, regional offices, diplomatic missions, WHO staff and key partner organizations will also be approached to propose potential nominations. Nominees will be requested to provide both a Curriculum Vitae and a completed Declaration of Interests form prior to being considered for membership on the Working Group.

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

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

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

On rare occasions joint reviews of evidence by SAGE and another area WHO advisory committee (focusing on another area than immunization but with expertise and relevance to the topic being considered) may have to be organized. As a result a SAGE Working Group may be formed in conjunction with this other solicited advisory committee. In this instance members of the solicited advisory committee might also be co-opted on the Working Group and a Working Group co-Chair may be appointed from among members of this other advisory committee. In this case, the selection of Working Group members will

equally involve the Chair and secretariat of the solicited advisory committee.

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

Working Group Process

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

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

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

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

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

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

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

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

Working Groups are encouraged to submit publications of the reviews of the scientific evidence to peer-review journals. This

could be done before or after the SAGE meetings. If published before the SAGE meeting, the publications should reflect the scientific evidence only and not pre-empt the view of SAGE with stating the proposed recommendations and if published after the SAGE meeting should reference the SAGE report.

Management of Conflict of Interest

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

CURRENT SAGE WORKING GROUPS

Disclaimer: this list includes the current working groups and their active members. These working groups are listed in the order in which they were established. For the complete history of current and previous working groups and their membership from inception, please visit the SAGE website (http://www.who.int/immunization/sage/working_mechanisms/en/).

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

Terms of Reference

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

Composition

SAGE Members

- Dr Ilesh Jani, (Co-Chair of the Working Group), National Institute of Health, Mozambique
- Ezzeddine Mohsni, Senior Technical Adviser in Global Health Development/ Eastern Mediterranean Public Health Network (Working Group member from February 2019)

Experts

- Yagob Al-Mazrou, Secretary General - Health Services Council of the Kingdom of Saudi Arabia, Saudi Arabia
- Guillaume Chabot-Couture, Director of research, global development, Institute for Disease Modeling , Seattle, WA, USA
- Shelley Deeks, Chief, Communicable Diseases, Emergency Preparedness and Response, Public Health Ontario, Toronto, Canada
- Peter Figueroa University of the West Indies, Jamaica (Co-Chair of Working Group and SAGE member until April 2015)
- Nick Grassly, Imperial College, UK
- Jeffrey Mphahlele, Vice President for Research, South African Medical Research Council, Pretoria, South Africa
- Jean-Marc Olivé, Chair of the Technical Advisory Group (TAG), Pakistan, Afghanistan, Horn of Africa and Lake Chad
- Walter Orenstein, Emory University, USA
- Jacob John Thekkekara, Advisor, Christian Medical College Hospital, Vellore, India Kimberley Thompson, Kids Risk Project, Harvard School of Public Health, USA
- Khalequ Zaman, Scientist and Epidemiologist, International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh

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)
- Ezzeddine Mohsni (joining SAGE in January 2019), Senior Technical Adviser in GHD/EMPHNET (Global Health Development / Eastern Mediterranean Public Health Network)

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)
- Yagob Al-Mazrou, Health Services Council, Saudi Arabia. (Former SAGE member 2012-2017)
- 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)
- Qinqian Zhao, Xiamen University, China. (Member of the Working Group from May 2016)

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

Terms of Reference

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

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

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

Composition

SAGE Members

- Fred Were, University of Nairobi, Kenya. (Co-Chair of the Working Group from April 2016)
- Shabir Mahdi, Professor of Vaccinology at the University of the Witwatersrand, Johannesburg, South Africa. (Serves as SAGE member on the Working Group as of January 2019)

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)
- Jean-Paul Jemmy, Médecins Sans Frontières, Belgium.
- Ann Kelly, University of Exeter, United Kingdom.
- Keymanthri Moodley, Stellenbosch University, South Africa.
- Diop Ndack, University Cheikh Anta Diop, Senegal.
- Cesar Velasco Muñoz, Hospital Clínico Lozano Blesa, Spain.
- 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)

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)
- Peter McIntyre, University of Sydney, Australia

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 Sanders, National Institute for Public Health and the Environment, The Netherlands
- Dafrossa Lyimo, Ministry of Health, Tanzania
- Elizabeth Miller, Public Health England, United Kingdom
- Edward Kim Mulholland, Murdoch Childrens Research Institute, Australia
- Tamara Pilishvili, Centers for Disease Control and Prevention, United States of America
- Betuel Sigauque, Manhica Health Research Centre, Mozambique
- Cristiana Toscano, Federal University of Goiás, Brazil
- Kate O'Brien, Johns Hopkins Bloomberg School of Public Health, United States of America (resigned from the Working Group in January 2019)

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.

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 Nicole, 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.

Composition

SAGE members

- Rakesh Aggarwal, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India (Chair of the Working Group, SAGE member since 2017);
- Andrew J. Pollard, University of Oxford, United Kingdom (SAGE member since 2016)

Experts

- Neerja Bhatla, All India Institute of Medical Sciences, India;
- Shereen Bhutta, Independent Expert, Pakistan;
- Eduardo Franco, McGill University, Canada;
- Silvia Franceschi, CRO Aviano National Cancer Institute IRCCS, Italy;
- Deepa Gamage, Ministry of Health, Sri Lanka;
- Suzanne Garland, University of Melbourne, Australia;
- Lauri Markowitz, U.S. Centers for Disease Control and Prevention, USA;
- You-Lin Qiao, Cancer Hospital, Chinese Academy of Medical Sciences, China;
- Helen Rees, University of the Witwatersrand, South Africa (SAGE member 2005-2013);
- John Schiller, Laboratory of Cellular Oncology, National Cancer Institute, NIH, USA;
- Margaret Stanley, University of Cambridge, UK

Strategic Advisory Group of Experts (SAGE) on Immunization
02 - 04 April 2019
Centre International de Conférences (CICG), Geneva, Switzerland

Provisional List of Participants

SAGE Members

Aggarwal, Prof Rakesh Professor Department of Gastroenterology Lucknow India
Cravioto, Prof Alejandro SAGE Chair Professor Facultad de Medicina Universidad Nacional Autónoma de México Puerto Vallarta Mexico
Jani, Dr Ilesh Director General Instituto Nacional de Saúde Maputo Mozambique
Jawad, Dr Jaleela Head of immunization group Public Health Directorate, Ministry of Health Manama Bahrain
Jee, Dr Youngmee Director General Center for Infectious Disease Research Cheongju Republic of Korea
Johansen, Dr Kari SAGE Vice-Chair Expert, European Centre for Disease Prevention and Control Solna Sweden
MacDonald, Prof Noni Professor of Pediatrics Division of Pediatric Infectious Diseases, Dalhousie University Halifax, Nova Scotia Canada
Madhi, Prof Shabir Vaccinology at the University of the Witwatersran Johannesburg South Africa

McIntyre, Prof Peter Department of Health Canberra Australia
Mohsni, Dr Ezzeddine Global Health Development (GHD) The Eastern Mediterranean Public Health Network (EMPHNET) Amman Jordan
Neuzil, Prof Kathleen University of Maryland School of Medicine Baltimore, Maryland USA
Pollard, Prof Andrew J. Professor, Department of Paediatrics, University of Oxford Oxford United Kingdom
Qadri, Dr Firdausi Senior Director Infectious Diseases Division Dhaka Bangladesh
Turner, Dr Nikki Associate Professor General Practice and Primary Care Wellington New Zealand
Were, Prof Fredrick Dean, School of Medicine Nairobi Kenya

Chairs of Regional Immunization Technical Advisory Groups (RITAGs)

Figueroa, Prof Peter Chair, AMRO/PAHO RITAG Department of Community Health & Psychiatry Kingston Jamaica
Finn, Prof Adam Chair, EURO RITAG University of Bristol Bristol United Kingdom
Kang, Dr Gagandeep Christian Medical College, Ida Scudder Road, Vellore Tamil Nadu India

Memish, Prof Ziad A.

Chair, EMRO RITAG
Senior consultant infectious Diseases and Director of Research Department
Department of Medicine and research Department
Riyadh
Saudi Arabia

Rees, Prof Helen

Executive Director
Chair, AFRO RITAG
Johannesburg
South Africa

Chairs of other WHO/HQ Immunization Advisory Groups**Kaslow, Dr David**

Chair, PDVAC
Vice President, Essential Medicines
Seattle
USA

Moore, Dr Kelly

Chair, IPAC
Vanderbilt School of Medicine
Nashville TN
USA

Orenstein, Prof Walter

Chair, IVIR-AC
Emory University
Atlanta
USA

NITAG Chairs and Secretariats**Aaberge, Ingeborg**

NITAG Norway
Norwegian Institute of Public Health
Invoice Receipt DFØ
Torgarden
Trondheim
Norway

AlSayyad, Adel Salman

NITAG Bahreïn
Consultant Family Medicine, Epidemiology & Public Health
Chief of Disease Control Section, MOH.
Associate Prof. of Family and community Medicine
Manama
Bahreïn

Al Shammary, Ms Aisha

NITAG Saudi Arabia
Ministry of Health
Riyadh
Saudi Arabia

Armah, Dr George E NITAG Ghana Noguchi Mem Inst. For Medical Research University of Ghana Ghana
Anh Dang, Dr Duc NITAG Vietnam National Institute of Hygiene and Epidemiology Van Phuc Diplomatic Compound Ba Dinh Hanoi Vietnam
Sabah Kadhim, Dr Haider NITAG Iraq M.B.Ch.B., PhD Microbiology Professor in Medical Microbiology College of Medicine / Al-Nahrain University Al-Jadriya Baghdad Irak
Mnati Al-Saadi, Dr Jawad Kadhim NITAG Iraq Professor of medicine College of Medicine / Al-Nahrain University Al-Jadriya Baghdad Irak
Kita, Yuske NITAG Singapore Ministry of Health Singapore College of Medicine Singapore
Nyamdavaa, Pagvajav NITAG Mongolia Ulaanbaatar Mongolia
Teteli, Dr Raissa NITAG Rwanda National Immunization Technical Advisory Group Rwanda Kigali Rwanda
Bichha, Dr Ram Padarath NITAG Nepal Director, Family Welfare Division Department of Health Services Nepal
Adhikari, Dr Ramesh Kant NITAG Nepal Chairperson, National Immunization Advisory Committee KIST Medical College, Satdobato Nepal

Representatives of Missions to the UN in Geneva

Akahane, Naoki Permanent Mission of Japan to the UN in Geneva Chemin des Fins Geneva Switzerland
Akinyemi, Florence I. Permanent Mission of the People's Democratic Republic of Nigeria to the UN in Geneva Chemin du Petit-Saconnex Geneva Switzerland
Chemakh, Amar Permanent Mission of the People's Democratic Republic of Algeria to the UN in Geneva Route de Lausanne Bellevue Switzerland
Falcon, Portugal Permanent Mission of the Republic of Panama to the UN in Geneva Rue de Lausanne Geneva Switzerland
Giron, Natalia Permanent Mission of the Republic of Honduras to the UN in Geneva Avenue de France Geneva Switzerland
Jong Myong, Hak Permanent Mission of DPRK to the UN in Geneva Chemin de Plonjon Geneva Switzerland
Kadiri, Audu A Permanent Mission of the People's Democratic Republic of Nigeria to the UN in Geneva Chemin du Petit-Saconnex Geneva Switzerland
Koizumi, Takato The Permanent Mission of Japan to the UN in Geneva Geneva Switzerland
Muhammad, Hussain Permanent Mission of Pakistan to the UN in Geneva Rue de Moillebeau Geneva Switzerland
Romao, Francelina Permanent Mission of Mozambique to the UN in Geneva Geneva Switzerland

Salmon, Lishann Permanent Mission of Jamaica to the UN in Geneva Avenue de France Geneva Switzerland
Simelane, Philomena Bawelile Permanent Mission of Royaum Eswatini to the UN in Geneva Chemin William Barbey Chambésy Switzerland
Stacey, Diego Permanent Mission Ecuador to the UN in Geneva Geneva Switzerland
Vaz, Suzana Permanent Mission of the Principality of Monaco to the UN in Geneva Rue de Moillebeau Geneva Switzerland
Zand, Niloofar Permanent Mission of Canada to the UN in Geneva Avenue de l'Ariana Geneva Switzerland

Industry

Barbosa, Ms Paula Vaccines Policy Manager, Vaccines IFPMA Chemin des Mines Geneva Switzerland
Benson, Dr Joan Exec. Director, Public Health Partnerships Public Health & Scientific Affairs Merck Vaccine North Wales USA
Bigger, Dr Laetitia IFPMA Chemin des Mines Geneva Switzerland
Desai, Samir Kumar Cadila Healthcare Ltd. Sarkhej-Dholka Road, Bhat Ahmedabad India

Fletcher, Dr Mark Andrew Pfizer Inc. New York USA
Gao, Mr Steven Xiamen Innovax Biotech Co., Ltd. Haicang District Xiamen Fujian China
Gessner, Bradford Pfizer Inc. New York USA
Homma, Akira BIO-MANGUINHOS/FIOCRUZ Pavilhão Rocha Lima Manguinhos, Rio de Janeiro-RJ Brazil
Ivol, Mr Sabrina Janssen Vaccines & Prevention Gubelstrasse Zug Switzerland
Jadhav, Dr Suresh Serum Institute of India PVT LTD Hadapsar Off Soli Poonawalla Road Pune India
Lobos, Fernando SINERGIUM BIOTECH Ruta Panamericana, Garin Buenos Aires Argentina
Maithal, Kapil Cadila Healthcare Ltd. Sarkhej-Dholka Road, Bhat Ahmedabad India
Makhoana, Morena Biovac Alexandra Rd, Ndabeni Cape Town South Africa
Masato, Nakamura Japan Association of Vaccine Industries JAVI/DENKA SEIKEN Business Innovation Centre Binley Business Park Harry Weston Road Coventry United Kingdom

Masayuki, Imagawa Japan Pharmaceutical Manufacturers Association Nihonbashi-Honcho, Chuo-ku Tokyo Japan
Matsuako, Seiji KM Biologics (Japan Association of Vaccine Industries) Okubo, Kita-ku, Kumamoto-shi Kumamoto Japan
McCabe, Ariane GSK Great West Road, Brentford Middlesex United Kingdom
Millogo, Dr Jules Director, Public Health Partnerships Merck & Co, Inc. North Wales, Galloping Hill Rd., Kenilworth New Jersey USA
Mingbo, Sun Institute of Medical Biology Chinese Academy of Medical Sciences Embassy of Switzerland; Sanlitun Dongwujie Beijing China
Prusik, Ted Temptime Corporation The American Rd, Morris Plains New Jersey USA
Qu, Jenny China National Biotec Group Company Limited China
Reers, Dr Martin Biological E Limited Jubilee Hills Hyderabad, Telangana India
Sun, Guang Xiamen Innovax Biotech Co., Ltd. Shan Bian Hong East Road, Haicang District Xiamen Fujian China
Tippoo, Patrick Biovac Cape Town South Africa
Tsai, Dr Theodore Immunization Science and Policy Takeda Vaccines Cambridge USA

Van den Hooff, Renaat Temptime Corporation The American Rd, Morris Plains New Jersey NJ USA
Yang, Lingjiang CHENGDU INSTITUTE OF BIOLOGICAL PRODUCTS CO., LTD Jinhua Road Jiangjiang District Chengdu China
Zhang, Yuntao China National Biotec Group Company Limited Chaoyang District Beijing China

Other Registered Participants

Aaby, Peter Bandim Health Project Apartado Guinea-Bissau
Aguado de Ros, Dr M. Teresa Independent Consultant Versoix Switzerland
Akiki, Mr Elie Gavi, the Vaccine Alliance Geneva Switzerland
Al-Khatib, Ms Hind Gavi, the Vaccine Alliance Geneva Switzerland
Benn, Christine Stabell Independent Consultant University of Southern Denmark Odense Danemark
Berkley, Dr Seth CEO Gavi, the Vaccine Alliance Geneva Switzerland
Biellik, Robin Independent Consultant Switzerland
Breggi, Gianluca Fondazione Achille Sclavo Via Fiorentina Siena Italy

Buanga-Lembwadio, Mireille Gavi, the Vaccine Alliance Geneva Switzerland
Bullock, Olivia Gavi, the Vaccine Alliance Geneva Switzerland
Cochi, Stephen Centers for Disease Control and Prevention Clifton Rd. NE Atlanta USA
Curry, David Executive Director Center for Vaccine Ethics and Policy West Upsal ST Philadelphia USA
de Gabrielli, Albane Gavi, the Vaccine Alliance Geneva Switzerland
Deehan, Heather UNICEF Canada Yonge Street Toronto, Ontario Canada
Denti, Veronica Gavi, the Vaccine Alliance Geneva Switzerland
Dochez, Carine Network for Education and Support in Immunisation (NESI)/University of Antwerp Antwerp Belgium
Edelstein, Michael Independent Consultant SAGE working group on immunisation data London School of Hygiene & Tropical Medicine Keppel Street London United Kingdom
Edward, Nicol Independent Consultant South African Medical Research Council/Stellenbosch University Pretoria South Africa
Esangbedo, Dr Dorothy Member and Immediate Past Chair, Gavi CSO Steering Committee Executive Committee member, International Pediatric Association International Pediatric Association - Nigeria, Gavi CSO Steering Lagos Nigeria

Feavers, Ian National Institute for Biological Standards and Control (NIBSC) Blanche Lane South Mimms Potters Bar Hertfordshire United Kingdom
Fisher, Laura Gavi, the Vaccine Alliance Geneva Switzerland
Fitter, David Centers for Disease Control and Prevention Clifton Rd. NE Atlanta USA
Folly, Mr Yann Secretariat Gavi, the Vaccine Alliance Geneva Switzerland
Hinman, Prof Alan Independent Consultant Center for Vaccine Equity Task Force for Global Health Decatur USA
Huang, Wendy Xiamen Innovax Biotech Co., Ltd. Xiamen Fujian China
Johnson, Dr Hope Director Monitoring and Evaluation Gavi, the Vaccine Alliance Geneva Switzerland
Jung, Hyungul Korea Centers for Disease Control and Prevention Heng Mui Keng Terrace Singapore
Kristensen, Debbie PATH Church St, Marietta USA
Kumar, Dr Ranjana Gavi, the Vaccine Alliance Geneva Switzerland
Kuo, Patricia Gavi, the Vaccine Alliance Geneva Switzerland

Lim, Yangfeng Clinton Health Access Initiative (CHAI) Dorchester Avenue Suite Boston MA USA
Lorenzo, David Managing Director, Policy Access and Introduction at PATH Westlake Ave. Ste Washington USA
Madrid, Dr Yvette Independent Consultant Geneva Switzerland
Malarski, Ms Maya Gavi, the Vaccine Alliance Geneva Switzerland
Malvolti, Mr Stefano Managing Director MMGH Consulting Zurich Switzerland
Mandal, Samya Gavi, the Vaccine Alliance Geneva Switzerland
Mantel, Dr Carsten Managing Director MMGH Consulting GmbH Zürich Switzerland
Mathewson, Ms Sophie Gavi, the Vaccine Alliance Geneva Switzerland
Mengistu, Ms Tewodaj Gavi, the Vaccine Alliance Geneva Switzerland
Menzio-Arnaus, Marion Gavi, the Vaccine Alliance Geneva Switzerland
Mok, Dr Wilson Gavi, the Vaccine Alliance Geneva Switzerland
Morice, Ana Independent Consultant Barrio Palermo Escazu, San Jose Postal Code Costa Rica

Nandy, Robin UNICEF Maiden Lane New York USA
Neels, Dr Pieter Vaccine Advice BVBA Zoersel Belgium
Nguyen, Ms Aurelia Director, Policy & Market Shaping Gavi, the Vaccine Alliance Geneva Switzerland
Nohynek, Dr Hanna Chief physician Deputy Head of Unit THL National Institute for Health and Welfare Vantaa Finland
Olivé, Jean-Marc Independent Consultant Representing Chair, IPAC Lochau Austria
Patel, Zeenat Gavi, the Vaccine Alliance Geneva Switzerland
Pearman, Jonathan Independent Consultant Avully Geneva Switzerland
Precali, Mr Carlo Independent Consultant MoRe Consulting GmbH Hoffeldstrasse Oberwaltersdorf Austria
Rahimi, Nargis Shifo Foundation Fryksdalsbacken, Stockholm Sweden
Randa, Ms Hamadeh Director of Social health and PHC EPI manager, UHC coordinator Ministry of Public Health Beirut Lebanon
Schluter, W. William Centers for Disease Control and Prevention Clifton Rd. NE Atlanta USA

Scobie, Heather Centers for Disease Control and Prevention Clifton Rd. NE Atlanta USA
Setayesh, Hamidreza Gavi, the Vaccine Alliance Geneva Switzerland
Smith, Peter Independent Consultant London School of Hygiene & Tropical Medicine Keppel St, Bloomsbury London United Kingdom
Strebel, Dr Peter Senior Specialist Country Programmes Gavi, the Vaccine Alliance Geneva Switzerland
Teutsch, Friederike Gavi, the Vaccine Alliance Geneva Switzerland
Uribe, Garcia Juanita Institut de Hautes Études Internationales et du Developpement (IHEID) Chemin Eugène-Rigot Geneva Switzerland
Vestrheim, Didrik Norwegian Institute of Public Health Invoice Receipt DFØ Torgarden Trondheim Norway
Walldorf, Jenny Centers for Disease Control and Prevention Clifton Rd. NE Atlanta USA
Wang, Dr Susan Associate Director for Research & Implementation Science Global Immunization Division Centers for Disease Control and Prevention Atlanta USA
Xie, Sheldon Clinton Health Access Initiative (CHAI) Dorchester Avenue Suite Boston MA USA

WHO/Regional Offices

Bahl, Dr Sunil Regional Adviser on Immunization (SEARO) Family Health, Gender and Life Course
Datta, Dr Siddhartha Programme Manager World Health Organization Regional Office for Europe
Mihigo, Dr Richard Regional Adviser on Immunization (AFRO) Programme Area Coordinator Immunization and Vaccine-Preventable Diseases
Ropero Alvarez, Sra. Alba Maria (AMRO) Adviser, Immunization Pan American Health Organization
Ruiz Matus, Dr Cuauhtémoc (AMRO) Regional Adviser on Immunization Pan American Health Organization
Takashima, Dr Yoshihiro Regional Adviser on Immunization (WPRO) Expanded Programme on Immunization
Chaudhri, Dr Irtaza Medical Officer (EMRO) Vaccine Preventable Diseases and immunization

WHO/HQ staff

Antoni, Mr Sebastien World Health Organization
Balakrishnan, Dr Madhava World Health Organization
Banerjee, Dr Kaushik World Health Organization
Bari, Ms Sona World Health Organization
Bentsi-Enchill, Dr Adwoa World Health Organization
Bloem, Mr Paul World Health Organization
Cazacu, Ms Ofelia World Health Organization
Cernuschi, Dr Tania World Health Organization
Chang Blanc, Ms Diana World Health Organization

Creo, Ms Clare World Health Organization
Danovaro, Dr Carolina World Health Organization
Dassanayake, Ms Nicolas Hemanthi World Health Organization
Del Pueyo, Ms Cristina World Health Organization
Den Boon, Ms Saskia World Health Organization
Desai, Dr Shalini World Health Organization
Dumolard, Dr Laure World Health Organization
Eisenhawer, Dr Martin World Health Organization
Fihman, Ms Johanna World Health Organization
Friede, Dr Martin Howell World Health Organization
Furrer, Ms Eliane World Health Organization
Gacic-Dobo, Ms Marta World Health Organization
Gardner, Ms Tracie World Health Organization
Giersing, Dr Birgitte World Health Organization
Grevendonk, Mr Jan Peter World Health Organization
Hamel, Dr Mary World Health Organization
Harish, Dr Verma World Health Organization
Hasan, Ms Hayatee World Health Organization
Hasso-Agopsowicz, Dr Mateusz World Health Organization
Henaff, Ms Louise World Health Organization
Henao Restrepo, Dr Ana Maria World Health Organization

Hombach, Dr Joachim Maria World Health Organization
Huang, Ms Xiao Xian World Health Organization
Hutubessy, Mr Raymond World Health Organization
Kahn, Ms Anna-Lea World Health Organization
Kamara, Ms Lidija World Health organization
Kirorei Corsini, Ms Catherine World Health Organization
Lambach, Dr Philipp World Health Organization
Lindstrand, Dr Ann World Health Organization
Mach, Dr Ondrej World Health Organization
Madhi, M. Carolina World Health Organization
Marti, Ms Melanie World Health Organization
Matzger, Ms Helen World Health Organization
Maure, Dr Christine World Health Organization
Menning, Ms Lisa World Health Organization
Moffett, Dr Daphne World Health Organization
Mulders, Dr Mick World Health Organization
Nakamura, Ms Tomoka World Health Organization
Nedelec, Mr Yoann World Health Organization
Nic Lochlainn, Dr Laura World Health Organization
O'Brien, Dr Katherine World Health Organization
Ogbuanu, Dr Ike World Health Organization

Perut, Mr Marc World Health Organization
Preziosi, Dr Marie-Pierre World Health Organization
Prudden, Dr Holly World Health Organization
Sahinovic, Ms Isabelle World Health Organization
Serhan, Dr Fatima World Health Organization
Shendale, Ms Stephanie World Health Organization
Steffen, Dr Christoph World Health Organization
Sutter, Dr Roland W. World Health Organization
Urfer, Ms Daniela World Health Organization
Vekemans, Dr Johan World Health Organization
Wadood, Dr Mufti Zubair World Health Organization
Wootton, Ms Emily World Health Organization
Zaffran, Mr Michel World Health Organization
Zuber, Dr Patrick World Health Organization



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Meeting of the Strategic Advisory Group of Experts on Immunization, October 2018 – Conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on Immunization¹ met on 23–25 October 2018. This report summarizes the discussions, conclusions and recommendations of the Group.²

Report from the WHO Department of Immunization, Vaccines and Biologicals

The report of the Director, “Immunization in a changing world from April–October 2018: What a difference 6 months makes”, noted that the first WHO investment case, published in September, shows that WHO, with its Member States and partners, could help to save up to 30 million lives, add up to 100 million years of healthy living to the world's population and thereby add up to 4% of economic growth in low-income countries (LICs) and middle-income countries (MICs) by 2023. He described the contribution of immunization to achieving the strategic priorities of the WHO's 13th Global Programme of Work, including immunization along the life-course by targeted approaches for improving vaccination activities in countries according to their needs, with direct assistance, strategic support for service delivery and dialogue on policy.

The report noted that, during the past 6 months, there have been multiple

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

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination¹ s'est réuni du 23 au 25 octobre 2018. Le présent rapport résume les délibérations du SAGE, ainsi que les conclusions et recommandations auxquelles il est parvenu.²

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

Le Directeur du Département a présenté un rapport intitulé «Vaccination dans un monde en évolution: avril à octobre 2018, 6 mois qui font toute la différence». Il a cité les conclusions du premier argumentaire d'investissement de l'OMS, publié en septembre, selon lesquelles l'OMS, en collaboration avec ses États Membres et ses partenaires, pourrait contribuer à sauver jusqu'à 30 millions de vies, à gagner jusqu'à 100 millions d'années de vie en bonne santé pour la population mondiale et à accroître de près de 4% la croissance économique des pays à revenu faible ou intermédiaire d'ici 2023. Il a décrit la contribution attendue de la vaccination pour atteindre les objectifs stratégiques prioritaires énoncés dans le 13^e programme général de travail de l'OMS, notamment la vaccination tout au long de la vie, qui repose sur des approches ciblées d'amélioration des activités de vaccination dans les pays, adaptées aux besoins nationaux et s'appuyant sur une assistance directe, un appui stratégique à la prestation des services et un dialogue politique.

Dans son rapport, le Directeur a indiqué que plusieurs flambées de maladies évitables par

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¹ Immunization, vaccines and biologicals. SAGE. Geneva: World Health Organization; 2018 (www.who.int/immunization/sage/en/index.html, accessed October 2018).

² Presentations and background materials used for the SAGE meeting, the list of SAGE members and summarized declarations of interests are available at www.who.int/immunization/en/, accessed October 2018.

¹ Vaccination, vaccins et produits biologiques. SAGE. Genève: Organisation mondiale de la Santé; 2018 (www.who.int/immunization/sage/fr/index.html, consulté en octobre 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/fr/, consulté en octobre 2018.

outbreaks of vaccine-preventable diseases (VPDs) and emphasized the importance of quality surveillance and data collection at national and subnational levels. Various means for strengthening data collection and management were presented, in particular a new effort to advance the data needs for vaccines, the WHO Immunization Information System (WIISE). Strengthening laboratory capacity in countries for surveillance of VPD was highlighted as an additional priority.

The Director described the considerable advances that have been made through the WHO “Market information for access to vaccines” project to address issues of affordability and shortages for countries that self-fund and self-procure. Gaps in information on demand and supply should be closed and the transparency of prices increased. Information on vaccine purchases is now reported to the project by 151 countries.

Overcoming vaccine hesitancy and creating vaccine demand remain high priorities. The Director emphasized the importance of SAGE’s recommendation³ on vaccine hesitancy in 2014. Indicators should be found of the reasons for vaccine hesitancy, and the degree of hesitancy should be assessed nationally and subnationally.

The WHO Regional Office for Africa (AFRO) reported on the outbreak of Ebola virus disease (EVD) in the Democratic Republic of the Congo (DRC) and the vaccination efforts that are being undertaken to stop it. EVD vaccination teams operate in an environment of great insecurity, resulting in considerable challenges for implementation. Outbreaks of yellow fever (YF) have occurred in the Congo, DRC, Ethiopia and Liberia, indicating that routine vaccination, laboratory capacity and surveillance must be strengthened in the context of the strategy to eliminate YF epidemics (EYE strategy). The RTS,S malaria vaccine is to be tested in a pilot study in 3 countries starting during the first quarter of 2019. The Regional Office reported renewed efforts to strengthen routine vaccination in Nigeria, with the support of GAVI, and an ambitious emergency plan to tackle challenges to routine vaccination in DRC has been initiated. The AFRO business case for immunization was launched in May 2018 during the Sixty-seventh World Health Assembly.

The WHO Regional Office for the Americas reported that over 7000 cases of measles had occurred in Bolivarian Republic of Venezuela and Brazil this year. In Bolivarian Republic of Venezuela, endemic transmission of measles has been re-established, with spread to neighbouring countries. As a result, the Region has lost its

la vaccination étaient survenues au cours des 6 derniers mois et a souligné l’importance d’une bonne surveillance et d’une collecte efficace des données aux niveaux national et infranational. Différentes méthodes d’amélioration de la collecte et de la gestion des données ont été présentées, en particulier une nouvelle initiative visant à répondre aux besoins en données dans le domaine de la vaccination, le Système d’information sur la vaccination de l’OMS (WIISE). Le rapport insistait également sur la nécessité de renforcer les capacités des laboratoires nationaux aux fins de la surveillance des maladies évitables par la vaccination.

Le Directeur a décrit les progrès considérables accomplis dans le cadre du projet «Market information for access to vaccines» de l’OMS (Informations sur les marchés pour l’accès aux vaccins) pour régler les problèmes d’accessibilité économique et de pénurie dans les pays qui assurent eux-mêmes le financement et l’approvisionnement. Des efforts devront être déployés pour combler les lacunes existantes en matière d’information sur l’offre et la demande et instaurer une plus grande transparence sur les prix. Des informations sur les achats de vaccins sont désormais communiquées au projet par 151 pays.

La lutte contre la réticence face à la vaccination et la stimulation de la demande en vaccins restent au premier plan des priorités. Le Directeur a rappelé l’importance de la recommandation émise par le SAGE en 2014³ au sujet de la réticence face à la vaccination. Il convient que des indicateurs soient établis concernant les motifs de cette réticence et que l’ampleur du phénomène soit évaluée aux niveaux national et infranational.

Le Bureau régional OMS de l’Afrique (AFRO) a présenté un rapport sur la flambée de maladie à virus Ebola (MVE) en République démocratique du Congo (RDC) et sur les efforts de vaccination entrepris pour la juguler. Les équipes de vaccination contre la MVE travaillent dans un contexte de grande insécurité, rendant la mise en œuvre extrêmement difficile. Des flambées de fièvre jaune sont apparues au Congo, en Éthiopie, au Libéria et en RDC, témoignant de la nécessité de renforcer la vaccination systématique, les capacités des laboratoires et la surveillance conformément à la stratégie pour l’élimination des épidémies de fièvre jaune (stratégie EYE). Il est prévu que le vaccin antipaludique RTS,S soit testé dans le cadre d’une étude pilote dans 3 pays au cours du premier trimestre de 2019. Le Bureau régional a fait état d’une intensification des efforts pour renforcer la vaccination systématique au Nigéria, avec l’appui de l’Alliance GAVI, et de la mise en place d’un ambitieux plan d’urgence pour surmonter les obstacles à la vaccination systématique en RDC. L’argumentaire économique de la Région africaine en faveur de la vaccination a été lancé en mai 2018 lors de la Soixante-Septième Assemblée mondiale de la Santé.

Le Bureau régional OMS des Amériques a indiqué que plus de 7000 cas de rougeole se sont déclarés cette année au Brésil et en République bolivarienne du Venezuela. En République bolivarienne du Venezuela, on a observé un rétablissement de la transmission endémique de la rougeole, avec une propagation de la maladie vers les pays voisins. Par conséquent, la Région

³ WHO SAGE working group dealing with vaccine hesitancy. Strategies for addressing vaccine hesitancy – a systematic review. Geneva: World Health Organization; 2014 (http://www.who.int/immunization/sage/meetings/2014/october/SAGE_working_group_revised_report_vaccine_hesitancy.pdf, accessed October 2018).

³ WHO SAGE working group dealing with vaccine hesitancy. Strategies for addressing vaccine hesitancy – a systematic review. Genève: Organisation mondiale de la Santé; 2014 (http://www.who.int/immunization/sage/meetings/2014/october/SAGE_working_group_revised_report_vaccine_hesitancy.pdf, consulté en octobre 2018).

status as having eliminated measles. The Regional Technical Advisory Group, which met in July 2018, emphasized the importance of Regional action and an urgent public health response to ensure re-verification of measles elimination in Bolivarian Republic of Venezuela. All countries in the Region are conducting mass vaccination and rapid response to sustain their measles-free status. YF and diphtheria are also high priorities in the Region.

The WHO Regional Office for the Eastern Mediterranean reported that, despite the many conflicts in the Region, coverage of penta-3 vaccine increased from 78% to 81%, and the annual number of vaccinated children increased by 820 000 between 2012 and 2017. Ten countries in the Region are progressing well towards measles elimination, while several others are still experiencing outbreaks. The strategy of immunization along the life-course is being followed in a number of countries, but 6 countries still do not provide a booster dose of diphtheria, pertussis and tetanus (DTP) vaccine. After the large outbreak of diphtheria in Yemen, the Region plans to implement the booster dose before 2021. MICs in the region continue to lag in introducing the life-saving pneumococcal conjugate and rotavirus vaccines. Only one third of children living in MICs access these vaccines, as compared with >95% of the children living in high-income and GAVI-supported countries in the Region.

The WHO Regional Office for Europe reported progress in vaccine coverage in the Region, with 94% average coverage of the third dose of DTP (DTP3). Nevertheless, vaccine coverage in the Region varies between and within countries, and over 56 000 measles cases were reported in 2017 and 2018, mainly in MICs but also in HICs. Of particular concern are un- and under-vaccinated urban poor and migrant populations. The availability of high-quality subnational data for assessing programme performance was highlighted. The Regional Office is working on an eHealth framework for an information system that covers all the components of an immunization programme. With UNICEF, the European Centre for Disease Prevention and Control and academia, the Regional Office is seeking to improve the quality of data on immunization coverage and disease surveillance, with “quality data and use” as the central theme.

The WHO Regional Office for South-East Asia announced progress in routine coverage, sustaining a DTP3 coverage rate of 88%, with 7 of the 11 countries achieving $\geq 90\%$ coverage (Bangladesh, Bhutan, Democratic People's Republic of Korea, Maldives, Nepal, Sri Lanka and Thailand). Six countries in the Region have achieved >80% DTP3 coverage in all districts. Measles elimination is a flagship programme of the Regional Office, and work to achieve measles elimination and rubella control are being accelerated. Four countries have been verified as having eliminated measles and 6 as

a perdu son statut de région exempte de rougeole. Le groupe consultatif technique régional, qui s'est réuni en juillet 2018, a souligné l'importance d'une action régionale et d'une riposte urgente de santé publique afin que l'élimination de la rougeole puisse de nouveau être vérifiée en République bolivarienne du Venezuela. Tous les pays de la Région mènent des activités de vaccination de masse et de riposte rapide pour conserver leur statut de pays exempts de rougeole. La fièvre jaune et la diphtérie constituent également des priorités de premier ordre pour la Région.

Le Bureau régional OMS de la Méditerranée orientale a indiqué qu'en dépit des nombreux conflits touchant la Région, la couverture de la vaccination par le penta-3 a progressé, passant de 78% à 81%, et que le nombre annuel d'enfants vaccinés a augmenté de 820 000 entre 2012 et 2017. Dix pays de la Région affichent des progrès satisfaisants vers l'élimination de la rougeole, tandis que plusieurs autres continuent de connaître des flambées. La stratégie de vaccination tout au long de la vie est bien appliquée dans de nombreux pays, mais 6 pays n'administrent toujours pas la dose de rappel du vaccin antidiphtérique-antitétanique-anticoquelucheux (DTC). Suite à une flambée de grande ampleur de diphtérie survenue au Yémen, la Région prévoit un déploiement de la dose de rappel avant 2021. Les pays à revenu intermédiaire de la Région continuent d'accuser un retard pour ce qui est de l'introduction des vaccins salvateurs que sont le vaccin antipneumococcique conjugué et le vaccin antirotavirus. Seulement un tiers des enfants vivant dans les pays à revenu intermédiaire ont accès à ces vaccins, contre >95% des enfants vivant dans les pays à revenu élevé et dans les pays bénéficiant de l'aide de l'Alliance GAVI dans la Région.

Le Bureau régional OMS de l'Europe a fait état d'une progression de la couverture vaccinale dans la Région, le taux moyen de couverture par la troisième dose de DTC (DTC3) s'élevant à 94%. Toutefois, la couverture varie d'un pays à l'autre, ainsi qu'à l'intérieur de chaque pays, et plus de 56 000 cas de rougeole ont été notifiés en 2017 et 2018, principalement dans les pays à revenu intermédiaire, mais aussi dans des pays à revenu élevé. L'absence ou l'insuffisance de la vaccination parmi les populations urbaines défavorisées et les populations migrantes est particulièrement préoccupante. L'accent a été mis sur la nécessité de disposer de données infranationales pour évaluer l'efficacité des programmes. Le Bureau régional élabore actuellement un cadre de cybersanté destiné à fournir un système d'information couvrant toutes les composantes des programmes de vaccination. En collaboration avec l'UNICEF, le Centre européen de prévention et de contrôle des maladies et des établissements universitaires, le Bureau régional s'emploie à améliorer la qualité des données sur la couverture vaccinale et la surveillance des maladies, axant principalement ses efforts sur le thème «qualité des données et utilisation».

Le Bureau régional OMS de l'Asie du Sud-Est a fait part d'une amélioration de la couverture par la vaccination systématique et du maintien de la couverture par le DTC3 à un taux de 88%, 7 des 11 pays étant parvenus à une couverture $\geq 90\%$ (Bangladesh, Bhoutan, Maldives, Népal, République populaire démocratique de Corée, Sri Lanka et Thaïlande). Six pays de la Région enregistrent un taux de couverture par le DTC3 >80% dans tous les districts. L'élimination de la rougeole constitue un programme phare du Bureau régional et ce dernier a accéléré ses efforts pour atteindre les objectifs d'élimination de la rougeole et de lutte contre la rubéole. L'élimination de la rougeole a été vérifiée

having controlled rubella. Recent outbreaks of diphtheria and measles in the Region have exposed substantial gaps in vaccination coverage, and all countries are identifying subnational areas and populations with suboptimal coverage in order to target strategies for improving vaccination coverage.

The WHO Regional Office for the Western Pacific reported progress in achieving the goals specified in the Regional Framework for Implementation of the Global Vaccine Action Plan (GVAP). Since 2009, the Region has maintained over 95% DTP3 coverage. As of September 2018, 5 countries had achieved and sustained rubella elimination. The Region has maintained polio-free status (wild type) since certification in 2000. In 2017, an outbreak of polio due to circulating vaccine-derived poliovirus (cVPDV) in the Lao People's Democratic Republic was controlled by vaccinating all children under 15 years of age with oral polio vaccine (OPV). In spring 2018, an outbreak of cVPDV1 was identified in Papua New Guinea, and the response is continuing. The Region is making significant progress in hepatitis B control; as of April 2018, 19 countries and areas had been verified as having achieved the 2017 Regional goal of <1% seroprevalence of hepatitis B surface antigen among 5-year-old children. In 2017, the Philippines achieved elimination of maternal and neonatal tetanus.

Report from GAVI Alliance

The presentation by GAVI updated its programmes, reported on activities and described the strategies beyond 2020. The close alignment between GAVI-supported activities and WHO policies was underlined. The presentation included a review of work on introduction of typhoid conjugate vaccine, constraints to the supply of human papillomavirus (HPV) vaccine, the anticipated increase in global demand for a more rapid response to YF outbreaks and opportunities to increase YF vaccination through routine programmes, more sustainable strategies for measles vaccination to reduce transmission, and support for a global stockpile of EVD vaccine.

The GAVI vaccine investment strategy beyond 2020 was reviewed. Six investment cases were presented: DTP-containing boosters, hepatitis B vaccine birth dose, oral cholera vaccine, post-exposure prophylaxis for rabies, multivalent meningococcal vaccine, and future respiratory syncytial virus vaccine and monoclonal antibodies. The cases demonstrate GAVI's commitment to immunization along the life-course. All of these investments will require strong technical and policy guidance at global level.

GAVI has increased its engagement with the Global Polio Eradication Initiative (GPEI). In June 2018, the GAVI Board approved funding for inactivated polio vaccine (IPV) from core resources (US\$ 200 million) for 2019–2020 and, in November 2018, will consider continued support beyond 2020.

dans 4 pays et la maîtrise de la rubéole dans 6 pays. De récentes flambées de diphtérie et de rougeole dans la Région ont mis en évidence des lacunes de la couverture vaccinale au niveau infranational et tous les pays ont entrepris d'identifier les populations et les zones infranationales affichant une couverture sous-optimale en vue d'établir des stratégies ciblées d'amélioration de la couverture.

Le Bureau régional OMS du Pacifique occidental a fait état des progrès accomplis vers la réalisation des objectifs fixés dans le Cadre régional de mise en œuvre du Plan d'action mondial pour les vaccins (GVAP). Depuis 2009, la couverture par le DTC3 s'est maintenue à un niveau supérieur à 95% dans la Région. En septembre 2018, les pays qui étaient parvenus à éliminer durablement la rubéole étaient au nombre de 5. La Région demeure exempte de poliomyélite (type sauvage) depuis sa certification en 2000. En 2017, une flambée de poliomyélite due aux poliovirus circulants dérivés d'une souche vaccinale (PVDVc) en République démocratique populaire lao a pu être endiguée par l'administration du vaccin antipoliomyélitique oral (VPO) à tous les enfants de moins de 15 ans. Au printemps 2018, une flambée de PVDVc1 a été identifiée en Papouasie-Nouvelle-Guinée et une riposte est en cours. La Région continue d'afficher des progrès notables dans la lutte contre l'hépatite B; en avril 2018, 19 pays et zones avaient atteint l'objectif régional de 2017 fixant à <1% la séroprévalence de l'antigène de surface de l'hépatite B parmi les enfants âgés de 5 ans. Les Philippines ont éliminé le tétanos maternel et néonatal en 2017.

Rapport de l'Alliance GAVI

L'Alliance GAVI a fait le point sur ses programmes et ses activités et a présenté ses stratégies pour l'après-2020. Elle a souligné l'étroite harmonie existant entre les activités soutenues par l'Alliance et les politiques de l'OMS. Elle a passé en revue les activités relatives à l'introduction du vaccin antityphoïdique conjugué, les difficultés d'approvisionnement en vaccins contre le papillomavirus humain (PVH), l'augmentation attendue de la demande mondiale en vaccin anti-morbilli pour permettre une riposte plus rapide aux flambées de fièvre jaune et l'intensification éventuelle de la vaccination anti-morbilli dans le cadre des programmes de vaccination systématique, l'adoption de stratégies plus pérennes de vaccination antirougeoleuse pour réduire la transmission, et le soutien apporté à la création d'un stock mondial de vaccins contre la maladie à virus Ebola.

La stratégie d'investissement en faveur de la vaccination de l'Alliance GAVI au-delà de 2020 a été examinée. Six argumentaires d'investissement ont été présentés, portant sur: les doses de rappel de vaccin contenant le DTC, la dose à la naissance de vaccin anti-hépatite B, le vaccin anticholérique oral, la prophylaxie postexposition contre la rage, le vaccin antiméningococcique multivalent et les futurs vaccins et anticorps monoclonaux contre le virus respiratoire syncytial. Ces argumentaires témoignent de l'engagement de l'Alliance à promouvoir la vaccination tout au long de la vie. Tous ces investissements exigeront des orientations techniques et politiques solides au niveau mondial.

L'Alliance a renforcé sa collaboration avec l'Initiative mondiale pour l'éradication de la poliomyélite (IMEP). En juin 2018, le Conseil d'administration de l'Alliance a approuvé le financement du vaccin antipoliomyélitique inactivé (VPI) à partir de ses fonds propres (US\$ 200 millions) pour 2019–2020; en novembre 2018, il décidera de la poursuite éventuelle de cette aide au-delà de 2020.

GAVI updated the following activities: (i) transitioning countries from GAVI support, (ii) progress by GAVI-supported countries in achieving the immunization targets of the Sustainable Development Goals (SDGs), (iii) investment in health systems strengthening to ensure equitable coverage, (iv) prioritization of subnational investments for immunization coverage and equity, (v) building institutional capacity to increase coverage and equity, (vi) building political will to improve immunization programmes, (vii) a new partner framework to generate demand and (viii) a current partnership pipeline. GAVI updated its list of countries facing fragility in 2018, noting that the Syrian Arab Republic will continue to be GAVI-eligible, while Ethiopia and Nigeria are no longer eligible. Nigeria may receive an additional US\$ 461 million in vaccine financing with a parallel commitment from the Nigerian Government for an extended accelerated transition period.

For its post-2020 strategy, GAVI is exploring 4 themes: (i) reaching every child in the remaining eligible countries, (ii) accelerating vaccination in MICs, (iii) contributing to global health security, and (iv) using GAVI's platform for other health and non-health interventions.

Reports from other advisory committees on immunization

Global Advisory Committee on Vaccine Safety (GACVS)

GACVS met in June 2018⁴ to discuss 5 topics: the safety of dengue vaccine in the Philippines, the "vaccine safety net" (VSN) project, pharmacovigilance in pilot studies of the RTS,S malaria vaccine, progress in the Global Vaccine Safety Initiative and communication about vaccine safety.

GACVS reviewed updated reports on the safety of CYD-TDV dengue vaccine and concluded that, in the absence of criteria for distinguishing vaccine failure from vaccine-related immune enhancement, individual cases should be classified as "indeterminate", irrespective of the time since vaccination. Both non-clinical and clinical evaluations show no evidence of an association between viscerotropic or neurotropic disease and the YF backbone of the vaccine.

GACVS welcomed the contribution of the VSN to identifying trustworthy information on the Internet and encouraged additional efforts such as web analytics and a digital toolkit to further its work.

Comprehensive pharmacovigilance has been developed for pilot introduction of the RTS,S malaria vaccine in Ghana, Kenya and Malawi, including general pharmacovigilance, sentinel surveillance for cerebral malaria

L'Alliance a fait le point sur les activités suivantes: i) transition des pays qui sont en passe de s'affranchir de l'aide de l'Alliance, ii) progrès accomplis par les pays soutenus par l'Alliance dans la réalisation des cibles de vaccination énoncées dans les objectifs de développement durable (ODD), iii) investissements consacrés au renforcement des systèmes de santé pour veiller à une couverture équitable, iv) priorité donnée aux investissements infranationaux axés sur la couverture vaccinale et l'équité, v) renforcement des capacités institutionnelles à accroître la couverture et l'équité, vi) promotion d'une volonté politique d'amélioration des programmes de vaccination, vii) nouveau cadre de partenariat pour stimuler la demande et viii) partenariats en cours d'établissement. L'Alliance GAVI a actualisé sa liste de pays confrontés à des fragilités en 2018 et a annoncé que la République arabe syrienne continuerait de bénéficier de l'aide de l'Alliance, tandis que l'Éthiopie et le Nigéria ne remplissent plus les critères correspondants. Une somme supplémentaire de US\$ 461 millions pourrait être allouée au Nigéria à des fins de financement des vaccins, avec un engagement parallèle du gouvernement nigérian, dans le cadre d'une prolongation de la période de transition accélérée.

L'Alliance explore actuellement 4 thèmes pour sa stratégie de l'après-2020: i) atteindre tous les enfants dans les pays encore soutenus par l'Alliance, ii) accélérer la vaccination dans les pays à revenu intermédiaire, iii) contribuer à la sécurité sanitaire mondiale, et iv) utiliser la plateforme de l'Alliance aux fins d'autres interventions sanitaires ou non sanitaires.

Rapport des autres comités consultatifs sur la vaccination

Comité consultatif mondial pour la sécurité des vaccins (GACVS)

Le GACVS s'est réuni en juin 2018⁴ pour aborder 5 sujets: l'innocuité du vaccin contre la dengue aux Philippines, le projet du «Réseau pour la sécurité des vaccins», la pharmacovigilance dans le cadre d'études pilotes sur le vaccin antipaludique RTS,S, les progrès de l'Initiative mondiale pour la sécurité des vaccins et la communication à propos de la sécurité des vaccins.

Le GACVS a examiné les derniers rapports sur l'innocuité du vaccin CYD-TDV contre la dengue et a conclu qu'en l'absence de critères permettant de faire la distinction entre l'échec vaccinal et l'exacerbation de la maladie liée au vaccin, les cas individuels devront être classés comme «indéterminés», quel que soit le temps écoulé depuis la vaccination. Les évaluations menées, qu'elles soient cliniques ou non cliniques, n'ont mis en évidence aucun lien entre la maladie viscérotrope ou neurotrophe et la souche amarile utilisée comme squelette de réplication pour le vaccin.

Le GACVS a salué les travaux du Réseau pour la sécurité des vaccins, qui ont contribué à l'identification d'informations fiables sur Internet, et a invité le Réseau à déployer des efforts supplémentaires dans ce sens, par exemple par la réalisation d'analyses Web et l'utilisation d'une boîte à outils numérique.

Une approche exhaustive de pharmacovigilance a été mise en place pour les projets pilotes d'introduction du vaccin antipaludique RTS,S au Ghana, au Kenya et au Malawi, s'appuyant sur des activités de pharmacovigilance générale, sur la surveillance

⁴ See No 29/30, 2018, 30, pp. 389–396.

⁴ Voir N° 29/30, 2018, pp. 389-396.

or meningitis and active and passive surveillance for adverse events following immunization (AEFI). Systems are being established in each country to prepare protocols, identify health care workers and facilities and provide training in reporting AEFI. For active surveillance, a manual on AEFI has been prepared, with case definitions. GACVS expressed concern that a late start in initiating pharmacovigilance protocols would mean that they were not available for the pilot studies.

The Global Vaccine Safety Observatory has been launched to strengthen global monitoring of vaccine safety. A new GACVS subcommittee on communication about vaccine safety has been established. Such communication requires coordination among stakeholders in many areas and partners to provide resources.

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

The IVIR-AC met in September 2018 to discuss: global research on vaccine demand and acceptance, modelling of the elimination of cervical cancer, maximizing the impact of vaccines in use, optimal intervals between measles supplementary immunization activities (SIAs), “total systems effectiveness”, the WHO guide on the cost-effectiveness of typhoid vaccine, guidelines for multi-model comparison, and organizing and using data to identify areas at risk for outbreaks of VPDs.

In the context of the WHO cervical cancer elimination agenda, the Committee reviewed the results of a comparison of models to determine the impact of various vaccination strategies, in combination with or in the absence of other disease control measures. The models were found to be consistent and suitable for informing vaccination strategies; an economic analysis is under way.

Various strategies for rationally defining the intervals between measles SIAs were reviewed. All were found relevant for defining the timing of national and subnational vaccination campaigns more precisely. It was noted, however, that the impact of campaigns on routine vaccination activities should be better documented, and ways should be found to minimize the negative and maximize the positive impacts and emphasize the importance of routine vaccination. More work is required to ensure that campaigns effectively reach hitherto unvaccinated children, the primary goal of SIAs.

Immunization Practices Advisory Committee (IPAC)

A growing focus of IPAC in the past year was innovation in improving programme impact. IPAC has closely followed the evolution of the “total system effectiveness” project and contributed to establishment of the “vaccine immunization prioritization strategy” in

sentinelle du neuropaludisme et de la méningite, ainsi que sur la surveillance passive et active des manifestations postvaccinales indésirables (MAPI). Des systèmes sont en train d'être établis dans chaque pays pour préparer les protocoles, identifier les agents de santé et les établissements concernés et offrir une formation à la notification des MAPI. Pour la surveillance active, un manuel sur les MAPI, accompagné des définitions de cas, a été rédigé. Le GACVS s'est inquiété du fait qu'un démarrage tardif des travaux d'élaboration des protocoles de pharmacovigilance pourrait se solder par une indisponibilité de ces protocoles pour les études pilotes.

L'Observatoire mondial pour la sécurité des vaccins a été lancé pour renforcer le suivi à l'échelle mondiale de la sécurité des vaccins. Un nouveau sous-comité du GACVS chargé de la communication sur la sécurité des vaccins a été établi. Ces activités de communication exigent une coordination entre les intervenants travaillant dans de nombreux domaines différents, ainsi que des partenaires susceptibles de fournir les ressources nécessaires.

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

L'IVIR-AC s'est réuni en septembre 2018 pour discuter des points suivants: recherche mondiale sur la demande en vaccins et l'acceptation des vaccins, modélisation de l'élimination du cancer du col de l'utérus, optimisation de l'impact des vaccins actuellement utilisés, intervalles optimaux entre les activités de vaccination supplémentaire (AVS) contre la rougeole, projet «efficacité du système global», guide de l'OMS sur le rapport coût-efficacité des vaccins antityphoïdiques, lignes directrices sur la comparaison multi-modèles, et organisation et utilisation des données pour identifier les zones à risque de flambées de maladies à prévention vaccinale.

Dans le cadre du programme OMS d'élimination du cancer du col de l'utérus, le Comité a examiné les résultats d'une comparaison de modèles pour déterminer l'impact de différentes stratégies de vaccination, qu'elles soient appliquées seules ou en association avec d'autres mesures de lutte contre la maladie. Les modèles se sont avérés cohérents et aptes à fournir des informations utiles pour guider les stratégies de vaccination; une analyse économique est en cours.

Le Comité a examiné diverses stratégies visant à définir de manière rationnelle les intervalles à observer entre les AVS contre la rougeole. Il a conclu que ces stratégies étaient toutes pertinentes pour définir de manière plus précise le calendrier des campagnes nationales et infranationales de vaccination. Il a toutefois fait valoir que l'impact de ces campagnes sur les activités de vaccination systématique devrait être mieux documenté et que des moyens devraient être trouvés pour limiter leur impact négatif, optimiser leur impact positif et mettre en exergue l'importance de la vaccination systématique. Des travaux supplémentaires sont nécessaires pour veiller à une couverture efficace des enfants jusqu'alors non vaccinés, ce qui est le but premier des AVS.

Comité consultatif sur les pratiques vaccinales (IPAC)

Au cours de l'année passée, l'IPAC a porté un intérêt croissant aux innovations destinées à améliorer l'impact des programmes. L'IPAC a suivi de près l'évolution du projet «efficacité du système global» et a contribué à l'élaboration de la stratégie d'établissement des priorités de vaccination, en collaboration

collaboration with GAVI and with shared oversight by the IVIR-AC and the Product Development for Vaccines Advisory Committee (PDVAC). The aim of these initiatives is to ensure appropriate consideration of countries' views in global prioritization of vaccine products and in their development by manufacturers and innovators.

IPAC has been providing direction on controlled temperature chains, issues concerning delivery technologies and optimizing vaccine supply by improved logistics.

Product Development for Vaccines Advisory Committee (PDVAC)

PDVAC has broadened its work from product development preferences and the most expeditious vaccine approval pathways in LMICs to encouraging early discussion on the data requirements for WHO vaccination recommendation. The vaccine and monoclonal antibody pipeline contains several candidates that are either in or progressing to late-stage clinical development. Those that will seek SAGE consideration within the next 5 years include vaccines against tuberculosis, HIV, *Shigella* and group B *Streptococcus*. Clear statements on the public health value of vaccines and the requirements for recommendations should be provided to vaccine manufacturers and donors. The example presented was on potential use of the "controlled human infection model" to accelerate the development of *Shigella* vaccines.

PDVAC will strengthen its collaboration with IPAC and IVIR-AC and also consult other stakeholders to determine the full public health value of products and innovations and to integrate product development with vaccine use. This will include delineation of clinical and regulatory pathways, creating a favourable, sustainable funding environment, defining the data requirements beyond licensure and considering an eventual procurement strategy to engage manufacturers and diminish the risk of development of truly global vaccines that are appropriate for use in LMICs.

Global Vaccine Action Plan: 2018 review of progress and recommendations

SAGE reviewed the draft assessment report and recommendations of the Decade of Vaccines Working Group and noted that, while progress was made in 2017 towards the goals set out in the GVAP,⁵ many targets are unlikely to be met by the end of the decade. SAGE noted the risk that hard-won gains are easily lost; gains must therefore be maintained, and more should be done, better and differently. Recent outbreaks are a sobering

avec l'Alliance GAVI et sous la direction commune de l'IVIR-AC et du Comité consultatif sur le développement de produits pour les vaccins (PDVAC). L'objectif de ces initiatives est de veiller à ce que la perspective des pays soit adéquatement prise en compte dans l'établissement des priorités mondiales de vaccination et dans le développement des produits vaccinaux par les fabricants et les innovateurs.

L'IPAC continue de fournir des orientations sur la chaîne de température contrôlée, les techniques d'administration des vaccins et les améliorations logistiques permettant d'optimiser l'approvisionnement en vaccins.

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

Le PDVAC a élargi son domaine d'action: outre l'établissement de préférences pour la mise au point des produits et l'identification des mécanismes d'approbation les plus rapides dans les pays à revenu faible ou intermédiaire, il encourage aussi une réflexion précoce sur les données qui seront nécessaires à la formulation d'une recommandation vaccinale par l'OMS. Parmi les vaccins et anticorps monoclonaux en cours de développement, plusieurs candidats ont atteint ou sont sur le point d'atteindre les dernières étapes du processus de développement clinique. Certains seront soumis à l'examen du SAGE au cours des 5 prochaines années, notamment des vaccins contre la tuberculose, le VIH, *Shigella* et les streptocoques du groupe B. Il faudra que des informations claires soient fournies aux fabricants et aux bailleurs de fonds concernant l'intérêt des vaccins pour la santé publique et les conditions requises pour la formulation de recommandations. Un exemple a été présenté, portant sur l'utilisation potentielle du «modèle d'infection humaine contrôlée» pour accélérer la mise au point des vaccins anti-*Shigella*.

Le PDVAC prévoit de renforcer sa collaboration avec l'IPAC et l'IVIR-AC et de consulter d'autres partenaires afin d'évaluer pleinement l'intérêt des produits et des innovations en termes de santé publique et d'intégrer la mise au point des produits à l'utilisation des vaccins. Cela impliquera de préciser les procédures cliniques et réglementaires, de créer un cadre de financement favorable et durable, de définir les données exigées au-delà de l'homologation et de réfléchir à une stratégie d'approvisionnement ultérieure favorisant la collaboration avec les fabricants et réduisant les risques associés au développement de vaccins véritablement mondiaux qui sont adaptés à une utilisation dans les pays à revenu faible ou intermédiaire.

Plan d'action mondial pour les vaccins: évaluation des progrès accomplis en 2018 et recommandations

Le SAGE a examiné le projet de rapport d'évaluation et de recommandations soumis par le Groupe de travail sur la Décennie de la vaccination et a noté que malgré les progrès réalisés en 2017 au regard des objectifs fixés dans le GVAP,⁵ de nombreuses cibles ne seront probablement pas atteintes d'ici la fin de la décennie. Le SAGE a fait valoir que les gains durement acquis peuvent aisément être perdus; il est donc essentiel de préserver les acquis et de déployer des efforts accrus, plus effi-

⁵ Global vaccine action plan. Geneva: World Health Organization; 2013 (http://www.who.int/immunization/global_vaccine_action_plan/en/, accessed November 2018).

⁵ Plan d'action mondial pour les vaccins. Genève: Organisation mondiale de la Santé; 2013 (http://www.who.int/immunization/global_vaccine_action_plan/fr/, consulté en novembre 2018).

reminder that no country can stop investing in immunization.

Looking to the future and a broader global health agenda, SAGE emphasized that immunization is a central pillar of universal health coverage, for attaining the SDGs, contributing to global health security and winning the battle against antimicrobial resistance. SAGE also stressed that countries should be at the heart of the future global immunization agenda. Regions will have a key role to play in supporting the development of national vaccination systems, and global immunization partners will continue to work together to create an enabling environment for vaccination.

In order to keep up the momentum towards the GVAP goals, including research and development targets, and to pave the way for a post-2020 global immunization agenda, SAGE issued 3 broad recommendations:

1. Countries, regions and global immunization partners should commit themselves 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 framework for a post-2020 strategy.
 - A post-2020 strategy should build on the lessons learned during the Decade of Vaccines and draw upon the key themes identified in this 2018 Assessment Report.
2. GVAP 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.
3. The contributions of research to immunization should be enhanced and expanded.
 - Vaccine research and development (R&D): Connections between vaccine R&D and implementation communities should be further strengthened to ensure close collaboration in

caces et plus diversifiés à cette fin. Les récentes flambées nous rappellent qu'aucun pays ne peut se permettre d'arrêter d'investir dans la vaccination.

Dans une perspective d'avenir et dans le contexte plus large du programme mondial d'action sanitaire, le SAGE a souligné que la vaccination est un pilier essentiel pour instaurer la couverture sanitaire universelle, atteindre les ODD, faire progresser la sécurité sanitaire mondiale et gagner la bataille contre la résistance aux antimicrobiens. Le SAGE a également rappelé que les pays doivent être au cœur du futur programme mondial de vaccination. Les régions auront un rôle essentiel à jouer pour faciliter l'établissement de systèmes nationaux de vaccination et les partenaires mondiaux impliqués dans les efforts de vaccination devront continuer de travailler de concert afin de créer un environnement propice à la vaccination.

Le SAGE a émis 3 recommandations générales pour maintenir la dynamique vers la réalisation des objectifs du GVAP, y compris des cibles relatives à la recherche et au développement, et jeter les bases du programme mondial de vaccination pour l'après-2020:

1. Les pays, les régions et les partenaires mondiaux dans le domaine de la vaccination doivent s'engager à élaborer une stratégie mondiale intégrée de vaccination pour l'après-2020.
 - Un examen exhaustif des progrès, de l'impact et de la mise en œuvre du Plan d'action mondial pour les vaccins devra être entrepris pour orienter la stratégie de l'après-2020.
 - Le cadre de suivi et d'évaluation du Plan d'action mondial pour les vaccins devra être examiné pour guider l'élaboration d'un cadre révisé applicable à la stratégie pour l'après-2020.
 - La stratégie pour l'après-2020 devra s'appuyer sur les enseignements tirés de la Décennie de la vaccination et se fonder sur les principaux points soulevés dans ce rapport d'évaluation de 2018.
2. Les activités de vaccination menées jusqu'à la fin de la Décennie de la vaccination doivent être axées sur les priorités du GVAP, adaptées pour tenir compte des évolutions et de l'expérience acquise.
 - L'un des enjeux majeurs est d'offrir un appui personnalisé aux pays pour les aider à établir et à maintenir des systèmes de vaccination nationaux robustes, efficaces et alignés sur les plans nationaux d'instauration de la couverture sanitaire universelle.
 - Un cadre de bonnes pratiques doit être élaboré afin de garantir un accès équitable aux services de vaccination pour les populations migrantes, déplacées et défavorisées, y compris celles qui sont confrontées à des situations d'urgence humanitaire.
 - La stimulation de la demande en vaccins, tant au niveau individuel que communautaire, doit être considérée comme une priorité de premier plan dans les pays.
3. Les contributions de la recherche dans le domaine de la vaccination doivent être enrichies et étendues.
 - Recherche et développement (R&D) sur les vaccins: les liens entre les milieux de la R&D et de la mise en œuvre doivent être encore resserrés pour favoriser une collaboration étroite en matière de conception,

new product design, development and evaluation.

- Immunization systems: More use should be made of implementation, operational and other research to improve the performance of national immunization systems and to evaluate innovations in service delivery to reach underserved populations.
- Immunization research capacity in low- and middle-income countries should be developed across all these areas.

SAGE was presented with a concept note outlining the components of a global immunization agenda for the next decade (2021–2030). SAGE took note of the tight timeline proposed for elaboration and submission of the agenda to the World Health Assembly in May 2020, when the agenda will be discussed, and emphasized that all lessons learned from the current GVAP be used to inform the new agenda. SAGE urged WHO to work with all relevant partners in immunization and wider public health, ensuring a “bottom-up approach”, with the involvement of civil society organizations.

Report of activities from international immunization partners

The Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT)⁶ working group was invited to make a presentation to the meeting. PREVENT is committed to developing concrete, actionable, consensus-driven guidance on equitable inclusion of the interests of pregnant women and their offspring in vaccine R&D for priority pathogens and emerging epidemic threats.

PREVENT is a multidisciplinary expert working group in bioethics, maternal immunization, maternal-fetal medicine, obstetrics, paediatrics, philosophy, public health and vaccine research. The secretariat is based at Johns Hopkins University (Baltimore (MD)). The group was established subsequent to the recent epidemics of Zika virus disease, Lassa fever, EVD and H1N1 influenza, which put pregnant women and their offspring at increased risk of serious disease and death or result in pregnancy loss or severe congenital harm. The interests of these groups must be taken into account in combating epidemic threats proactively.

PREVENT is preparing a roadmap for ethically responsible, socially just, respectful inclusion of the interests of pregnant women in the development and deployment of vaccines against emerging pathogens. The aims of the guidance are to ensure that:

- pregnant women and their offspring benefit from advances in vaccine technologies and are not left behind as new vaccine products are developed;

de mise au point et d'évaluation des nouveaux produits.

- Systèmes de vaccination: il convient de s'appuyer davantage sur la recherche opérationnelle et la recherche dans d'autres domaines pour améliorer les performances des systèmes nationaux de vaccination et évaluer les innovations en matière de prestation des services qui permettraient d'atteindre les populations mal desservies.
- Les capacités de recherche vaccinale des pays à revenu faible ou intermédiaire doivent être renforcées dans tous ces domaines.

Une note conceptuelle décrivant les éléments d'un programme mondial de vaccination pour la prochaine décennie (2021-2030) a été présentée au SAGE. Le SAGE a pris note du calendrier serré proposé pour l'élaboration et la soumission de ce programme à l'Assemblée mondiale de la Santé de mai 2020, où il fera l'objet de discussions, et a souligné la nécessité de tirer tous les enseignements du GVAP actuel pour orienter ce nouveau programme. Le SAGE a vivement encouragé l'OMS à collaborer avec tous les partenaires pertinents dans les domaines de la vaccination et de la santé publique en général et à promouvoir une approche ascendante, fondée sur la participation des organisations de la société civile.

Rapport d'activité des partenaires internationaux dans le domaine de la vaccination

Le groupe de travail Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT)⁶ a été invité à faire une présentation lors de cette réunion. L'objectif de PREVENT est de formuler des orientations concrètes, exploitables et consensuelles sur l'inclusion équitable des intérêts des femmes enceintes et de leurs enfants dans les activités de R&D sur les vaccins contre les agents pathogènes prioritaires et les menaces épidémiques émergentes.

PREVENT est un groupe de travail pluridisciplinaire composé d'experts dans les domaines de la bioéthique, de la vaccination maternelle, de la médecine maternelle et fœtale, de l'obstétrique, de la pédiatrie, de la philosophie, de la santé publique et de la recherche vaccinale. Son secrétariat se trouve à l'Université Johns Hopkins (Baltimore, États-Unis d'Amérique). Ce groupe a été créé à la suite des récentes épidémies de maladie à virus Zika, de fièvre de Lassa, de maladie à virus Ebola et de grippe H1N1, qui ont exposé les femmes enceintes et leurs enfants à un risque accru de maladie grave et de décès et provoqué des fausses couches ou des atteintes congénitales graves. Les intérêts de ces populations doivent être pris en compte dans les efforts proactifs de lutte contre les menaces épidémiques.

Le groupe PREVENT prépare actuellement une feuille de route pour une prise en compte respectueuse, éthiquement responsable et socialement équitable des intérêts des femmes enceintes dans le développement et le déploiement des vaccins contre les agents pathogènes émergents. L'objectif de ces orientations est de veiller à ce que:

- les femmes enceintes et leurs enfants profitent des avancées des technologies vaccinales et ne soient pas laissés pour compte lorsque de nouveaux produits vaccinaux sont mis au point;

⁶ See <http://guidance.zikapregnancyethics.org>

⁶ Voir <http://guidance.zikapregnancyethics.org>

- pregnant women are not unjustifiably excluded from participating in studies on vaccines; and
- pregnant women have safe, effective, accessible vaccines to protect them and their offspring against emerging and re-emerging pathogenic threats.

SAGE members welcomed the initiative, which is timely with regard to R&D of vaccines against emerging infectious diseases and projects for standardizing the reporting of pregnancy outcomes. SAGE cautioned that aspects such as the attitudes of health care providers, vaccine hesitancy and co-morbid conditions in pregnancy should also be considered. Careful risk-benefit assessments should be conducted when live vaccines are tested in pregnant women. SAGE members suggested that the guidance being prepared be extended to include lactating women, who represent another important group frequently excluded from vaccine development and use.

Polio

SAGE noted the work of the GPEI and the progress achieved in eradication, including the current situation in the 3 countries in which wild poliovirus (WPV) continues to circulate, namely Afghanistan, Nigeria and Pakistan. SAGE was also briefed on the outbreaks of circulating vaccine-derived polioviruses (cVDPVs) in DRC, Niger, Nigeria, Papua New Guinea and Somalia.

SAGE reiterated the importance of continuing to vaccinate unvaccinated children in countries in the most inaccessible areas of the globe and especially in the countries with continued transmission of WPV or which are experiencing outbreaks of cVDPVs.

In addition, SAGE stressed that the polio programme should work closely with the Expanded Programme on Immunization in strengthening routine vaccination and health systems in general. The underlying problem in cVDPV outbreaks is weak routine vaccination with OPV, yet the guidance for outbreak response consists only of well-developed standard operating procedures for polio SIAs and not maintaining, sustaining and strengthening routine vaccination as an integral part of the response. SAGE called for deliberate integration of the polio response into strengthening of routine vaccination and proposed the establishment of joint planning and joint implementation at country, regional and global levels.

SAGE was informed by the chair of the Independent Monitoring Board of an external review of polio programmes in the remaining countries endemic for WPV (Afghanistan, Nigeria with the last reported case in 2016 and Pakistan). SAGE agreed that solutions to elimination of WPV1 in Afghanistan and Pakistan must include active participation of communities and local leaders and coordination and collaboration with other sectors and programmes.

- les femmes enceintes ne soient pas indûment exclues de la participation aux essais sur les vaccins; et
- les femmes enceintes aient accès à des vaccins sûrs et efficaces pour se protéger et pour protéger leurs enfants des menaces pathogènes émergentes et réémergentes.

Les membres du SAGE ont salué cette initiative, qui est opportune en termes de R&D sur la vaccination contre les maladies infectieuses émergentes et au vu des projets de standardisation des rapports sur les issues de la grossesse. Le SAGE a rappelé qu'il faut également tenir compte de certains facteurs, comme l'attitude des prestataires de soins, la réticence face aux vaccins et la présence de comorbidités lors de la grossesse. Le rapport bénéfice/risque doit être soigneusement évalué pour tout essai de vaccins vivants chez la femme enceinte. Les membres du SAGE ont suggéré que les orientations en cours d'élaboration soient élargies pour inclure les femmes allaitantes, un autre groupe important qui est souvent négligé dans la mise au point et l'utilisation des vaccins.

Poliomyélite

Le SAGE a pris connaissance des travaux accomplis par l'IMEP et des progrès réalisés vers l'éradication, notamment de la situation actuelle dans les 3 pays où des poliovirus sauvages (PVS) continuent de circuler, à savoir l'Afghanistan, le Nigéria et le Pakistan. Des informations lui ont également été présentées concernant les flambées de poliovirus circulants dérivés d'une souche vaccinale (PVDVc) au Niger, au Nigéria, en Papouasie-Nouvelle-Guinée, en République démocratique du Congo et en Somalie.

Le SAGE a rappelé qu'il est important de poursuivre la vaccination des enfants non vaccinés dans les pays se trouvant dans les zones les plus inaccessibles de la planète, tout particulièrement dans les pays concernés par la persistance de la transmission de PVS ou par des flambées de PVDVc.

En outre, le SAGE a souligné que le programme de lutte contre la poliomyélite doit travailler en lien étroit avec le programme élargi de vaccination afin de renforcer la vaccination systématique et les systèmes de santé en général. Le problème qui sous-tend les flambées de PVDVc réside dans l'insuffisance de la vaccination systématique par le VPO. Cependant, les orientations relatives à la riposte aux flambées contiennent uniquement des modes opératoires normalisés complets concernant les activités de vaccination supplémentaire (AVS) contre la poliomyélite, et pas d'indication sur le moyen de maintenir, de pérenniser et de renforcer la vaccination systématique en tant que partie intégrante de la riposte. Le SAGE a appelé à une intégration délibérée de la riposte antipoliomyélitique aux efforts de renforcement de la vaccination systématique et a proposé que soient établies une planification et une mise en œuvre communes aux niveaux national, régional et mondial.

Le président du Comité de suivi indépendant a informé le SAGE de la réalisation d'un examen externe des programmes de lutte antipoliomyélitique dans les pays où les PVS demeurent endémiques (Afghanistan, Nigéria – où le dernier cas a été signalé en 2016 – et Pakistan). Le SAGE a convenu que pour éliminer le PVS1 en Afghanistan et au Pakistan, toute solution devra reposer sur la participation active des communautés et des dirigeants locaux, ainsi que sur la coordination et la collaboration avec d'autres secteurs et programmes.

SAGE noted that the supply of IPV is now sufficient for routine vaccination globally but is insufficient for SIAs and for catch-up activities to cover the approximately 42 million children who never received IPV because of supply constraints after the switch from trivalent to bivalent OPV. SAGE emphasized that IPV catch-up vaccination activities are necessary, should be conducted as soon as the supply allows and should be prioritized according to the risk criteria developed by the programme.

SAGE welcomed the appraisal of the Global Certification Commission (GCC) as a suitable means for reviewing the criteria for certification of eradication of polio. SAGE considered that eradication of cVDPVs should be included in the criteria for certification of global eradication. SAGE recognized that WPV3 has not been detected since November 2012 and agreed with the GCC that eradication of both WPV3 in addition to WPV2 could be certified before eradication of WPV1.

SAGE agreed that guidelines are required for public health management of exposure to live polioviruses in facilities and requested that a draft be presented for endorsement at its next meeting, in early 2019.

The development of criteria to assess readiness for withdrawal of bivalent OPV had previously been discussed; SAGE agreed that certification of WPV eradication is the most critical criterion, with the following:

- adequate population immunity, especially in high-risk communities;
- surveillance for poliovirus excretion by immunodeficient people and the availability of therapeutic options (antivirals) for clearing infections;
- no persistent circulation of cVDPV1 or cVDPV3 (i.e. beyond 6 months after first notification); and
- a sufficient IPV supply for all countries to adopt a 2 IPV dose schedule (either full or fractional).

SAGE welcomed progress in the development of whole-cell pertussis hexavalent vaccine and agreed that it increased the options for including IPV in routine vaccination schedules.

Measles and rubella

SAGE was given an update on global measles and rubella elimination. The Group noted the substantial progress in reducing the global incidence and mortality of measles since 2000 and the low measles incidence in the WHO Western Pacific Region in 2017. SAGE expressed concern, however, about the loss of elimination status for measles in the WHO Region of the Americas and in some countries in the WHO European Region, and the resurgence of measles in 4 of the 6 WHO Regions. SAGE highlighted the fragility of the gains made in measles elimination and the urgency of prioritizing measles in the global health agenda in order to achieve and sustain global and regional goals.

Le SAGE a constaté que l'approvisionnement en VPI est à présent suffisant pour les besoins de la vaccination systématique à l'échelle mondiale, mais reste insuffisant pour les AVS et les activités de rattrapage visant à couvrir les quelque 42 millions d'enfants n'ayant jamais reçu le VPI en raison de difficultés d'approvisionnement après la transition du VPO trivalent au VPO bivalent. Le SAGE a souligné que la vaccination de rattrapage par le VPI est indispensable et qu'elle devrait être effectuée dès que l'approvisionnement le permettra, avec un ordre de priorité établi en fonction des critères de risque définis par le programme.

Le SAGE a favorablement accueilli l'évaluation de la Commission mondiale de certification (GCC) comme constituant un moyen adapté d'examiner les critères applicables à la certification de l'éradication de la poliomyélite. Le SAGE a estimé que l'éradication des PVDVc devrait être incluse parmi les critères de certification de l'éradication mondiale. Vu qu'aucun PVS3 n'a été détecté depuis novembre 2012, le SAGE a partagé l'avis de la GCC selon lequel l'éradication du PVS3, en sus de celle du PVS2, pourrait être certifiée avant celle du PVS1.

Le SAGE a convenu de la nécessité de lignes directrices sur la gestion en santé publique de l'exposition à des poliovirus vivants dans les établissements et a demandé qu'un projet lui soit présenté pour approbation lors de sa prochaine réunion, au début 2019.

L'élaboration de critères pour évaluer l'état de préparation à l'arrêt du VPO bivalent avait déjà fait l'objet de discussions; le SAGE a convenu que la certification de l'éradication des PVS est le critère le plus important, défini comme suit:

- immunité adéquate de la population, en particulier dans les communautés à haut risque;
- surveillance de l'excrétion de poliovirus par les sujets immunodéficients et disponibilité d'options thérapeutiques (antiviraux) contre les infections;
- aucune circulation persistante de PVDVc1 ou PVDVc3 (c'est-à-dire plus de 6 mois après la première notification); et
- approvisionnement suffisant en VPI pour la mise en place d'un schéma vaccinal à 2 doses de VPI (complètes ou fractionnées) dans tous les pays.

Le SAGE s'est félicité des progrès accomplis dans la mise au point du vaccin hexavalent à valence coquelucheuse à germes entiers, estimant que cela offre des options supplémentaires pour l'inclusion du VPI dans les calendriers de vaccination systématique.

Rougeole et rubéole

Des informations actualisées sur l'élimination mondiale de la rougeole et de la rubéole ont été présentées au SAGE. Le SAGE a pris note des progrès substantiels réalisés depuis 2000 en termes de réduction de l'incidence et de la mortalité rougeoleuses à l'échelle mondiale, ainsi que du faible taux d'incidence enregistré dans la Région OMS du Pacifique occidental en 2017. Le SAGE s'est toutefois dit préoccupé par le fait que la Région OMS des Amériques et certains pays de la Région européenne aient perdu leur statut de zones exemptes de rougeole, ainsi que par la résurgence de la rougeole dans 4 des 6 Régions de l'OMS. Le SAGE a souligné la fragilité des gains acquis en matière d'élimination de la rougeole et la nécessité urgente de faire de la rougeole une priorité dans le programme mondial d'action sanitaire afin d'atteindre durablement les objectifs mondiaux et régionaux.

At the World Health Assembly in 2017, the Director-General was requested to report through the Executive Board to the World Health Assembly in 2020 “on the epidemiological aspects and feasibility of, and potential resource requirements for, measles and rubella eradication”. SAGE agreed with the proposed content of the feasibility report and requested that, given the slow progress in meeting existing global and regional goals, the report include the potential risks of proceeding with the global eradication goal should the report conclude that the goals are feasible. SAGE further recommended that the report include: (i) an assessment of the impact of the capacity of countries’ health systems on a measles eradication goal, (ii) the essential role of routine vaccination in a life-course approach and of health system strengthening to eradicate measles, (iii) a discussion on the financial sustainability of strategies to achieve and sustain eradication, and (iv) the place of eradication goal within the SDGs.

SAGE was presented with new data on co-administration of measles and rubella-containing (MR) vaccines with YF vaccine, as a study had shown less seroconversion to rubella, mumps and YF antibodies when the vaccines were co-administered. New data from randomized controlled trials (RCTs) confirmed interference only in antibody titres and not in seroconversion. The trials provide evidence of interference with the magnitude of the antibody response against rubella, mumps and YF when the vaccines are co-administered; however, although the magnitude is lower, the titres are robust in all groups. Co-administration of MR or measles, mumps and rubella (MMR) and YF vaccines does not interfere with measles seroconversion or the magnitude of the antibody response against measles. There was no evidence of safety concerns in any of the studies. The conclusion was that delaying vaccination with one of the vaccines to a later visit instead of co-administering them would probably have a far more deleterious effect on population immunity than any potential reduction in the immune response due to co-administration. SAGE therefore recommended that WHO maintain its current guidance that MR/MMR and YF vaccines be administered at the same visit or at least 4 weeks apart (the schedule that maximizes coverage of all antigens in national vaccination schedules) and that WHO remove all cautionary statements about co-administration. SAGE stated that additional research should be conducted to determine whether the lower titres or antibody concentrations against rubella, mumps and YF observed after co-administration affect long-term immunity and cause secondary vaccine failures.

SAGE reviewed new guidance to support countries in identifying and addressing gaps in immunity to measles and rubella in order to increase population immunity. SAGE endorsed the following guiding principles for vaccination programmes in all countries, according to

Lors de l’Assemblée mondiale de la Santé de 2017, il a été demandé au Directeur général de faire rapport à l’Assemblée mondiale de la Santé de 2020, au travers du Conseil exécutif, sur «les aspects épidémiologiques, la faisabilité et les besoins potentiels en ressources de l’éradication de la rougeole et de la rubéole». Le SAGE a approuvé le contenu du rapport de faisabilité qui était proposé. Compte tenu de la lenteur des progrès accomplis vers la réalisation des objectifs mondiaux et régionaux existants, le SAGE a demandé que le rapport aborde les risques potentiels associés à la poursuite de l’objectif mondial d’éradication si le rapport conclut que les objectifs sont réalisables. Le SAGE a en outre recommandé que le rapport contienne: i) une évaluation de l’impact de la capacité des systèmes de santé nationaux sur l’objectif d’éradication de la rougeole, ii) un rappel du rôle essentiel de la vaccination systématique dans une approche prenant en compte toutes les étapes de la vie, ainsi que du renforcement des systèmes de santé, pour éradiquer la rougeole, iii) une discussion sur la viabilité financière des stratégies destinées à atteindre et maintenir l’éradication, et i) une description de la place dévolue à l’objectif d’éradication dans le cadre des ODD.

De nouvelles informations sur la coadministration des vaccins à valences rougeole et rubéole (RR) avec le vaccin anti-*amari* ont été présentées au SAGE, faisant suite à une étude qui avait indiqué une séroconversion réduite pour les anticorps de la rubéole, des oreillons et de la fièvre jaune lorsque les vaccins étaient coadministrés. De nouvelles données issues d’essais contrôlés randomisés ont confirmé une interférence uniquement au niveau des titres d’anticorps, et non de la séroconversion. Les essais ont démontré la présence d’une interférence au niveau de l’ampleur de la réponse en anticorps contre la rubéole, les oreillons et la fièvre jaune lorsque les vaccins sont coadministrés; cependant, bien que d’ampleur plus faible, les titres demeurent solides dans tous les groupes. La coadministration des vaccins RR ou ROR (rougeole, oreillons et rubéole) avec le vaccin anti-*amari* n’interfère pas avec la séroconversion rougeoleuse ou l’ampleur de la réponse en anticorps contre la rougeole. Aucune des études n’a révélé de motifs d’inquiétude en matière d’innocuité. Il a été conclu que la décision de retarder l’administration de l’un des vaccins à une visite ultérieure plutôt que de procéder à une coadministration aurait probablement des effets beaucoup plus délétères pour l’immunité de la population que la baisse potentielle de réponse immunitaire résultant de la coadministration. Le SAGE a donc recommandé que l’OMS maintienne ses orientations actuelles, qui prévoient l’administration des vaccins RR/ROR et anti-*amari* lors de la même visite ou à un intervalle d’au moins 4 semaines (schéma permettant une couverture maximale pour tous les antigènes dans les calendriers nationaux de vaccination), et que l’OMS supprime tous les énoncés de mise en garde relatifs à la coadministration. Le SAGE a indiqué que des travaux de recherche supplémentaires devraient être menés pour déterminer si les faibles titres d’anticorps contre la rubéole, les oreillons et la fièvre jaune qui ont été observés après une coadministration altèrent l’immunité à long terme et entraînent des échecs vaccinaux secondaires.

Le SAGE a examiné les nouvelles orientations formulées pour aider les pays à identifier et à combler les lacunes de l’immunité à la rougeole et à la rubéole en vue d’accroître l’immunité de la population. Le SAGE a approuvé les principes directeurs suivants pour les programmes de vaccination de tous les pays,

a “continuous quality improvement” approach that entails following 4 steps in regular cyclical review: (i) review all available national and subnational data on the epidemiology of measles and rubella or congenital rubella syndrome and potential immunity gaps; assess the general epidemiological profile of the country; identify, prioritize and implement interventions; and assess the outcomes of interventions. (ii) Strengthen routine vaccination as the primary strategy for increasing population immunity. (iii) Conduct campaigns (as rescue measures) when routine vaccination with 2 doses of measles and rubella-containing vaccines is suboptimal and to address specific gaps in immunity. (iv) During and after campaigns, quickly prioritize activities to strengthen routine vaccination.

SAGE stressed that vaccination campaigns are resource intensive and are not sustainable as a strategy. Countries should therefore prioritize routine strengthening, so that they become less reliant on campaigns. The primary goal of campaigns should be to reach unvaccinated (also known as “zero dose”) and under-vaccinated children. Unvaccinated children should be identified, monitored and documented so that they can also be given other vaccines and health interventions. Campaigns should be used as opportunities to strengthen the immunization system and integrate other health interventions, to the extent that additional interventions or activities do not compromise the quality of the campaign.

Countries with medium disease incidence and periodic outbreaks, inadequate immunity in some populations and moderate programme capacity (e.g. MCV1 coverage of 85–90% and MCV2 coverage of 80–90%) can conduct targeted campaigns according to the epidemiological profile of the subnational areas concerned if high-quality data are available for accurate subnational analysis.⁷

Countries should also use strategies to fill known gaps in immunity in populations such as health care workers and migrants and increase preparedness for outbreaks so that they can be rapidly detected, investigated and contained.

Human papilloma virus

SAGE welcomed the WHO Director-General’s launch in May 2018 of a multi-stakeholder “Call for action: towards cervical cancer elimination”. Cervical cancer is the fourth most common cancer among women globally, with an estimated 570 000 new cases and 311 000 deaths annually in 2018. Unless services are increased urgently, the burden is projected to increase to almost 460 000 deaths per year by 2040, a nearly 50% increase over 2018. The increase will be uneven, with the greatest

conformément à une approche d’amélioration continue de la qualité consistant en une évaluation périodique régulière à 4 étapes: i) examen de toutes les données nationales et infranationales disponibles concernant l’épidémiologie de la rougeole et de la rubéole ou du syndrome de rubéole congénitale et les lacunes immunitaires potentielles; évaluation du profil épidémiologique général du pays; identification, hiérarchisation et mise en œuvre des interventions; et évaluation des résultats des interventions; ii) renforcement de la vaccination systématique en tant que stratégie principale d’amélioration de l’immunité de la population; iii) conduite de campagnes (à titre de mesures de secours) lorsque la vaccination systématique par 2 doses de vaccin à valences rougeole et rubéole est insuffisante ou pour combler des lacunes immunitaires particulières; iv) avant et après les campagnes, identification rapide des activités prioritaires pour renforcer la vaccination systématique.

Le SAGE a souligné que les campagnes de vaccination nécessitent d’importantes ressources et ne constituent pas une stratégie durable. Les pays doivent donc accorder la priorité au renforcement de la vaccination systématique pour devenir moins dépendants de ces campagnes. L’objectif principal des campagnes doit être d’atteindre les enfants non vaccinés («enfants zéro dose») et insuffisamment vaccinés. Il convient d’identifier, de suivre et d’enregistrer les enfants non vaccinés pour veiller à ce qu’ils bénéficient d’autres vaccins et d’autres interventions de santé. Les campagnes fournissent l’occasion de renforcer le système de vaccination et d’intégrer d’autres interventions de santé, dans la mesure où ces interventions ou activités supplémentaires ne compromettent pas la qualité de la campagne.

Les pays affichant une incidence moyenne de la maladie, des flambées périodiques, une immunité insuffisante de certaines populations et des capacités programmatiques modérées (par exemple, couverture de 85-90% par le MCV1 et de 80-90% par le MCV2) peuvent mener des campagnes ciblées en fonction du profil épidémiologique des zones infranationales concernées si des données de qualité sont disponibles pour permettre une analyse exacte au niveau infranational.⁷

Des stratégies doivent également être mises en œuvre par les pays afin de combler les lacunes immunitaires connues parmi certaines populations, comme les agents de santé et les migrants, et d’améliorer la préparation aux flambées pour assurer une détection, une investigation et un endiguement rapides des flambées.

Papillomavirus humain

Le SAGE a salué l’appel à l’action pour l’élimination du cancer du col de l’utérus lancé par le Directeur général de l’OMS en mai 2018. Le cancer du col de l’utérus est au quatrième rang des cancers les plus courants chez la femme dans le monde. On estime qu’en 2018, le nombre annuel de nouveaux cas s’établissait à 570 000, avec 311 000 décès. À moins d’une intensification rapide des services, les prévisions indiquent que la charge de la maladie devrait progresser pour atteindre près de 460 000 décès par an d’ici 2040, soit presque 50% de plus qu’en 2018. Cette

⁷ This also requires epidemiologically distinct, heterogeneous geographical areas, and the subnational approach must be programmatically feasible. The SAGE working group on measles and rubella is working on more precise guidance for countries using a targeted subnational approach, which will be presented to SAGE in 2019.

⁷ Cela suppose également que les zones géographiques soient distinctes et hétérogènes sur le plan épidémiologique et que l’approche infranationale soit réalisable d’un point de vue programmatique. Le groupe de travail du SAGE sur la rougeole et la rubéole est en train d’élaborer des orientations plus précises pour les pays qui utilisent une approche infranationale ciblée. Ces orientations seront présentées au SAGE en 2019.

relative increase in LICs, further compounding the wide variation in the rates of cervical cancer incidence and mortality across the world; nearly 90% of deaths occur in LICs and MICs.

Globally, 85 countries (44%) have introduced HPV vaccine into their national vaccination programmes; however, introduction in countries with the highest burden of cervical cancer is lagging. It is estimated that only 25% of the world's population of 10-year-old girls lives in countries with access to HPV vaccine. HPV vaccine has been introduced in 84% of high-income countries but in only 31% of MICs and 12% of LICs. Impediments such as affordability, availability, access, hesitancy, supply and decision-making affect the introduction and uptake of HPV vaccination in most countries.

SAGE reviewed the latest evidence on the immunogenicity, efficacy and effectiveness of HPV vaccines, their administration schedules, number of doses and intervals, and use in HIV-infected and in male populations. SAGE concluded that the WHO position paper in 2017 remains valid. For the prevention of cervical cancer, HPV vaccination with a 2-dose schedule of the WHO-recommended target population, 9–14-year-old girls, is the most effective strategy. A 3-dose schedule continues to be recommended for girls in this age group who are immunocompromised and for girls and women ≥ 15 years of age. To accelerate the impact, vaccination of multiple cohorts of girls aged 9–14 years is recommended when the vaccine is first introduced. SAGE noted that, although use of a 1-dose schedule would facilitate the vaccine's use, there is insufficient evidence at this time to recommend it.

All 3 licensed HPV vaccines have excellent safety, efficacy and effectiveness profiles. The choice of HPV vaccine should be based on an assessment of locally relevant data and a number of other factors, including the scale of the prevailing HPV-associated public health problem (cervical cancer, other HPV-associated cancers, anogenital warts). Decision-makers should also consider unique product characteristics, such as price, availability and programmatic considerations.

The results of a comparison of 3 models with optimistic assumptions of the life-time duration of vaccine protection and highly effective cervical cancer screening show the impact and effectiveness of various HPV vaccination and screening strategies and the potential for cervical cancer elimination at proposed incidence thresholds of $<10/100\,000$ and $<4/100\,000$ women-years. The 3 models produced consistent findings. Vaccination of girls only at a coverage rate $>80\%$ could eliminate cervical cancer in most countries and regions without changes to any current screening practices. In the same vaccination scenario, adding 1 or 2 highly effective cervical cancer screenings during the lifetime of each woman would lead to a lower cervical cancer incidence, sooner. Because vaccination of girls only has high population-level effectiveness and a strong herd effect, it was

hausse sera inégale, les pays à revenu faible étant ceux où l'augmentation relative sera la plus forte, ce qui ne fera qu'amplifier la variabilité déjà forte des taux d'incidence et de mortalité du cancer du col dans le monde; près de 90% des décès surviennent dans les pays à revenu faible ou intermédiaire.

À l'échelle mondiale, 85 pays (44%) ont introduit le vaccin contre le PVH dans leur programme national de vaccination, mais les pays présentant la plus forte charge de cancer du col sont à la traîne. On estime que seulement 25% des filles de 10 ans dans le monde vivent dans des pays où le vaccin anti-PVH est accessible. Le vaccin a été introduit dans 84% des pays à revenu élevé, mais seulement 31% des pays à revenu intermédiaire et 12% des pays à revenu faible. Certains facteurs, comme le prix, la disponibilité, l'accessibilité, la réticence face à la vaccination, l'approvisionnement et le processus de prise de décision, entravent l'introduction et l'adoption de la vaccination anti-PVH dans la plupart des pays.

Le SAGE a examiné les données les plus récentes concernant l'immunogénicité et l'efficacité des vaccins anti-PVH, leurs schémas d'administration, le nombre et l'espacement des doses et leur utilisation chez les personnes infectées par le VIH et chez les sujets de sexe masculin. Le SAGE a conclu que la note de synthèse publiée en 2017 par l'OMS reste valable. Pour la prévention du cancer du col de l'utérus, la vaccination anti-PVH selon un schéma à 2 doses dans la population cible recommandée par l'OMS, à savoir les filles âgées de 9 à 14 ans, est la stratégie la plus efficace. Un schéma à 3 doses reste recommandé pour les filles de cette tranche d'âge qui sont immunodéprimées, ainsi que pour les adolescentes et les femmes de ≥ 15 ans. Pour accélérer l'impact de cette intervention, il est recommandé de vacciner plusieurs cohortes de filles âgées de 9 à 14 ans au moment où le vaccin est introduit dans le programme de vaccination. Le SAGE a indiqué que l'utilisation d'un schéma à dose unique, bien que plus facile, ne peut être recommandé à ce stade par manque de données.

Les 3 vaccins anti-PVH homologués possèdent tous d'excellents profils de sécurité et d'efficacité. Le choix du vaccin devra reposer sur l'évaluation des données localement pertinentes et sur un certain nombre d'autres facteurs, dont l'ampleur du problème prévalent de santé publique associé au PVH (cancer du col, autres cancers liés au PVH ou condylomes anogénitaux). Les décideurs devront aussi tenir compte des caractéristiques propres au produit, comme le prix, la disponibilité et les considérations programmatiques.

Une comparaison de 3 modèles, reposant sur des hypothèses optimistes d'une protection à vie conférée par le vaccin et d'un dépistage très efficace du cancer du col, a permis de montrer l'impact et l'efficacité de différentes stratégies de dépistage et de vaccination anti-PVH et la probabilité d'éliminer le cancer du col aux seuils d'incidence proposés de $<10/100\,000$ et $<4/100\,000$ femmes-années. Les 3 modèles ont donné des résultats cohérents. Une vaccination effectuée uniquement chez les filles à un taux de couverture de $>80\%$ pourrait éliminer le cancer du col de l'utérus dans la majorité des pays et des régions sans aucune modification des pratiques actuelles de dépistage. Dans le même scénario de vaccination, l'ajout de 1 ou 2 dépistages très efficaces du cancer du col au cours de la vie de chaque femme entraînerait une baisse plus rapide de l'incidence du cancer du col. Comme l'approche consistant à vacciner uniquement les filles est très efficace au niveau de la

found to be highly cost-effective, irrespective of the vaccine used. In all countries, increasing coverage of girls has a greater impact on cervical cancer disease than extending vaccination to boys. With the optimistic assumptions and depending on the strategy and threshold used, elimination could be achieved in all countries between 2085 and 2105 if vaccination is introduced now in all countries at 90% coverage. Increasing the number of screens per woman to 2, as modelled, and vaccinating cohorts of several age groups would accelerate elimination by 5–15 years.

SAGE agreed that the modelling exercise was robust, helpful and informative and affirmed that HPV vaccination is the most critical intervention for eliminating cervical cancer. With respect to immunization, the following interim goals were proposed: by 2030, all countries should have introduced HPV vaccination in their national vaccination programme for at least one age cohort of girls and achieved at least 80% final dose coverage. Introduction of HPV vaccine should be prioritized in countries with the highest cervical cancer rates.

SAGE recommended that the options for monitoring indicators – introduction of HPV vaccine, a reduction in the prevalence of high-risk 16/18 genotypes, screening and treatment for cervical cancer and the rates of high-grade cervical intra-epithelial neoplasia and cervical cancer – should be further reviewed by a multi-sectoral group at WHO, which should also review the rationale for selecting indicators and the quantifiable targets set.

Concerned about the impact of a constrained HPV vaccine supply forecast until at least 2024, SAGE urged that a globally more equitable distribution of the available doses be encouraged to ensure optimal global public health access to the vaccine. Countries that currently implement extended vaccination strategies (including target groups of boys, cohorts of different ages and older age groups) may consider rationalizing their vaccine use in order to make urgently needed vaccine available in countries with a high burden of disease. Additionally, SAGE called for: (i) collaboration with all current and future manufacturers to expedite increases in the vaccine supply and (ii) comprehensive evaluation of the options for best use and allocation of the limited vaccine supply, including extended intervals between doses until additional data become available on use of a single dose, and targeting of vaccine to high-burden countries.

SAGE noted that research and further review of the evidence are required on: alternative vaccination schedules (e.g. single-dose schedule), including guidance on possible extension of the timing of the second dose; vaccine effectiveness in HIV-infected and malnourished populations; the comparative effectiveness and cost-effectiveness of the 9-valent HPV vaccine; and the burden of disease other than cervical cancer associated with HPV infection.

population et produit un fort effet d'immunisation collective, elle présente un très bon rapport coût/efficacité quel que soit le vaccin utilisé. Dans tous les pays, l'amélioration de la couverture chez les filles a un impact plus important sur le cancer du col que l'élargissement de la vaccination aux garçons. Sur la base des hypothèses optimistes définies et selon la stratégie et le seuil utilisés, tous les pays pourraient parvenir à l'élimination entre 2085 et 2105 si la vaccination est introduite dès à présent dans tous les pays à un taux de couverture de 90%. L'augmentation du nombre de dépistages pour passer à 2 dépistages par femme, comme dans la modélisation, et la vaccination de cohortes de différentes tranches d'âge accélérerait l'élimination, qui serait atteinte 5 à 15 ans plus tôt.

Le SAGE a estimé que cet exercice de modélisation était rigoureux, utile et instructif et a affirmé que la vaccination anti-PVH est l'intervention la plus importante pour éliminer le cancer du col de l'utérus. En termes de vaccination, les objectifs intermédiaires suivants ont été proposés: d'ici 2030, il faudrait que tous les pays aient introduit le vaccin anti-PVH dans leur programme national de vaccination pour au moins une cohorte d'âge de filles et aient atteint une couverture d'au moins 80% pour la dose finale. L'introduction du vaccin anti-PVH doit se faire en priorité dans les pays enregistrant les taux les plus élevés de cancer du col.

Le SAGE a recommandé que les options en termes d'indicateurs de suivi – introduction du vaccin anti-PVH, réduction de la prévalence des génotypes 16/18 à haut risque, dépistage et traitement du cancer du col et taux de cancer du col et de néoplasie intraépithéliale cervicale de haut grade – soient étudiées de manière plus approfondie par un groupe multisectoriel de l'OMS, qui devra également examiner les motifs justifiant le choix des indicateurs, ainsi que les cibles quantifiables fixées.

Préoccupé par les répercussions qu'auront les difficultés d'approvisionnement en vaccin anti-PVH escomptées jusqu'en 2024 au moins, le SAGE a insisté sur la nécessité d'encourager une distribution plus équitable des doses disponibles pour garantir un accès de santé publique optimal au vaccin à l'échelle mondiale. Les pays qui appliquent actuellement des stratégies de vaccination élargie (incluant des groupes cibles de garçons, des cohortes d'âges différents et des groupes d'âge plus avancé) pourraient envisager de rationaliser leur utilisation du vaccin pour permettre aux pays à forte charge de morbidité de disposer des vaccins dont ils ont ardemment besoin. En outre, le SAGE a appelé à: i) une collaboration avec tous les fabricants actuels et futurs pour accélérer la hausse de la production de vaccins et ii) une évaluation exhaustive des options qui permettraient une utilisation et une allocation optimales des stocks limités de vaccin, notamment en augmentant l'écart entre les doses jusqu'à ce que des données supplémentaires sur l'utilisation d'une dose unique soient disponibles et en ciblant les pays à forte charge de morbidité.

Le SAGE a indiqué que des travaux de recherche supplémentaires et un examen approfondi des données sont nécessaires dans les domaines suivants: autres schémas d'administration du vaccin (par exemple, dose unique), avec notamment des orientations sur la possibilité d'administrer la seconde dose plus tardivement; efficacité du vaccin chez les sujets infectés par le VIH et les personnes souffrant de malnutrition; efficacité et rapport coût/efficacité comparatifs du vaccin anti-PVH non-valent; et charge des maladies autres que le cancer du col associées à une infection à PVH.

Ebola virus disease

SAGE discussed a review of data submitted by developers of candidate vaccines and of published data. Thirteen candidate monovalent, bivalent and multivalent vaccines against EVD have been or are currently being evaluated in clinical trials. SAGE recognized that significant progress has been made in the development and evaluation of several candidate vaccines against Ebola virus and other filoviruses. SAGE also reviewed the epidemiology of EVD and the progress in implementation of the “expanded access and compassionate use” protocol in the DRC, where over 20 000 individuals at risk have received the rVSV-ZEBOV vaccine. SAGE recognized the massive efforts made by the Government of DRC and its partners to fight the epidemic.

SAGE discussed the results of modelling of the impact of various preventive and reactive vaccination strategies. For reactive vaccination, the results suggest that ring vaccination would best reduce the duration of outbreaks and the number of cases, if it were implemented in conjunction with reactive vaccination of health care and front-line workers and with full non-vaccine outbreak control measures. Comprehensive contact tracing is essential for effective ring vaccination, as missed infected contacts can seed outbreaks in new areas. For preventive strategies, vaccination of health care workers has significant potential for reducing the scale and duration of outbreaks.

SAGE reiterated that, should an EVD outbreak due to the Zaire strain occur before a candidate vaccine is licensed, rVSV-ZEBOV vaccine should be promptly deployed within the expanded access framework, with informed consent and in compliance with good clinical practice. Ring vaccination, as used in the phase-3 study in Guinea, is the recommended strategy for delivery, to be adapted to the social and geographical conditions of the outbreak areas and include people at risk: (i) contacts and contacts of contacts, (ii) local and international health care and front-line workers in affected areas and (iii) health care and front-line workers in areas at risk due to extension of the outbreak. A geographically targeted vaccination strategy may be considered in when it is impossible to identify the individuals who make up ring vaccination cohorts because of serious security, social or epidemiological issues. In this case, the geographical area immediately around a case of EVD, such as a village or a neighbourhood, is most likely to include those individuals who were contacts or contacts of contacts of the index case.

If an outbreak is caused by an Ebola virus strain other than Zaire, consideration should be given to using candidate vaccines that target the respective viral strain. Currently, 1 multivalent vaccine (Ad26.ZEBOV/MVA-BN-Filo) is in phase 2 of clinical development. SAGE noted that opportunities should be sought to assess the efficacy of other candidate EVD vaccines, such as in health care and front-line workers in areas that are not at high risk for EVD and are thus not eligible to receive the

Maladie à virus Ebola

Le SAGE a examiné une revue des données soumises par les concepteurs de vaccins candidats, ainsi que des données publiées. Treize vaccins candidats contre la MVE – monovalents, bivalents et multivalents – ont été évalués ou sont en cours d'évaluation dans le cadre d'essais cliniques. Le SAGE a reconnu les progrès considérables accomplis dans la mise au point et l'évaluation de plusieurs vaccins candidats contre le virus Ebola et d'autres filovirus. Il a en outre fait le point sur l'épidémiologie de la MVE et sur la mise en œuvre du protocole «d'accès élargi et d'usage compassionnel» en RDC, où le vaccin rVSV-ZEBOV a été administré à plus de 20 000 personnes à risque. Le SAGE a salué les efforts massifs déployés par le gouvernement de la RDC et ses partenaires pour combattre cette épidémie.

Le SAGE a examiné les résultats d'une modélisation de l'impact de diverses stratégies de vaccination préventive et réactive. S'agissant de la vaccination réactive, les résultats semblent indiquer que la vaccination en anneau est mieux à même de réduire la durée des flambées et le nombre de cas si elle s'accompagne d'une vaccination réactive des agents de santé et des agents de première ligne, ainsi que de mesures non vaccinales complètes de lutte contre les flambées. Pour que la vaccination en anneau soit efficace, il est essentiel de procéder à une recherche exhaustive des contacts, car tout contact infecté qui n'aurait pas été détecté peut être à l'origine de flambées dans de nouvelles zones. Pour ce qui est des stratégies préventives, la vaccination des agents de santé peut sensiblement réduire l'ampleur et la durée des flambées.

Le SAGE a réaffirmé que si une flambée de MVE due à la souche Zaire devait survenir avant l'homologation d'un vaccin candidat, il conviendrait de déployer rapidement le vaccin rVSV-ZEBOV dans le cadre du protocole d'accès élargi, en veillant à recueillir le consentement éclairé des bénéficiaires et à respecter les bonnes pratiques cliniques. La vaccination en anneau, telle qu'elle est utilisée dans l'étude de phase 3 en Guinée, est la stratégie recommandée pour l'administration du vaccin. Elle doit être adaptée aux conditions sociales et géographiques des zones touchées par la flambée et inclure les personnes à risque, notamment: i) les contacts et les contacts de contacts, ii) les agents de santé et agents de première ligne locaux et internationaux dans les zones touchées et iii) les agents de santé et agents de première ligne dans les zones où il existe un risque de propagation de la flambée. Une stratégie de vaccination ciblée sur le plan géographique peut être envisagée lorsqu'il est impossible d'identifier les individus formant les cohortes de la vaccination en anneau en raison de graves problèmes sécuritaires, sociaux ou épidémiologiques. Dans ce cas, la zone géographique se trouvant dans le voisinage immédiat d'un cas de MVE, comme un village ou un quartier, est considérée comme la plus susceptible d'inclure des personnes qui sont des contacts ou des contacts de contacts du cas indicateur.

Si une flambée est provoquée par une souche de virus Ebola autre que Zaire, on envisagera d'utiliser des vaccins candidats ciblant la souche virale en question. Actuellement, 1 vaccin multivalent (Ad26.ZEBOV/MVA-BN-Filo) est en phase 2 de développement clinique. Le SAGE a préconisé d'explorer les possibilités d'évaluation de l'efficacité d'autres vaccins candidats contre la MVE, notamment chez les agents de santé et les agents de première ligne qui travaillent dans des zones non sujettes à un risque élevé de MVE et qui ne remplissent donc pas les

rVSV-ZEBOV vaccine in current study protocols and SAGE recommendations.

Particular consideration should be given to the inclusion of pregnant and lactating women into vaccine research. Data on use of the vaccine in paediatric populations in such trials should be recorded. SAGE reviewed the data on the risks and safety of vaccinating pregnant women with the replicating live virus vaccine rVSV-ZEBOV. The preliminary results of a risk-benefit analysis to compare the safety of rVSV-ZEBOV vaccination in pregnancy with the risk of acquiring EVD in a setting of ring vaccination were examined. The risk for acquiring EVD of unvaccinated people, including pregnant women, in vaccination rings is very low (0.12%, 95% CI 0.02; 0.28) at a vaccination coverage of eligible people of $\geq 50\%$, probably as a result of herd immunity. It was noted that the data were insufficient to establish the risk for EVD of vaccinated rings at lower coverage. Data on the safety of rVSV-ZEBOV vaccination in pregnancy are relatively limited.

The STRIVE trial is the single conducted RCT which includes pregnant women. In this study, 2.7% of the enrolled women had an estimated date of conception within 60 days of enrolment or vaccination. The frequency of pregnancy loss was 45% (14/31) in the immediately vaccinated group and 28% (5/18) in the group assigned to deferred crossover vaccination. In the unvaccinated group, the frequency of pregnancy loss was 31% (11/35). These results indicate that the relative risk of pregnancy loss was 1.35 (95% CI 0.73, 2.52) for women who became pregnant within 60 days of vaccination and 1.33 (0.56, 3.20) for those who became pregnant within 14 days of vaccination. The reasons for the difference in risk are not clear. The difference in pregnancy loss between the 2 groups was not statistically significant, but the sample size was small. Data are lacking on other pregnancy outcomes, on gestational age at time of vaccination and on follow up of mothers and children for 9 months after birth.

In summary, SAGE noted that (i) EVD in pregnancy is associated with in very high risks of maternal and fetal loss; (ii) in outbreaks, with no vaccination, the risk for EVD of contacts and contacts of contacts of patients with EVD is moderately high; and (iii) the risk of unvaccinated people in a ring vaccination cohort with vaccination coverage of $\geq 50\%$ is low. SAGE further noted that the risk of pregnant women for adverse effects after administration of the replicating live virus vaccine, rVSV-ZEBOV, remains largely unknown, given the limited data. SAGE recognized that a decision on whether to offer rVSV-ZEBOV, a systemically replicating vaccine virus, to pregnant women is complex, with ethical, clinical, epidemiological and social considerations. Inclusion of pregnant women in an EVD vaccine research protocol depends on local national regulatory authorities and local ethics review committees. SAGE encourages these bodies to assess the benefits and risks

critères établis pour recevoir le vaccin rVSV-ZEBOV au titre des protocoles d'étude actuels et des recommandations du SAGE.

Le SAGE a estimé qu'une attention particulière doit être accordée à la question de l'inclusion des femmes enceintes et allaitantes dans la recherche vaccinale. Les données relatives à l'utilisation du vaccin chez l'enfant dans le cadre des essais doivent être consignées. Le SAGE a étudié les données disponibles concernant les risques et l'innocuité de la vaccination par le rVSV-ZEBOV à virus vivant répliquatif chez la femme enceinte. Il a examiné les résultats préliminaires d'une analyse bénéfice/risque comparant la sécurité de la vaccination par le rVSV-ZEBOV pendant la grossesse au risque de contracter la MVE dans un contexte de vaccination en anneau. Dans un anneau de vaccination, le risque pour les personnes non vaccinées, y compris les femmes enceintes, de contracter la MVE est très faible (0,12%, IC à 95%: 0,02-0,28) lorsque la couverture s'élève à $\geq 50\%$ des personnes justiciables de la vaccination, probablement en raison de l'effet d'immunité collective. Il a été indiqué qu'on ne dispose pas de données suffisantes pour établir le risque de MVE dans les anneaux vaccinés lorsque le taux de couverture est plus faible. Les données sur l'innocuité du vaccin rVSV-ZEBOV pendant la grossesse sont relativement limitées.

L'essai STIVE est le seul essai contrôlé randomisé effectué qui inclut des femmes enceintes. Parmi les femmes ayant participé à cet essai, 2,7% ont présenté une grossesse avec une date estimée de conception survenue dans les 60 jours suivant l'inclusion dans l'étude ou la vaccination. Le taux de fausses-couches était de 45% (14/31) dans le groupe qui avait été vacciné immédiatement, de 28% (5/18) dans le groupe assigné à une vaccination différée après permutation et de 31% (11/35) dans le groupe non vacciné. Selon ces résultats, le risque relatif de fausse-couche était de 1,35 (IC à 95%: 0,73-2,52) chez les femmes dont la grossesse a débuté dans les 60 jours suivant la vaccination et de 1,33 (0,56-3,20) chez celles dont la grossesse a débuté dans les 14 jours suivant la vaccination. Les raisons de cet écart de risque ne sont pas claires. La différence des taux de fausses-couches entre ces 2 groupes n'était pas significative sur le plan statistique, mais la taille de l'échantillon était faible. On ne dispose pas de données sur les autres issues de la grossesse, sur l'âge gestationnel au moment de la vaccination et sur le suivi des mères et des enfants dans les 9 mois après la naissance.

En résumé, la SAGE a observé que i) la MVE pendant la grossesse est associée à un risque très élevé de décès maternel et fœtal; ii) lors de flambées, en l'absence de vaccination, le risque de MVE est modérément élevé pour les contacts et les contacts de contacts des patients atteints de MVE; et iii) le risque est faible pour les personnes non vaccinées appartenant à une cohorte de vaccination en anneau avec une couverture vaccinale $\geq 50\%$. Le SAGE a en outre indiqué que chez la femme enceinte, le risque d'effets indésirables consécutifs à l'administration du vaccin à virus vivant répliquatif, rVSV-ZEBOV, reste très incertain, compte tenu des données limitées dont on dispose. Le SAGE a reconnu que la décision d'offrir ou non le rVSV-ZEBOV, un virus vaccinal à répllication systématique, aux femmes enceintes est une décision complexe, devant tenir compte de nombreux aspects éthiques, cliniques, épidémiologiques et sociaux. L'inclusion des femmes enceintes dans un protocole de recherche sur les vaccins contre la MVE relève des autorités locales de réglementation et des comités locaux d'examen éthique. Le SAGE

of offering rVSV-ZEBOV to pregnant and lactating women during an outbreak. As front-line and health workers are at increased risk of exposure in an outbreak, SAGE recommends that national authorities consider offering the EVD vaccine to those who are pregnant or lactating, with an informed consent procedure.

SAGE encourages further review of emerging clinical and non-clinical evidence and encouraged researchers to find opportunities to gather more data on the benefits and risks of administering the replicating live virus experimental vaccine to pregnant women, particularly under conditions that permit close, sufficiently long follow-up of the women and their newborns to document the outcomes more completely.

SAGE reiterated that WHO should support the national regulatory authorities of countries endemic for EVD to reach consensus on pathways for the evaluation and marketing authorization of candidate EVD vaccines. Licensure of such vaccines remains a high, urgent priority, including candidates based on non-replicating technologies.

Lessons learned from diphtheria outbreaks: opportunities for early warning and preventive action

Outbreaks of VPDs continue to occur, despite the availability of effective vaccines. There are many reasons for outbreaks, including migration or internal displacement of populations, humanitarian crises, weak health infrastructure resulting in weak routine vaccination programmes, inadequate policy implementation and vaccine hesitancy. The cost of an outbreak response may be high, underlining the importance of preventive vaccination. SAGE used the case study of the outbreak of diphtheria among the Rohingya people in Cox's Bazaar, Bangladesh, in 2017 to review data from the global immunization programme and to determine whether they could be used to identify populations at risk for VPDs to better anticipate and prevent outbreaks.

Identification of at-risk populations and geographical areas is based on data on vaccination coverage and national and subnational surveillance. Analysis of granular, timely, good-quality data on coverage and surveillance can guide programmatic action on the basis of appropriate immunization policies. Since 2017, district-level data have been reported to WHO by 141 Member States. Collation and reporting of these data are time consuming, and their quality is variable. Many countries do not conduct surveillance for diphtheria, and even those that do rely on a clinical case definition, as they lack the laboratory capacity to diagnose and report confirmed diphtheria cases. While WHO recommends a total of 6 doses of diphtheria-containing vaccine, 178 of 194 countries have not given booster doses beyond the priming doses in the first year of life, which are required

encourage ces organes à évaluer les avantages et les risques associés à l'administration du rVSV-ZEBOV aux femmes enceintes et allaitantes au cours d'une flambée. Étant donné que les agents de santé et les agents de première ligne sont exposés à un risque accru lors d'une flambée, le SAGE recommande aux autorités nationales d'envisager l'administration du vaccin contre la MVE aux femmes enceintes ou allaitantes qui font partie de cette population, en veillant à recueillir leur consentement éclairé.

Le SAGE préconise de continuer à analyser les données probantes émergentes, tant cliniques que non cliniques, et encourage les chercheurs à trouver les moyens de recueillir davantage de données sur les avantages et les risques de l'administration du vaccin expérimental à virus vivant répliquatif aux femmes enceintes, en particulier dans des conditions permettant un suivi étroit et suffisamment long des femmes et de leurs nouveau-nés pour permettre une documentation plus complète des résultats.

Le SAGE a réaffirmé que l'OMS doit soutenir les autorités nationales de réglementation des pays d'endémie de la MVE pour qu'elles parviennent à un consensus sur les mécanismes d'évaluation et d'autorisation de mise sur le marché des vaccins candidats contre la MVE. L'homologation de tels vaccins, y compris des vaccins candidats reposant sur des techniques non répliquatives, demeure une priorité urgente et absolue.

Enseignements tirés des flambées de diphtérie: possibilités d'alerte précoce et de mesures préventives

Les maladies évitables par la vaccination continuent de donner lieu à des flambées, malgré la disponibilité de vaccins efficaces. De nombreux facteurs peuvent expliquer ces flambées, notamment la migration ou le déplacement interne des populations, les crises humanitaires, l'inadéquation des infrastructures sanitaires se traduisant par une vaccination systématique insuffisante, une mauvaise mise en œuvre des politiques et la réticence face aux vaccins. Les interventions de riposte à une flambée peuvent être coûteuses, ce qui rend la vaccination préventive d'autant plus importante. Se fondant sur une étude de cas traitant d'une flambée de diphtérie survenue parmi la population Rohingya de Cox's Bazaar, au Bangladesh, en 2017, le SAGE a examiné les données provenant du programme mondial de vaccination afin de déterminer si ces dernières pourraient être utilisées pour identifier les populations à risque de maladie à prévention vaccinale et mieux anticiper et prévenir les flambées.

Les populations et les zones géographiques à risque sont identifiées sur la base des données de la couverture vaccinale et de la surveillance nationale et infranationale. L'analyse des données de couverture et de surveillance, pour autant qu'elles présentent une bonne granularité, qu'elles soient disponibles en temps utile et qu'elles soient de qualité, peut guider les actions programmatiques sur la base de politiques de vaccination appropriées. Depuis 2017, 141 États Membres communiquent à l'OMS des données à l'échelon des districts. Le travail de regroupement et de notification de ces données prend du temps et est de qualité variable. De nombreux pays n'assurent pas de surveillance de la diphtérie. Cela vaut même pour ceux qui utilisent une définition de cas clinique, car ils ne disposent pas des capacités de laboratoire nécessaires pour diagnostiquer et notifier les cas confirmés de diphtérie. Alors que l'OMS recommande 6 doses de vaccin antidiphtérique au total, 178 pays sur

to combat waning immunity. Therefore, population immunity against diphtheria may be low despite good DTP3 coverage. To stop outbreaks of diphtheria, WHO recommends replacement of tetanus toxoid (TT) vaccine with tetanus-diphtheria (Td) vaccine and promotes booster vaccination.⁸ SAGE re-emphasized its previous recommendation to accelerate the availability of diphtheria antitoxin and to explore the use of monoclonal antibodies.

Opportunities to increase global data through the WIISE project were discussed. Both numerators and denominators of populations, including hidden and mobile populations, are required. SAGE advised greater collaboration with other stakeholders and United Nations agencies such as the International Organization for Migration for a multi-sectoral approach, with population mobility mapping exercises already under way. SAGE noted that use of data locally is the first step, as it demonstrates the usefulness of data and improves data quality. Locally, the issue is often not lack of data but lack of data analysis and use. Examples were provided of combinations of existing datasets and opportunities for using country data to predict risks. VPD outbreaks expose gaps in vaccination coverage, surveillance and policy implementation. Improving immunization and pre-empting outbreaks require data, investment in data and broad collaboration among countries, regions and at global level. ■

⁸ See No. 22, 2017, pp. 319–320.

194 n'administrent pas les doses de rappel après la primovaccination de la première année de vie, qui sont nécessaires pour combattre le déclin de l'immunité. Par conséquent, la population peut présenter un faible niveau d'immunité contre la diphtérie même si la couverture par le DTC3 est bonne. Pour interrompre les flambées de diphtérie, l'OMS recommande de remplacer le vaccin à base d'anatoxine tétanique (AT) par le vaccin antitétanique-antidiphtérique (Td) et encourage la mise en œuvre d'une vaccination de rappel.⁸ Le SAGE a réitéré sa recommandation précédente, qui préconisait une mise à disposition accélérée de l'antitoxine diphtérique et l'utilisation éventuelle d'anticorps monoclonaux.

Les possibilités offertes par le projet WIISE pour accéder à un plus grand nombre de données mondiales ont été examinées. Il est indispensable de disposer des numérateurs et des dénominateurs relatifs aux populations, y compris les populations «cachées» et mobiles. Le SAGE a prôné une plus grande collaboration avec d'autres partenaires et institutions des Nations Unies, comme l'Organisation internationale pour les migrations, afin de mettre en œuvre une approche multisectorielle, avec des exercices de cartographie de la mobilité des populations déjà en cours. Le SAGE a indiqué que l'utilisation locale des données est une première étape, car elle permet de démontrer l'utilité des données et d'en améliorer la qualité. À l'échelon local, le problème réside souvent moins dans le manque de données que dans le fait que ces données ne sont pas exploitées et analysées. Des exemples ont été fournis, reposant sur la combinaison d'ensembles de données existants et d'utilisations potentielles des données des pays pour prédire les risques. Les flambées de maladies à prévention vaccinales mettent en évidence les lacunes de la couverture vaccinale, de la surveillance et de la mise en œuvre des politiques. L'amélioration de la vaccination et la prévention des flambées exigent des données, des investissements dans les systèmes de données et une vaste collaboration interpayes, interrégionale et mondiale. ■

⁸ Voir N° 22, 2017, pp. 319-320.

How to obtain the WER through the Internet

- (1) WHO WWW server: Use WWW navigation software to connect to the WER pages at the following address: <http://www.who.int/wer/>
- (2) An e-mail subscription service exists, which provides by electronic mail the table of contents of the WER, together with other short epidemiological bulletins. To subscribe, send a message to listserv@who.int. The subject field should be left blank and the body of the message should contain only the line subscribe wer-reh. A request for confirmation will be sent in reply.

Comment accéder au REH sur Internet?

- 1) Par le serveur Web de l'OMS: A l'aide de votre logiciel de navigation WWW, connectez-vous à la page d'accueil du REH à l'adresse suivante: <http://www.who.int/wer/>
- 2) Il existe également un service d'abonnement permettant de recevoir chaque semaine par courrier électronique la table des matières du REH ainsi que d'autres bulletins épidémiologiques. Pour vous abonner, merci d'envoyer un message à listserv@who.int en laissant vide le champ du sujet. Le texte lui-même ne devra contenir que la phrase suivante: subscribe wer-reh.

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SAGE TRACKING RECORD OF RECOMMENDATIONS AND ACTION POINTS

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

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

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

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
General	SAGE stressed that additional disaggregation was needed in the analysis of the progress achieved on the ground, and in identifying bottlenecks for progress, and recommended that reports display disparities observed at sub-national levels.	Apr 2015	Ongoing	WHO headquarters (HQ) is working closely with regional offices to obtain subnational level data. Surveillance data for measles and rubella as well as for new vaccines is collected at the district level on regular basis and there are efforts to collect sub-national level coverage data. Currently this is happening in the African Region on monthly as well as annual basis; and in the South East Asian Region and the European Region it is done on annual basis. In October 2016, at the Global Monitoring Meeting all regions agreed to collect and submit to HQ district level coverage data (numerator, denominator and coverage from DTP1, DTP3 and MCV1) as part of annual data collection exercise. 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/
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.
AEFI reporting	SAGE urged that efforts be pursued to enhance Adverse Events Following Immunization (AEFI) reporting worldwide.	Apr 2016	Ongoing	Progress with adverse events following immunization (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, particularly in the context of establishment and governance of national immunization technical advisory groups (NITAGs). Preliminary results were presented at Decade of Vaccines (DoV) Working Group meeting in Aug 2018 and at the meeting of the Global NITAG Network in December 2018. Additional analysis is ongoing. Sabin Vaccine Institute conducted a landscape analysis of immunization legislation in the European region and developed case studies. Potential follow up studies to assess the impact of the legislation in select countries is under discussion.
Data quality	SAGE requested the establishment of a Working Group on Quality and Use of Global Immunization and Surveillance Data.	Apr 2017	Ongoing	The Working Group was established in August 2017. Thirteen members are part of this Working Group, 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 (shareable report is available upon request). The Working Group explored coordination with other WHO programmes collecting subnational data. The Working Group will report to SAGE in April 2019.

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	<p>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 2018 was published online and is available at: http://www.who.int/immunization/global_vaccine_action_plan/en/</p> <p>This year the SAGE DoV WG will be overseeing the development of the overall GVAP review and lessons learnt. A highlevel interim lessons learnt item will be presented at SAGE in April 2019 (after the post 2020 Global immunization strategy development multistakeholder meeting in March 2019).</p> <p>The full GVAP report will be prepared for the October 2019 SAGE meeting. The GVAP review will replace the formal annual GVAP secretariat report and SAGE assessment report.</p>
Diphtheria	SAGE expressed concern with the shortage of Td vaccine (tetanus toxoid + reduced diphtheria toxoid content) for routine immunization of children and adolescents, catch-up vaccination of adults and tetanus prevention after injury, and recommended that the demand and supply scenarios for Td vaccines should be assessed.	Apr 2017	Ongoing	<p>An assessment of global demand and supply for Diphtheria and Tetanus containing vaccines has been finalized and is available for SAGE members and wider public. The main objective of the assessment was to understand possible supply implications of global implementation of WHO recommended schedule for D&T containing vaccines. The assessment can also be useful to guide current supply access issues. The assessment was conducted with support from Linkbridge and MMGH consulting group. A temporary Advisory Group of expert was convened to guide this work advising on methodology, assess current and future supply risks and advice on policy implications. A final meeting of the Advisory Group was held on September 13th concluding that: • 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</p> <ul style="list-style-type: none"> • 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	Completed	The English version of the new surveillance standards was released in September 2018; the French version was released in December 2018. The WHO/UNICEF Joint Reporting Form (JRF) was modified for 2019 requesting age and vaccination status of diphtheria cases to assist SAGE in future decisions.
Ebola	SAGE reiterated that WHO should support the national regulatory authorities of countries endemic for ebola virus disease (EVD) to reach consensus on pathways for the evaluation and marketing authorization of candidate EVD vaccines.	Oct 2018	Ongoing	Work is ongoing within WHO in order to ensure continuous support to national regulatory authorities and to reach consensus on pathways for new candidate vaccines.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Ebola vaccines	Noting WHO's unique position to coordinate the development of Ebola vaccines, SAGE stressed the importance of transparent and prompt sharing of information on the trial protocols and data from the phase 3 clinical trials, and the need for a greater role for WHO in facilitating the sharing of information so that results between studies will generate the greatest benefit for policy decision-making.	Apr 2015	Ongoing	<p>SAGE established an Ebola working group (WG) in Nov 2014 which met regularly via teleconference as well as during a face-to-face meeting on the 9-10 Mar 2015. The WG reviewed the epidemiological data on Ebola Virus Disease (EVD), the preliminary results of the phase 1 trials, the status of the phase 2 and 3 trials, and the preparations for the large scale deployment of vaccines. They also identified the scope of the recommendations and the key questions and data for formulating recommendations. The framework was presented to SAGE at the Apr 2015 meeting. The WG met again on 19-20 Aug 2015 to review the available information and to start framing recommendations, based on the framework approved by SAGE in Apr 2015. The WG input was presented to SAGE at the Oct 2015 meeting.</p> <p>Now, that the final results of the Ring trial have been published in the Lancet in Dec 2016, a WG meeting took place 14-15 Mar 2017 to discuss the results.</p> <p>Regulatory evaluation of the vaccine is currently ongoing.</p> <p>There is information regarding a Russian developed vaccine that was licensed in Russia, but despite WHO requests no detailed data are available. The emerging data and draft recommendations were discussed during the face to face meeting of the WG which took place Mar 2017. The evidence was presented during the April 2017 SAGE meeting. In October 2018, SAGE discussed a review of data submitted by developers of candidate vaccines and of published data.</p>
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	<p>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 FPHVV 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.</p>

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Hepatitis A	Long-term protection from single or 2-dose schedules should be regularly monitored by countries and reviewed by SAGE.	Apr 2012	Ongoing	<p>Post-market surveillance continues in Argentina and a detailed report on the recent epidemiological situation was provided to WHO in March 2017. The next active follow-up report will be requested ahead of the April 2018 SAGE meeting.</p> <p>In 2014, in the context of a localized outbreak in a border area, 8 potential breakthrough cases were identified. For 5 of them there is uncertainty about the vaccination status and/or conditions (cold chain) in which vaccination was administered. Seven of these cases are in the 5-9 age group (distributed throughout the period) and one in the 1-4 age group. This resulted in an enhanced vigilance in the country. As exemplified by the outbreak in San Martín, 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.</p> <p>After now 11 years of follow-up, there is currently still no evidence of waning immunity and the outbreak experienced in 2014 was compatible with very high vaccine effectiveness. Hepatitis A cases have remained low in 2014, 2015, and 2016. Although a reduction in hepatitis A rates was experienced in all age groups, there is an increasing proportion of the remaining cases occurring in persons > 14 years of age in the post vaccination period. Most of these represent non-vaccinated adolescents or adults that escaped HAV-infection in previous outbreaks.</p> <p>Both Colombia and Paraguay also introduced a single dose national immunization schedule for 1 year old children. Yearly review of the Argentinian surveillance data will continue as Argentina was the front runner country to introduce a 1 dose schedule with the inactivated vaccine.</p> <p>The results of the phase 2 study conducted in 2013 with a median post-vaccination interval of 7.7 years were quite reassuring with a prevalence of protective antibodies of 97.4% (95% CI: 96.3-98.3) still protected. More recent analysis (phase 3) indicates that the prevalence of protective antibodies in children > 9 years following a single dose of hepatitis A vaccine was still 87.6% but a decrease was observed in all centers with decreased GMCs. It is still unclear if different samples or differences in methodology or recall bias in seronegative individuals could actually account for the difference, but this requires continued follow up. For the time being epidemiologic surveillance continues to show very low infection rates in all regions and age groups with sporadic cases occurring mainly in frontier regions and non-vaccinated adolescents.</p> <p>Currently, a study is ongoing to assess the immunological response after ten years of vaccination. Results are anticipated by the end of 2019.</p>

Hepatitis B	SAGE strongly urges all the pre-qualified vaccine manufacturers of monovalent hepatitis B vaccine to pursue regulatory approval for Controlled Temperature Chain (CTC) as soon as possible, given the available evidence of compatibility with CTC requirements.	Oct 2016	Ongoing	<p>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, Euvox 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. In November 2018, LG Chem informed WHO PQT of their decision to withdraw their request for pre-qualification and not proceed with a CTC label variation. The main reason for the latter concerned the low potency preferred by the manufacturer which was not meeting the approval of PQT.</p> <p>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.</p>
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Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Hepatitis B	SAGE recommended that the timely delivery of a birth dose of hepatitis B vaccine (that is, within 24 hours of birth) should be used as a performance measure for all immunization programmes. Reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose.	Apr 2009	Ongoing	<p>WER on status of global introduction and implementation of hepatitis B birth dose has been drafted and cleared; scheduled for publication in Feb 2018.</p> <p>A new indicator for Hepatitis B birth dose has been added to the WHO /UNICEF Joint Reporting Form (JRF) 2017. This new indicator will allow the distinction between timely (24 hours) and late birth dose administration.</p> <p>In Jan 2015 the African Regional Office (AFRO), and in Mar 2015 WPRO, held Hepatitis B birth dose consultations to improve birth dose coverage. In February 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 December 2015. Senegal held a Hepatitis B birth dose training workshop in Dec and introduced birth dose in Jan 2016.</p> <p>Guidance for hepatitis B birth dose introduction was published on June 2016 ('Preventing Perinatal Hepatitis B Virus Transmission: A Guide for Introducing Hepatitis B Birth Dose Vaccination', available from: http://www.who.int/immunization/documents/general/ISBN9789241509831/en/ in English, French and Spanish. An Arabic version is under development). The guidance includes a chapter on reporting and monitoring birth dose vaccination.</p>
Hexavalent IPV-based combination vaccines PQ and supply	Track 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. Gavi is launching a market shaping roadmap with partners on Hexavalent vaccine.
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 in 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 submitted for publication. Partner discussions are ongoing to update WHO recommendations on research priorities.
HPV	SAGE urged that a globally more equitable distribution of the available HPV doses be encouraged to ensure optimal global public health access to vaccines.	Oct 2018	Ongoing	A workplan for the assessment of options to achieve more equitable allocation of HPV vaccine under supply constraints is currently ongoing.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
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	SAGE established a Working Group in 2018. In October 2018, SAGE reviewed the latest evidence on the immunogenicity, efficacy and effectiveness of HPV vaccines, their administration schedules, number of doses and intervals, and use in HIV-infected and in male populations. SAGE also reviewed the results of 3 models showing the impact and effectiveness of various HPV vaccination and screening strategies, and the potential for cervical cancer elimination. SAGE also expressed concern about the constrained HPV vaccination supply forecast until at least 2024. Work is being done by the SAGE Working Group to assess options for more equitable distribution of HPV vaccines.
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/ The Working Group deliberations are ongoing in 2019.
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 understanding of IPV supply; this is available upon request. UNICEF does not anticipate a market with multiple suppliers and sufficient supply capacity to fully meet programmatic requirements of at least 2 doses of IPV to materialize before 2023.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Lower middle-income countries: sustainable adoption and financing for new vaccines	SAGE requested that WHO facilitate the establishment of a partnership among all relevant stakeholders to consider: pooled procurement; tiered pricing; greater transparency of pricing; and exploring the role that UNICEF, the Pan American Health Organization and foundations can have in assisting these countries with procuring and financing vaccines.	Nov 2010	Ongoing	<p>WHO set up a Middle Income Countries (MIC) Task Force in June 2014 with main immunization stakeholders (WHO, UNICEF, World Bank, Gavi Secretariat, BMGF, AMP, Sabin, Task Force for Global Health), which led to the creation of the "MIC strategy", presented at SAGE in April 2015. The strategy aims at improving sustainability of immunization programmes and access to vaccines in non-Gavi MICs. The MIC strategy is based on four pillars : i) Strengthening evidence-based decision-making; ii) Enhancing political commitment and ensuring financial sustainability of immunization programmes; iii) Enhancing demand for and equitable delivery of immunization services; and iv) Improving access to timely and affordable supply.</p> <p>The timeline for the strategy is up to 2020 to align with the GVAP timeframe and up to 2025 for a longer term horizon. 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. Selected countries were Romania, Swaziland, Jordan and Philippines.</p> <p>AAIso, some efforts to support all MIC countries in the area of access to timely and affordable supply have been implemented. Notably, the creation of a mechanism for access to supply in humanitarian emergencies in MICs not supported by Gavi; set up of a peer platform and regional workshop to strengthen country procurement capacity; work on price transparency continues successfully with 85% of world (n. of countries) sharing vaccine product, price and procurement information since the beginning of WHO price transparency efforts and the recent launch of the Market Information for Access to Vaccine (MI4A) project. Despite these efforts, progress in implementation of the strategy across its 4 pillars is very slow due to lack of funding. As discussed at the Apr 2015 SAGE meeting, the partners would require about US\$20M per year to fully implement the strategy.</p> <p>In Oct 2016, a meeting of the MIC Task Force was held to review progress and discuss next steps. The TF determined having concluded its mandate through a review of the MIC issue and the development of a partner-shared MIC strategy. It was thus proposed that the TF comes to a close. Anticipating that considerable time may be needed for funding to become available, the TF proposed that partners focus on i) regular normative/guidance work benefitting all countries including non Gavi MICs and ii) access to affordable and timely supply (continuing working on implementation of ongoing activities and potentially new one as possible). Partners committed to continue information sharing and collaborative spirit in these efforts.</p> <p>With the development of Gavi 5.0 strategy and development of post GVAP strategy, WHO and partner are exploring opportunities of complementary, coordinated approach to support access to vaccines in MICs.</p>

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Malaria Vaccine	SAGE requested continued review of the planning of the pilot implementations and to receive regular updates on the results.	Oct 2015	Ongoing	<p>Preparations continued at global, regional and country levels towards start of pilot malaria vaccine implementation in Ghana, Malawi, Kenya, expected in Q1 – Q2 2019. The national EPI Programmes have intensified stakeholder engagement activities and finalization of information/communication materials for health workers and communities. The first national Training of Trainers for regional health officials was held in Ghana – marking the start of a series of trainings for sub-national officers and health workers. Risk communications plans for global and local handling of potential vaccine safety issues, and key information products for community, national and global stakeholders were finalized, and crisis management trainings for stakeholders were conducted in Ghana and Malawi.</p> <p>An update was provided to MPAC in October 2018 and included a report from the long-term follow-up study (MAL-076) conducted in a subset of the phase 3 trial sites. MPAC was pleased to note that children living in areas with moderate to high perennial malaria transmission who receive three or four doses of RTS,S appear to benefit for at least seven years after vaccination and do not have an excess risk of clinical or severe malaria. The results were found to provide further reassurance that the period of rebound in immunized children was limited and to reinforce the safety profile of the vaccine.</p> <p>As suggested by MPAC and SAGE, a working group for the development of the Framework for Policy Decision on RTS,S has been constituted (including 2 SAGE members) and met for the second time in December 2018. The proposed Framework will be presented to SAGE and MPAC in their upcoming meetings. A progress update was also provided to RITAG on 15 January 2019.</p>
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. SAGE requested WHO to follow-up with a broad based consultation on vaccination of pregnant and lactating women.	Apr 2015	Ongoing	<p>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 (all influenza risk groups); 5) field guide for the evaluation of influenza vaccine effectiveness and influenza programme evaluation tool (all influenza risk groups); and 6) implementation guidance document for HWs (guidance for pregnant women is available), and 7) literature review and multicenter study assessing of vaccine confidence/hesitancy in pregnant women and/or health care workers. IVR is collaborating with several research and public health groups to pilot some of these tools in low and middle income countries.</p>
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	Completed	<p>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.</p>
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	<p>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 and the outcomes and recommendations will be shared with SAGE (report to be published in Q1 2019).</p> <p>The MR-MAP Target Product Profile (TPP) has been posted for public consultation until end of Jan 2019 and will be finalized shortly thereafter. A background paper on the applicability of MAPs to LMICs has been submitted to Vaccine (currently under review).</p>
Measles	SAGE requested feedback on the utility of the M&R immunity gap guidance.	Oct 2018	Ongoing	<p>Assessments are ongoing and feedback to SAGE will be provided as soon as available.</p>

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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 additional 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. Additional work is needed to validate the models and revise the recommendations. This work is ongoing and will be presented to SAGE in October 2019.
Measles	SAGE noted that there is a need to address the substantial information gap on the role of factors such blunting and maternal immunity in infants aged <6 months, and the impact of vaccination <6 months of age on subsequent MCV doses.	Oct 2017	ongoing	This is an information gap and research is needed. The SAGE WG is working to prioritize research areas in order to increase interest of donors to fund and of research institutions to carry out the needed research
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 investment case is ongoing. The draft concept paper of the feasibility of measles and rubella eradication (which includes the investment case) was presented at the October 2018 SAGE. IVIR-AC raised a number of concerns with the model, therefore alternatives are being pursued in order to complete this work for presentation at the October 2019 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 surveillance 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/ . Eleven 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 (n= 6 countries: 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 (n= 1 country: Ghana, November 2016); or at the age of 15 months (n= 1 country: Burkina Faso, March 2017), respectively. The remaining three countries intend to do so in 2019 (The Gambia, Nigeria) and in 2020 (Togo). Another 2 countries (Guinea and Guinea Bissau) have applied to Gavi through its new country engagement framework for an introduction in 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 January and May 2019, except for 4 countries located in the east end of the meningitis belt who intend to wait for the availability of affordable multivalent vaccines to consider an introduction into their routine programme while enhancing surveillance in the meantime. Further, one additional country has conducted its initial mass vaccination campaign in 2018 (Burundi) while Kenya has planned to do so in Q1-2019 and Eritrea in Q2-2019.
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	This important item has been highlighted again in the 2018 GVAP assessment report. The approach to address this item is currently being discussed by SAGE secretariat in liaison with IVB senior management.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Missed opportunities for vaccination (MOV)	WHO should discuss and develop guidelines on how to reduce missed opportunities to vaccinate.	Oct 2014	Ongoing	<p>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 (PLOS ONE, 2019) and Kenya in 2016 (manuscripts in preparation), 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 Q1-2019. 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), Zimbabwe and Uganda), 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).</p> <p>Since March 2016, a network of partners engaged in MOV has been established 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 sixth partner coordination call took place in September, 2018.</p> <p>WHO priorities include supporting countries 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 in 2018/2019 and are supporting a consultant in Malawi to assist the country office and MoH with MOV activities in 2018/2019.</p> <p>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.</p> <p>In December 2018 WHO published a resource guide on integration named "Working together: An integration resource guide for planning and strengthening immunization services throughout the life course". This document brings together a range of resources to provide an overview of the global policies, potential interventions and strategies related to the integration of immunization services. It also provides guidance and country examples on the integration of immunization with additional health interventions throughout the life course.</p>

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	<p>Despite the rejection by the Gavi PPC of the proposal submitted to it to request for financial assistance to support the production and availability of compact pre-filled auto-disable device (cPAD) to increase access to the Tetanus Toxoid vaccine in remote parts of some selected countries, the use of the devices and costs were clearly included in the investment case and highlights presented to donors at the Nov 2018 recent conference in NY. BD indicated some interest in funding Uniject procurement for some of the countries. The initiative will continue to follow up with this and other donors for funds to support financing of the device in the most difficult-to-reach parts of countries. WHO/HQ will continue to advocate with partners and donors to fund the procurement of cPAD for use to deliver TTCV in remote and hard-to-reach areas during SIAs.</p>
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Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
MNTE	UNICEF, United Nations Population Fund (UNFPA), and WHO should support countries in securing the necessary resources to implement their national elimination plans, including procurement of Td vaccine and operational costs for SIAs.	Oct 2016	Ongoing	The first phase of the maternal and neonatal tetanus elimination (MNTE) investment case that focuses on the remaining countries yet to attain elimination (14 at the moment) has been completed and both online and hard copies disseminated to all levels. The investment case highlights the areas of resources' need, and is being used for resource mobilization, especially from partners and donors as well as domestically mobilized resources. In addition, WHO/HQ is working closely with UNICEF/HQ to ensure that country tetanus toxoid (TT) supplemental immunization activities (SIAs) plans submitted are timely and adequately funded. Country SIAs plans were recently received from Central Africa Republic, Guinea, Nigeria and South Sudan to conduct rounds of TT SIAs in 2019. Disbursement of funds by UNICEF/HQ has been done for Guinea, Nigeria and South Sudan, while plan for Central African Republic is being reviewed.
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	WHO/HQ working closely with the US CDC/Atlanta to integrate tetanus immunity assessment into the ongoing HIV serosurvey in some high-risk districts in Nigeria and in the Lymphatic Filariasis (LF) serosurvey in Cambodia. WHO/HQ is facilitating the collaboration work between CDC Offices and country offices in Nigeria and Cambodia for the integration of the two aspects of serosurveys.
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	As part of efforts to generate and sustain political commitments to sustaining elimination, a regional workshop was conducted in Aug 2018 for 19 countries in the African region including those that have already eliminated maternal and neonatal tetanus (MNT), to develop their sustainability plan. Similar workshops will be conducted in other regions in 2019, immediately after the Global maternal and neonatal tetanus elimination (MNTE) sustainability guideline is finalized and disseminated to countries. Post-validation surveys, which were commenced in 2018 will continue in priority countries in 2019, as part of efforts to sustain MNTE. All opportunities including the Regional Immunization Technical Advisory Group (RITAG) meetings and Immunization Managers' meetings are being utilized to advocate for efforts by countries to sustain their MNTE status. Update on the status of implementation of the AFR RITAG recommendations were presented at the annual meeting of the AFR RITAG in January 2019. Official announcement of MNT elimination in Kenya was made in a high profile event involving key country stakeholder with wide media coverage. A joint WHO/UNICEF HQ assessment and planning mission to Papua New Guinea discussed MNTE progress and challenges in that country. Participants were updated on the status of MNTE in the Central & West Africa RWG meeting in March 2019. The WHO guidelines on sustaining MNTE was finalized and access link posted on WHO website. Several countries have developed or are in the process of developing their MNTE sustainability plans, which will be mostly funded through domestic resources.
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 the 14 countries that are yet to eliminate has been finalized, online link and hard copies shared with stakeholders. Highlights were presented to MNTE donors during a Donor conference in Nov 2018 in New York. 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.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
National immunization programme management	SAGE welcomed the initiative and stressed the importance and urgency of developing guidance that can be tailored to each country's unique structure and needs. SAGE emphasized the importance of looking at functions and competencies from a health-system perspective whereby all the immunization functions are adequately addressed with competent staff, regardless of the country's health system structure. SAGE recommended sharing of experiences between countries and regions on immunization workforce planning. SAGE suggested creating tools to assist countries in different aspects of immunization human resources management including: staff turnover and rotation policies, performance evaluations, and design of training. SAGE recommended that this work be piloted in a range of countries.	Apr 2017	Ongoing	A joint meeting with the US CDC and other relevant partners (JSI, BMGF, GAVI) was conducted in November 2017, to review the competencies needed at different level of the programme. A final list of competencies needed at national level will be available by Mar, 2019. The US CDC had drafted an article on this topic for a peer-reviewed journal, which was published in February 2019 (Traicoff et al. Developing standardized competencies to strengthen immunization systems and workforce). 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 third Global NITAG Network (GNN) meeting was successfully held from the 6th to 7th of December 2018 in Ottawa, Canada. The meeting was attended by 35 NITAG country representatives (NITAG Chair, member or secretariat) from a total of 26 countries. The next meeting is scheduled in October 2019/February 2020 in Atlanta and will be hosted by the US-CDC. The simplified evaluation tool and the training material package are being reviewed following the pilot testing in several countries. The NITAG Resource Center will be revamped in 2019.
Non-specific effects of vaccines	SAGE requested to be updated on the finalization of statement and publication on non-specific effects (NSE) of vaccines as well as finalization of study protocols.	Oct 2018	Ongoing	Feedback received from the public consultation on the protocols has been collated. A meeting to discuss and finalize the protocols is envisaged in 2019.
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 that will be published in February 2019. 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. This was discussed at the ICG meeting and African meningitis meeting in Q3 2018. We plan continued work in this area in 2019.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Polio	SAGE advised GPEI to accelerate implementation of the WHO Global Action Plan for containment (GAP/II) including: a) all countries completing phase I; b) regional focal points closely monitoring country activities and ensuring each country completes its inventories of facilities that hold or handle polioviruses, and destroys or commits to destroying WPV2 by end 2015 and any other type 2 containing materials including Sabin poliovirus by July 2016.	Oct 2015	Ongoing	Phase I of GAP/II (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 Global Commission for Certification of Poliomyelitis Eradication (GCC) recommended its implementation by April 2019. Phase II of GAP/II (PV2 containment period): 27 countries reported the intention to retain PV2 materials (WPV2 or OPV2/Sabin2) in 79 designated poliovirus-essential facilities (PEFs). Surveys of facilities retaining type 2 infectious materials are complete. Surveys of facilities that may retain type 2 potentially infectious materials are ongoing. 24 of these countries have nominated a national authority for containment (NAC). Lately, Three designated facilities (one in Sweden, one in South Africa and one in Indonesia) have currently been recognized by their NACs and the GCC as suitable candidates to become PEFs and have been issued certificates of participation (CPs).
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 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 the Global Commission for Certification of Poliomyelitis Eradication (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.
Polio	SAGE encouraged further engagement of WHO regional offices in regard to the polio legacy planning to ensure adequate technical support to countries.	Oct 2015	Ongoing	WHO Regional Offices from AFRO, EMRO and SEARO 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 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	<p>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).</p> <p>SAGE also requested reconsideration of terminology from fractional IPV to intradermal; explore if PEF safety monitoring can be linked to IH regulation (April 2018)</p>	Oct 2016	Ongoing	IPV supply has improved 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 is now available for use in the polio program. First IPV campaign was carried out using Tropis in Karachi in February 2019. Discussions on change of terminology of fractional dose 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 February 2019 Polio Working Group meeting, will be provided during the April 2019 SAGE meeting.
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.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
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	<p>The Regulation and other health Technologies (RHT) aims to strengthen regulatory preparedness for public health emergencies through:</p> <ul style="list-style-type: none"> • 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 <p>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.</p> <p>RHT has mapped regulatory provisions for emergency clinical trial and marketing authorization in 40 countries</p> <p>In November 2017, RHT organised a tabletop exercise on regulatory preparedness in a simulated emergency setting.</p> <p>Several activities under the norms and standards have been implemented/planned as follows:</p> <ul style="list-style-type: none"> • 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. <p>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.</p> <p>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.</p> <p>The main principles of the revision includes:</p> <ul style="list-style-type: none"> • 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 <p>The document was published in the WHO website for comments and disseminated to several stakeholders. Comments are under collection and will be published Q1 2019.</p> <p>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</p>

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
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 I/II 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	Completed	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 have also been developed, in collaboration with UNICEF. The guidance document "Establishing and strengthening immunization in the second year of life: Practices for vaccination beyond infancy" has been published and is available online in English, French and Portuguese (http://www.who.int/immunization/documents/WHO_IVB_ISBN9789241513678/en/) and a companion implementation handbook will be published in January 2019. WHO and UNICEF are moving ahead to finalize 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.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
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	<p>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.</p> <p>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.</p> <p>A procedure for assessment of smallpox vaccine was developed as well as a safety monitoring guidelines. The Pre-Emergency phase of the revised EUL, will be considered for the assessment of smallpox vaccine. WHO is also mapping regulatory provisions for emergency use of medical countermeasures.</p>
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	<p>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.</p> <p>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. These figures are included in the global report on a yearly basis.</p> <p>NITAG side meetings are organized back to back to SAGE meetings.</p>

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	<p>Concerns about ongoing shortages of vaccines persist. This has been stressed through the SAGE session on vaccine shortages held in April 2016, resolution 69.25 on "Addressing the global shortage of medicines and vaccines", the fifth objective of the Global Vaccine Action Plan (GVAP), the Middle Income Country (MIC) Strategy endorsed by SAGE in April 2015 and the 68th World Health Assembly (WHA) resolution on the GVAP in May 2015. A report on 'Addressing the global shortage of, and access to, medicines and vaccines' was presented to the 71st World Health Assembly in May 2018.2 As a result, WHO was requested to develop a roadmap to outline the programming of WHO's work on access to medicines and vaccines, including activities, actions and deliverables for the period 2019-2023. Efforts on addressing supply shortages will be part of the post GVAP strategy.</p> <p>WHO IVB Department, in collaboration with Essential medicines and health products (EMP) and with support from Linkbridge consulting funded by the Bill & Melinda Gates Foundation and MMGH consulting, has leading a Vaccine Shortage Project over the years 2016-2017. The aim of the project was to act upon the recommendations and requests of SAGE and WHA by providing concrete proposals on WHO's role and actions to enhance information sharing for pre-empting and managing vaccine supply shortages. While all countries can benefit from this work, particular attention is paid to countries not supported by UNICEF Supply Division, PAHO, or Gavi.</p> <p>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.</p> <p>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.</p> <p>The proposal was successfully submitted to the Bill and Melinda Gates foundation for funding and the new project, Market Information for Access to Vaccines (MI4A) was kicked off in January 2018. Under this project, WHO commits to conduct to enhance available GLOBAL vaccine market information to enhance timely access to affordable vaccines. The work will entail: i) two global vaccine market studies per year in collaboration with Linkbridge SPC and MMGH Consulting to assess global supply, demand and pricing challenges of vaccines at risk (availability & affordability). ii) development of tools and materials for countries to improve market knowledge and enhance procurement outcomes. iii) creation of an information sharing ecosystem for enhanced information exchange among key stakeholders. iv) development of guidance and strategies for suppliers and countries aimed at enhancing access.</p> <p>MI4A undertook its first market study on global availability of HPV vaccines to inform the WHO Call for Action on Elimination of Cervical Cancer. The second study focused on Meningococcal meningitis vaccines with the public summary to be available on the MI4A page by February. The study focuses on short term analysis of demand and supply and an update on long term forecast will be developed later in 2019, in line with the development of the Defeating Meningitis disease control strategy. In 2019 two additional global studies will be conducted – with decision on vaccines selected later in Q1.</p>

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Surveillance	<p>SAGE endorsed the recommendations of the ad hoc TAG for improving the quality of the IB-VPD surveillance network and urged that the objectives of this network be more clearly defined, that collaboration with other surveillance systems and laboratory networks (i.e. the polio/measles laboratory networks) be continued, and that, where feasible, activities be linked with other programmes enhancing country capacity, including implementation of the International Health Regulations. SAGE urged greater attention to integration of data systems, which would facilitate real-time analysis and performance monitoring. SAGE also noted the opportunities for integration by building upon the enhanced capacity developed by these networks to conduct surveillance for other diseases using a similar case-definition and personnel trained in applying and adhering to rigorous surveillance protocols. Both networks should continue to share experiences with the polio surveillance network. Integration efforts must be strategically designed in ways that are logical and synergistic.</p>	Nov 2013	Ongoing	<p>Since 2013, significant progress has been made to strengthen the Global IB-VPD and Rotavirus Surveillance Networks through recommendations from the 2013 global strategic review and annual meetings and consultations. By the end of 2018, 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 and 2018. 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 (Global Pediatric Diarrhea Surveillance). 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 used in one Region (AMRO/PAHO) and has great potential to improve data quality and sharing across the Network. We are discussing how to better integrate IB-VPD meningitis surveillance with existing meningococcal meningitis surveillance systems. We also continue to support sites where PCV and/or RV vaccine impact evaluations may be feasible due to sufficient pre- and post-vaccine introduction data, including using secondary data sources such as hospital administrative data. Finally, one of our main activities is to work with countries on making surveillance sustainable in the long term.</p>

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

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Tuberculosis vaccines	SAGE endorsed the establishment of a WHO TB vaccine technical expert group with representation from SAGE. An annual written report on TB vaccine developments should be provided to SAGE. SAGE would be provided with two-page summaries of progress every year. TB would only be included on the agenda of SAGE when there is a meaningful development of decision from SAGE required.	Nov 2011	Ongoing	<p>WHO IVR, with the support from an TB vaccine expert working group, with further advise from PDVAC, continues to progress its activities on new TB vaccines development. Major new developments have been recently noted in the field.</p> <p>M72/AS01E a GSK adjuvanted protein vaccine candidate in phase IIb evaluation in Southern Africa, being tested for prevention of pulmonary TB. Two doses of M72/AS01E administered one month apart to HIV-negative adults showing evidence of latent Mycobacterium tuberculosis infection, provided 54% protection (90% CI, 13.9 to 75.4; 95% CI, 2.9 to 78.2; P = 0.04) against pulmonary TB, over approximately two years of follow-up. The study, still blinded at an individual level, showed no concerning imbalance in the occurrence of serious adverse events, with more local and flu-like general reactivity, including some grade 3 reactions reported in the vaccinated group. This result constitutes a major progress and provides an unprecedented opportunity to advance the field of TB vaccine towards potential public health impact. WHO is engaging leading stakeholders aiming to define the best pathway forward for accelerated availability of an effective, affordable, new TB vaccine for public health impact.</p> <p>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. The Gates foundation has shown interest to fund follow-up research to further understand the significance of this result.</p> <p>VPM 1002 is a recombinant BCG, originally developed by the Max Planck Institute; now licensed to the Serum Institute of India (SII) and being developed with Vakzine Projekt Management (VPM), Hannover, Germany. It is currently in Phase IIb/III trials, being compared to BCG in neonates in South Africa, as well as being tested for prevention of TB recurrence in adults in India. Discussions are ongoing about neonatal BCG comparison phase 3 study design to ensure appropriate data is generated, supporting robust policy decision on possible BCG replacement.</p> <p>Upon PDVAC recommendation, WHO has developed guidance on preferred product characteristics for TB vaccines. The document is now publically available through the WHO IVR website: http://www.who.int/immunization/research/development/tuberculosis/en/.</p>
Un/under-immunized children	SAGE requested that WHO quickly roll out tools so that other countries can address low coverage of vaccination.	Nov 2010	Ongoing	<p>A range of new and updated tools are being developed on the topic of strategic communications, service quality and health worker capacity, and new documentation on 'Tailoring Immunization Programmes'. TIP. All will be published on a soon to be expanded version of the WHO vaccine hesitancy web page.</p>

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccine coverage	SAGE recommended that WHO explore alternative survey methods to improve the precision, reduce the cost and improve the usefulness of survey results to national and local immunization programmes.	Nov 2011	Ongoing	<p>Following a thorough review of sampling methodologies; 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, WHO published, in 2018, its "Vaccination Coverage Cluster Survey Reference Manual", see http://www.who.int/immunization/documents/who_ivb_18.09/en/.</p> <p>A tool named "Vaccination Coverage Quality Indicators (VCQI)" – a 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 – was developed in 2016-2017 and is being expanded to include additional analysis. 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. Other survey support material, like model questionnaires, model protocols, reports, etc, as well as practical "how to" guides have been developed; one practical with a focus on post campaign surveys is underway. Another important survey-related activity was, in 2018, the development of a White Paper to standardize and support the generation of immunization-related survey indicators, along with model questionnaires.</p> <p>Several capacity building activities around vaccination coverage surveys have been conducted since 2015. These have included briefings with all regions (but EUR) and selected countries, and trainings for regional focal points, consultants, statisticians and immunization program officers. 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 in 2017. Survey Scholar participants, from almost 50 countries, were engaged. In mid-2018, a repeat of module A3, on survey analysis and interpretation was conducted. The French version of the distance-based Survey Scholar, Module A1 on planning a survey, was done in Q4 2018 and the material for the rest of the training is being adapted to francophone Africa, for running modules A2 and A3 in 2019. A community of Survey Scholar Alumni has been created and, in partnership with Gavi, activities to further develop survey consultants are underway.</p> <p>Finally, in collaboration with countries and partners, a research agenda related to surveys was developed and published, see: https://www.ncbi.nlm.nih.gov/pubmed/30041880 and efforts are undergoing to start supporting that research.</p> <p>All WHO survey related-materials are available here: http://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/index2.html</p>

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 (India, Uganda, Malaysia) with further two countries being planned for 2019 (Cameroon and Ghana) to determine the operational feasibility of using POCT/OF in a field setting. 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 finalizing 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. 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 finalized 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. At the March 2019 IVIR-AC meeting, IVIR-AC will continue to discuss research to minimize barriers and improve coverage of vaccines currently in use.

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	<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>
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	<p>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 have been conducted (results pending), and fractional dose studies in infants have been launched (both Africa). Immunogenicity study in DRC is on track, and 1 month immunogenicity data have been published, 1 year data to follow soon (already presented at WHO meetings). In June 2018, Martins et al. published 8 year follow-up immunogenicity data from a YF vaccine dose finding study in military personnel, 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.</p>

Report of the Regional Immunization Technical Advisory Group meeting

Congo-Brazzaville

15–17 January 2019

Executive summary

The January 2019 meeting of the Regional Immunization Technical Advisory Group (RITAG), the principal advisory group to the WHO Regional Office for Africa, was held at the WHO Regional Office in Brazzaville, the Congo, on 15–17 January 2019. The meeting reviewed progress towards the objectives set out in the Regional Strategic Plan for Immunization and included sessions dedicated to yellow fever, polio, malaria, measles, maternal and neonatal tetanus, Ebola, vaccination demand generation, surveillance and National Immunization Technical Advisory Groups (NITAGs).

The meeting noted that considerable progress is being made in reducing the burden of vaccine-preventable diseases in the region, but further efforts are required if regional immunization targets for 2020 are to be met. Stalling immunization levels and frequent infectious disease outbreaks – including measles, yellow fever and circulating vaccine-derived poliovirus (cVDPV) – are clear signs that national immunization programmes are not achieving the population coverage required to control these vaccine-preventable infections.

Among the key themes to emerge from the meeting was the need for countries to assume greater ownership of national immunization programmes – in many cases still funded primarily through support from partners. One specific area where this is required is in polio transitioning planning, where countries need to accelerate efforts to absorb polio assets into national immunization programmes and take on responsibility for their support.

Importantly, strengthening of national immunization programmes should reflect their central importance to primary health care and universal health coverage, as well as to national and global health security. A strategic approach can ensure that health systems strengthening exercises can build more effective and resilient infrastructure for the delivery of immunization and other services and for the surveillance of infectious diseases.

Yellow fever is a resurgent threat requiring stronger commitments to national immunization programmes and more effective campaigns to prevent and control outbreaks. The Eliminating Yellow Fever Epidemics (EYE) initiative, launched in the region in 2018, is providing new impetus to enhance control efforts, with an ultimate target of elimination by 2030. Vaccine shortages have been addressed through ‘fractional dosing’ – use of one-fifth of the normal volume of vaccine – which encouraging data from field studies suggest still provides good protective immunity. Given ongoing supply limitations, fractional dosing may provide an option for preventive campaigns in at-risk populations.

No new wild **poliovirus** cases were detected in the region in 2018, an important milestone on the journey towards polio eradication on the continent – which would be a truly landmark achievement. Countries need to energetically pursue the steps needed to achieve national and ultimately regional certification of eradication, which will be tracked by a new certification scorecard as requested by ministers of health.

Less positively, several **cVDPV outbreaks** in the region have highlighted weaknesses in national immunization programmes, particularly in insecure and inaccessible areas. Extensive vaccination responses are underway to extinguish these outbreaks.

In **malaria**, seven-year follow up of clinical trial participants has confirmed the efficacy of RTS,S/AS01 and found no evidence of significant safety signals seen in earlier studies. A four-dose schedule appears to provide greater benefits, although a modelling study has raised questions about the size of this effect; further data analysis is underway to explore this issue.

A large-scale implementation project – the Malaria Vaccine Implementation Programme (MVIP) – is underway in Malawi, Kenya and Ghana. A joint regulatory review of RTS,S/AS01 was undertaken by the respective national regulatory authorities under the African Vaccine Regulatory Forum (AVAREF). The intervention is being implemented through collaboration between national immunization and malaria control programmes within ministries of health in selected districts with implementation of all major malaria control services. Vaccine introductions are due to start in the first quarter of 2019.

The **Ebola** outbreak in the DRC is the second largest ever recorded. Extensive efforts are being made to control the outbreak, including ring vaccination with the VSV-EBOV vaccine around clusters of infections. VSV-EBOV is not yet licensed but has been approved for compassionate use in accordance with recommendations from WHO's Strategic Advisory Group of Experts on Immunization (SAGE). At the time of the RITAG meeting, more than 60,000 people had been vaccinated, including health workers, and neighbouring countries were preparing their staff in case of cross-border spread. Use of the vaccine in DRC will provide important data on the safety and efficacy of VSV-EBOV, and in addition clinical development of other candidate Ebola vaccines is being encouraged.

The region is off-track to achieve **measles** elimination by 2020, and experienced multiple outbreaks in 2018. The outbreaks point to the need to strengthen national immunization programmes and to improve targeting of underserved populations, and to accelerate the introduction of a second dose of measles-containing vaccine (MCV2). Well-planned and executed supplementary immunization activities (SIAs) are essential, and should be seen as opportunities to deliver additional immunization services and to enhance immunization programmes.

Reliable data are essential for monitoring and evaluating immunization programmes and initiatives, and for prioritizing use of resources. A range of initiatives are underway nationally, regionally and globally to enhance immunization **data quality** and programmatic use of data. Data management should be seen as a core function of national immunization programmes. To avoid incentives to record inaccurate data, rewards for performance and penalties should not be based solely on unverified coverage data.

Vaccine logistics and management is a further crucial function of national immunization programmes, ensuring the timely supply of vaccines to the places they are needed. Countries should continue to ensure they develop and implement plans to reach all populations in need efficiently, looking to integrate supply chains whenever feasible.

Although vaccine hesitancy has not yet emerged as a major issue in the region, it would be highly complacent to assume the region will not be affected. Furthermore, coverage rates will rise if populations are actively seeking vaccination

services and are holding authorities accountable for delivery of such services. National immunization programmes need to embed **vaccination demand promotion** activities within their work, strengthening their links with civil society and developing a deeper understanding of the barriers to and enablers of immunization through community consultation. A demand hub being developed by UNICEF and partners will provide a platform for more coordinated and evidence-based support for demand generation activities.

Surveillance contributes to both immunization and national and global health security. Assessments associated with International Health Regulations (IHR) suggest that integrated disease surveillance systems in the region require significant strengthening efforts and harmonization. A strategic approach could ensure that such strengthening delivers both immunization and health security benefits. The surveillance value report commissioned by the Regional Office, which identifies and quantifies the benefits to be gained from investment in surveillance, will be a valuable advocacy tool.

NITAGs have a critical role to play in countries as independent bodies providing evidence-based advice and assessments to ministries of health and national immunization programmes. The number of NITAGs in the region has shown encouraging growth, although a recent slowing is a cause for concern. Presentations by NITAG representatives identified some of the challenges they face, including ensuring they have sufficient breadth of expertise and adequate financing. There is a need to move beyond process indicators to assess the function and impact of NITAGs, and also to ensure they are adequately funded within national immunization programmes and receive sufficient secretariat support to ensure that they can fulfill their key roles.

Recommendations

YELLOW FEVER

1.1 At-risk countries

At-risk countries yet to introduce yellow fever vaccination into their national immunization programmes should do so as soon as possible

Deliverable/outcome measure and timescale: National introduction or plan for introduction; update to RITAG in January 2020

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

1.2 MCV1 synergies

Reasons for differences in yellow fever and national immunization coverage should be explored, to identify possible approaches to increase yellow fever vaccine coverage, and countries should be encouraged to link MCV1 and yellow fever vaccination in national immunization programmes and SIAs

Analysis and communication plan to be presented to RITAG in January 2020

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

1.3 Host and vector surveillance

Yellow fever surveillance should incorporate monitoring of local primate populations and vector surveillance through One Health partnerships

Communication to at-risk countries by June 2019

Main responsibility: Countries; other key stakeholders: WHO Regional Office, research funders

1.4 Vulnerable populations

Countries should identify potential unvaccinated populations in high-risk areas, such as mineworkers and/or migrant populations, with a view to carrying out targeted yellow fever vaccination campaigns

Communication to at-risk countries by June 2019

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

1.5 Serosurveys

Countries should consider the potential use of serosurveys in managing immunization programmes for yellow fever and other targeted vaccine-preventable diseases, to obtain a clearer picture of the size and distribution of immunity gaps in populations

Communication to at-risk countries by June 2019

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

1.6 Catch-up campaigns

In the context of limited yellow fever vaccine supply, SAGE should provide advice on use of fractional dosing in preventive catch-up campaigns for vulnerable populations in at-risk countries, and also review use of the term 'fractional dosing' which could mistakenly interpreted as suboptimal dosing

SAGE recommendation by end of 2019

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

1.7 Long-term fractional dosing data

Long-term follow-up data should be collected in the CDC-sponsored trial of yellow fever vaccine fractional dosing in the Democratic Republic of the Congo, and in other trials of fractional dosing, to determine long-term protective efficacy

Published long-term data on efficacy of fractional dosing

Main responsibility: Study funders; other key stakeholders: countries, regulatory agencies

1.8 Fractional dosing in excluded populations

Protective efficacy of fractional dosing should be explored in other special populations, such as children under 2 years and people living with HIV

Published data on efficacy of fractional dosing

Main responsibility: Study funders; other key stakeholders: countries, regulatory agencies

POLIO

2.1 National ownership of polio transition process

The WHO Regional Office should develop a clear advocacy and communications strategy to encourage more active national ownership of the polio transition process, including implementation and domestic financing, and ensure greater commitment to investment in polio asset redeployment to maintain polio-free status and enhance national immunization programmes

Draft advocacy and communications strategy to be presented to RITAG in June 2019

Main responsibility: WHO RO; other key stakeholders: countries, WHO HQ (polio transition team)

2.2 Polio transition planning dashboard

The WHO Regional Office should provide RITAG with a dashboard summarizing national progress in the polio transition process, incorporating the categorization of countries according to their transition plan implementation capabilities

Dashboard to be presented to RITAG in June 2019

Main responsibility: WHO RO; other key stakeholders: countries, WHO HQ (polio transition team)

2.3 Polio vaccine hesitancy

Data on reasons for non-vaccination in cVDPV campaigns should be collated, to determine nature and scale of vaccine hesitancy, to monitor trends, and to identify any need for corrective interventions

Analysis to be presented to RITAG in June 2019

Main responsibility: WHO Regional Office; other key stakeholders: countries, Global Polio Eradication Initiative

MALARIA

3.1 Interdivisional collaboration

MVIP should document factors facilitating coordination of malaria vaccine activities, national immunization programmes and malaria control programmes, to provide guidance on the development of effective interdivisional collaborations involving national immunization programmes

Document to be presented to RITAG in January 2020

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

3.2 Health-seeking behaviour

MVIP should monitor health-seeking behaviour in intervention and control areas to determine whether the approach to implementation alters caregivers' health-seeking behaviour; in control areas, ongoing monitoring of attitudes and behaviour should be undertaken to detect any unintended programmatic impacts

Update to be presented to RITAG in January 2020

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

3.3 Key elements of implementation strategy

MVIP should identify the key elements of its approach to implementation, to provide guidance on the introduction of RTS,S/AS01 elsewhere or of other new malaria vaccines

Update to be presented to RITAG in January 2020

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

3.4 Decision-making tools

Given the links between malaria transmission dynamics, vaccine efficacy and cost-effectiveness, MVIP should develop tools that enable countries to enter local malaria data, conduct subnational analyses and make decisions on vaccine introduction based on the potential impact of different vaccination strategies

Update to be presented to RITAG in January 2020

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

EBOLA

4.1 Ebola vaccine licensing

To facilitate field use, Merck, licensing authorities and the WHO prequalification team should accelerate their efforts towards licensure of the VSV-EBOV vaccine, including in country of manufacture and in countries where trials and/or licensure might occur

Licensing of VSV-EBOV by 2020

Main responsibility: Merck, licensing authorities, WHO prequalification team; other key stakeholders: national regulatory authorities

4.2 Ebola vaccine candidates

Other Ebola candidate vaccines should continue to undergo clinical evaluation, to provide a range of options and products with additional features (e.g. wider or longer-lasting protection)

Ebola phase II and phase III vaccine trials

Main responsibility: Pharmaceutical industry, WHO, partners; other key stakeholders: countries, national regulatory authorities

4.3 Advice on Ebola vaccine use

WHO should extend guidance on Ebola vaccine implementation to other countries at risk of an outbreak or that send medical, peacekeeping or other personnel to affected regions

Guidance to be developed by June 2019

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

4.4 Ebola vaccine use in specific groups

Specific advice should be issued on Ebola vaccine use in specific groups including breastfeeding mothers and infants less than 1 year

Guidance to be developed by June 2019

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

4.5 Community engagement

Guidance on best practice in community engagement during Ebola vaccine deployment in outbreak situations should be shared with countries and other stakeholders

Guidance to be developed by June 2019

Main responsibility: WHO HQ; other key stakeholders: SAGE, WHO Regional Office, countries, manufacturers, academia, vaccine development and evaluation consortia (e.g. EBODAC)

4.6 Research in outbreaks

Research in Ebola outbreaks and other public health emergencies is important but should be aligned with the local strategy and agenda for managing the outbreak, should undergo local regulatory and ethical review, and should be country-led

Main responsibility: Research institutions; other key stakeholders: countries, national regulatory authorities, ethical review committees, AVAREF, WHO Regional Office

REGIONAL STRATEGIC PLAN FOR IMMUNIZATION

5.1 Post-2020 global immunization strategy

NITAGs should be consulted on post-2020 priorities and their input integrated into RITAG submissions to the post-2020 global immunization strategy planning process

Consultation to be completed by June 2019

Main responsibility: WHO Regional Office; other key stakeholders: NITAGS, WHO HQ

5.2 Addis Declaration roadmap

RITAG should have an opportunity to comment on the draft presentation on progress towards the commitments made in the Addis Declaration on Immunization to be presented to heads of state in July 2019

Draft to be provided to RITAG by March 2019

Main responsibility: WHO Regional Office

5.3 Underserved urban populations

Countries should be supported to undertake rapid assessments of underserved urban settings, and to use tools such as the revised Reaching Every District (RED) guidelines and UNICEF urban toolkit to develop, implement and evaluate strategies to enhance coverage

Communication to countries by June 2019

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

5.4 Resource allocation

Countries should develop multiyear budgets that include dedicated budget allocations for data improvement, vaccine logistics, surveillance, community engagement and NITAGs, and ensure allocated resources are made available in a timely manner

Communication to countries by June 2019; presence of such budget lines to be reported to RITAG in January

2020

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

5.5 Data accuracy

To avoid perverse incentives and to increase the accuracy of administrative and other data, neither rewards nor punitive measures should be linked to unverified coverage data, with recognition instead given to high accuracy and transparency by all partners

Communication to countries by June 2019

Main responsibility: countries; other key stakeholders: partners

5.6 Data improvement plans

Countries should be supported by WHO and partners to implement national data improvement plans as rapidly as possible, and to commit funds to ongoing data improvement through dedicated national immunization programme funding

Update on implementation of data improvement plans to be presented to RITAG in January 2020

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

MEASLES AND MATERNAL AND NEONATAL TETANUS

6.1 MCV2 targets

A consultation should be undertaken to develop a regional target and country targets for MCV2 coverage

Draft targets to be discussed at RITAG in June 2019

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

6.2 SIAs

When planning SIAs, countries should ensure they take account of existing WHO guidance on use of SIAs to strengthen national immunization programmes and vaccine coverage

Communication to countries by June 2019

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

6.3 SAGE measles guidance

To provide a clearer basis for operationalization of its latest measles guidance, SAGE should consider clarifying its criteria for categorization of countries with periodic outbreaks and moderate programme capacity to take account of the great diversity of such countries, the need to prioritize national immunization programme strengthening, and the risk that targeted SIAs will leave immunization gaps

Updated guidance provided by June 2019

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

6.4 Age range

Countries should use local epidemiological data to define target age ranges and geographical scope for measles SIAs and mobilize resources accordingly

Communication to countries by June 2019

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

6.5 SIA planning

Countries should place greater focus on pre-campaign preparation to ensure the quality of measles SIAs, drawing on WHO, partner support and successful practices adopted in other WHO regions, such as the South-East Asia Region

Communication to at-risk countries by June 2019

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

6.6 Year 2 platform

To encourage use of MCV2 and other second-year vaccines, the ‘fully immunized child at 24 months’ should be introduced and monitored as a national immunization programme indicator

Number of countries using indicator to be reported at RITAG January 2020 meeting

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

6.7 Combining HPV and Td vaccination

To improve efficiency and drive uptake of human papillomavirus (HPV) vaccine use, countries should consider combining HPV and a Td booster in a school-based vaccination programme

Number of countries combining HPV and Td vaccines to be reported at RITAG January 2020 meeting

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

DEMAND

7.1 Benchmarking regional practice

A review should be undertaken of demand and behaviour change activities adopted in the African Region, to identify successful strategies, key contextual factors influencing effectiveness, evidence gaps, and potential interventions for wider implementation

Draft review to be discussed at RITAG January 2020 meeting

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

7.2 RITAG agenda

Vaccination demand generation should be a standing item on the agenda for RITAG’s annual review meeting

Standing item to be introduced at RITAG January 2020 meeting

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

SURVEILLANCE

8.1 Surveillance advocacy

Given the dependency of vaccine-preventable disease surveillance on polio funding, the importance of maintaining vaccine-preventable disease surveillance activities should be strongly emphasized in Addis Declaration feedback to heads of state and in polio transition planning discussions

Surveillance incorporated in Addis Declaration feedback

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

8.2 Surveillance value report

Detailed comments from RITAG members should be taken into account during revision of the surveillance value report

Surveillance valuation report finalized by June 2019

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

8.3 Alignment with regional and global initiatives

The revised surveillance value report should include discussion of alignment with other regional surveillance initiatives (e.g. under the umbrella of the Africa Centres for Disease Control and Prevention, including national public health institutes) as well as relevant global initiatives including Integrated Disease Surveillance and Response

Surveillance valuation report finalized by June 2019

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

NITAGs

9.1 Committee glossary

To promote clarity in roles and responsibilities, a glossary should be developed of all the national committees relevant to national immunization programme function, their terms of reference and interrelationships

Draft glossary presented to RITAG in June 2019

Main responsibility: WHO Regional Office; other key stakeholders: NITAGs, EPI Programme Managers

9.2 NITAG indicators

NITAG functional indicators should be developed to complement the core six process indicators, including robust evidence-based decision-making processes and uptake of recommendations by national immunization programmes

Draft indicators to be presented to RITAG in June 2019

Main responsibility: WHO Regional Office; other key stakeholders: NITAGs, WHO HQ

9.3 NITAG resourcing

Ministries of health and national immunization programmes should ensure they have a dedicated annual budget for NITAG operations, including adequate secretariat support, and for NITAG set up where appropriate

NITAG budget lines included in comprehensive multiyear plans by end of 2020

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

9.4 Academic expertise

NITAGs should explore and exploit collaborative opportunities with local academic and research institutes to strengthen national vaccination policy-making and, when local expertise is not available, liaise with the WHO Regional Office to identify suitable resources

Communication to NITAGs by June 2019

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

Introduction

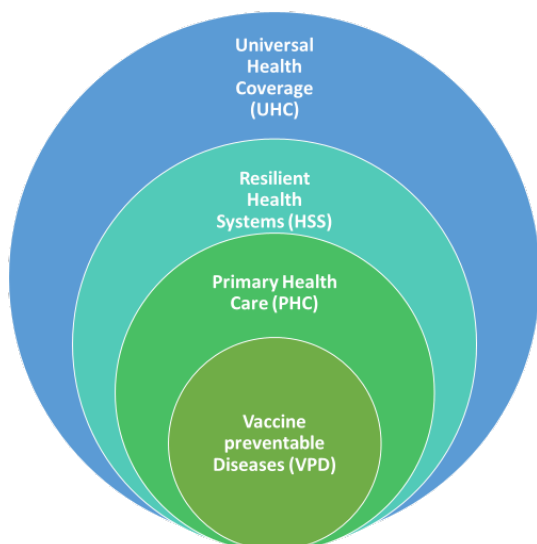
The Regional Immunization Technical Advisory Group (RITAG) serves as the principal advisory group to the WHO Regional Office for Africa, providing strategic guidance on regional immunization policies and programmes. It holds two meetings a year; the January 2019 RITAG meeting took place at the WHO Regional Office, the Congo, on 15–17 January 2019.

On behalf of WHO Regional Director **Dr Matshidoso Moeti**, **Dr Felicitas Zawaira**, Director of the Family and Reproductive Health Cluster, opened the meeting and welcomed delegates. The meeting was notable for its emphasis on integration and partnerships. In attendance at various points of the meeting were senior staff from other areas of the WHO Regional Office, including Raul Thomas, Director, General Management and Coordination Cluster, Dr Francis Kasolo, Director of the Office of the Regional Director, and Dr Soce Fall, Director, Health Securities and Emergencies Cluster. RITAG also welcomed the new head of WHO's Immunization, Vaccines and Biologicals Department, Dr Kate O'Brien, as well as representatives from the African Union Commission and other partners.

RITAG chair **Professor Helen Rees**, Founder and Executive Director of the Wits Reproductive Health and HIV Institute at the University of Witwatersrand, Johannesburg, South Africa, highlighted some of the major issues facing global health, as well as the social and political challenges facing the region. RITAG's role was to consider recommendations made by global bodies such as WHO's Strategic Advisory Group of Experts on Immunization (SAGE) and how they might be implemented within a regional context, providing an independent body offering advice and holding people accountable for implementation, monitoring and evaluation. RITAG also provides a channel through which national concerns and the views of National Immunization Technical Advisory Groups (NITAGs) can feed into global discussions.

Dr Zawaira emphasized how immunization benefited children, families and countries' economies more generally – delivering a US\$44 return for each US\$1 invested. While much progress has been made, and millions of lives are saved each year by vaccination, much remains to be done. One in five children in the region still do not gain the benefits of immunization.

Future progress would be based on partnerships Dr Zawaira suggested. Stakeholders such as partners and civil society are crucial to the development of better immunization services, which are increasingly seen as integral components of primary healthcare systems and contributing to universal health coverage.



The close relationship between immunization, primary healthcare and universal health coverage.

It was critical for countries in the region to assume greater responsibility for their immunization systems. Having made concrete commitments in the 2011 Addis Declaration on Immunization, national political leaders now had to be held accountable – with a heads of state meeting in July 2019 providing an opportunity to review progress and advocate for accelerated efforts to reach regional immunization goals.

Dr Richard Mihigo, Immunization, Vaccines and Biologicals Programme Manager, went on to provide an overview of progress in the implementation of previous RITAG recommendations and some of the priority areas for immunization in the Regional Office. The December 2017 and June 2018 RITAG meetings had made more than 50 recommendations, most of which were still in progress.

Among the most notable recent developments were the major commitments being made to immunization in priority countries, including Nigeria, the Democratic Republic of the Congo (DRC) and Chad, all discussed later in the meeting. Close engagement with the African Union Commission was laying the ground for a progress report on the Addis Declaration for the heads of state meeting in July 2019.

Improving the **quality of data** and national use of data for decision-making was a further regional priority. Use of subnational data will be crucial in tackling inequities in access to immunization services within countries. Various activities had been undertaken to improve surveillance for **cholera** and to mitigate the risk of outbreaks. A global investment case has been developed to mobilize resources to achieve **maternal and neonatal tetanus elimination**.

Various activities are underway to prepare for wider use of **typhoid conjugate vaccine** in the region, to control outbreaks and through integration into national immunization programmes. Significant efforts have also been made to enhance preparedness for **influenza pandemics** and to promote an evidence-based approach to vaccination against **seasonal influenza**. The Regional Office has also been supporting efforts to control the **Ebola outbreak** in the DRC, where vaccination is being used as part of control efforts, and to prevent its spread to neighbouring countries. The Regional Office is also supporting activities to control cVDPV outbreaks in the DRC, Nigeria and Niger.

During 2018, a **regional immunization research strategy** was finalized and published. A key aim has been the strengthening of links between the Regional Office, national immunization programmes and academic institutions, to develop research programmes to enhance the delivery of immunization services.

YELLOW FEVER

African Region update on progress in implementation of the Eliminate Yellow Fever Epidemics strategy

Laurence Cibrelus, Kausik Banerjee, EYE Secretariat, WHO

In 2016, Angola and the DRC were hit by a major linked yellow fever outbreak. More than 950 cases were confirmed, leading to 137 deaths. Cases were exported to other African countries, as well as to China. More than 30 million people were vaccinated in mass campaigns. The outbreaks provided clear evidence that populations had not been adequately protected by earlier vaccination campaigns.

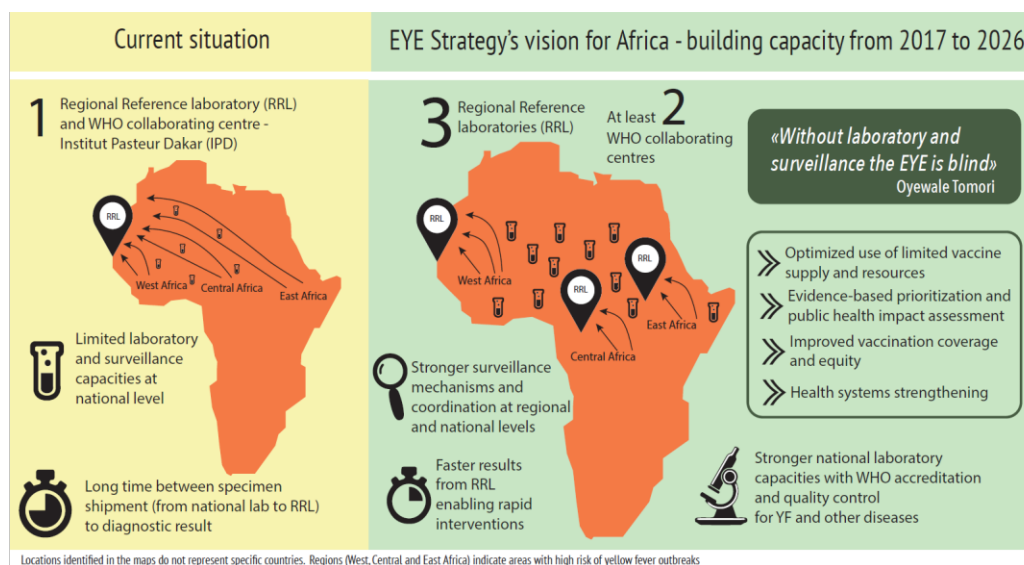
Since then, other countries in the region have been affected by sporadic yellow fever outbreaks. Multiple requests were made in 2018 to the global yellow fever vaccine stockpile, which was replenished on several occasions. A total of 50 million vaccine doses were provided during the year.

In 2017, Nigeria was affected by a major yellow fever outbreak which is still ongoing. Approximately 4000 suspected cases have been reported. Population movements and urbanization increase the risk that the infection will be introduced into urban centres and potentially disseminated internationally; worryingly, the outbreak is gradually moving south towards Lagos. A mass vaccination campaign has immunized 36 million people in at-risk areas (see Box).

Protection against yellow fever is dependent on high coverage in immunization programmes following mass vaccination, but only five countries are achieving coverage of greater than 80%. Subnational variation in coverage is also a concern, creating pockets of vulnerable unimmunized people.

The **Eliminate Yellow Fever Epidemics (EYE)** initiative was launched in 2016, with the goal of eliminating yellow fever outbreaks globally by 2026. As the infection cannot be eradicated, the focus is on control of infection risk. A regional framework for implementation of EYE was formally launched in April 2018.

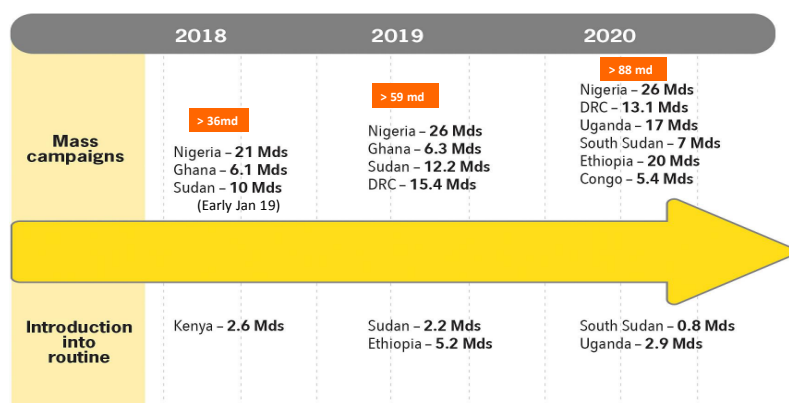
The EYE initiative focuses on four areas. Risk prioritization activities identify countries, and areas within countries, on which preventive action should be focused. Supply and demand activities aim to map out likely future vaccine needs and manufacturing capacity, and have revealed potential future shortfalls in vaccine supply. A laboratory capacity workstream is building national and regional laboratory capacity in yellow fever, to reduce the reliance on the Regional Reference Centre in Dakar, Senegal. Finally, immunization operational guidelines and an EYE country guidance toolkit provide practical advice on campaigns.



EYE's capacity-building strategy for yellow fever detection.

EYE has short-term aims of controlling and containing current outbreaks, alongside a longer-term approach to reduce outbreak risks. Extensive country engagement has been undertaken to raise political awareness, with several countries responding with requests to the global stockpile for vaccine for use in immunization programmes and/or mass

campaigns. The EYE programme has adopted a three-pillar preventive approach based on preventive mass campaigns, strengthening national immunization programmes and use of targeted catch-up campaigns. Despite the importance of high coverage in national immunization programmes, yellow fever coverage often lags behind MCV1 coverage and four at-risk countries have still to introduce yellow fever into their immunization programmes.



Executed and planned yellow fever vaccination campaigns in the region.

One-year follow-up of fractional-dose yellow fever vaccine recipients: Kinshasa summary results

Rebecca Casey, CDC

The yellow fever vaccine is generally given in 0.5 ml doses, which confers lifelong immunity. It has been part of the DRC immunization programme since 2003, but the country nevertheless experienced a major yellow fever outbreak in 2015. Targeted vaccine campaigns were launched to control the outbreak, which led to a depletion of the global vaccine stockpile. In response, in 2016, SAGE recommended that fractional dosing – vaccination with 0.1 ml doses, which evidence suggested should still provide protective immunity – should be used in outbreak situations and when vaccine supplies were limited.

In the DRC, 7.6 million children and non-pregnant adults received a fractional dose (0.1 ml) of vaccine. To evaluate the impact of fractional dosing on yellow fever protective immune responses, the CDC organized a trial at six sites in Kinshasa, integrated within the vaccination campaign. The study collected blood samples from people 2 years and older before vaccination, and at one month and one year after vaccination, testing for the presence and levels of virus-neutralizing antibodies.

Data from one month have been published¹ and suggest that the fractional dose elicits good antibody production; 98% of initially seronegative children converted to seropositivity and no significant differences in seroconversion rates were seen between age groups or sexes. For people with pre-existing yellow fever antibodies, immunization boosted antibody production fourfold (considered a protective response) in 66% of recipients, although increases depended on the age of recipients (increases were smaller in the 50+ age group) and baseline antibody levels (the greatest responses were seen in those with the lowest initial antibody levels).

¹ Ahuka-Mundike S *et al.* Immunogenicity of Fractional-Dose Vaccine during a Yellow Fever Outbreak - Preliminary Report. *N Engl J Med.* 2018 Feb 14. doi: 10.1056/NEJMoa1710430. [Epub ahead of print]

New data on responses at one year revealed that seropositivity across the study population as a whole was very high – 97%. Again, no significant differences were seen across age groups or between sexes.

The new data suggest that fractional dosing of yellow fever vaccine is eliciting protective immunity for at least one year. The data provide reassurance that fractional dosing in response to vaccine shortages can contribute to outbreak control. Although they raise the possibility that fractional dosing could be adopted more widely, for example in national immunization programmes, these remain the only data reported so far at one year, and no evidence is yet available on longer-term protection. Furthermore, no data are available for other prequalified vaccines or for responses in children under 2 years.

Implementation of the EYE strategy: challenges and perspectives at country level

Bassey Okposen Bassey, MoH Nigeria

Nigeria experienced significant yellow fever outbreaks in the early 1990s. It introduced yellow fever vaccination into its immunization programme in 2004 and undertook a national risk assessment exercise in 2008, identifying 20 high-risk states. During 2013–14, mass vaccination campaigns were organized in three out of 20 states, vaccine shortages limiting population coverage.

Nevertheless, a major yellow fever outbreak began in 2017 and is ongoing, affecting 14 states, with 67.3 million people at risk. The outbreak is affecting all ages but children and young adults are bearing the brunt – 80% of cases are in individuals younger than 26.

As well as hosting the launch of the global EYE strategy in April 2018, Nigeria developed a national EYE strategy with four key objectives: protection of populations at risk, organization of preventive and reactive campaigns, strengthening of surveillance and laboratory support, and prevention of international spread.

A risk analysis undertaken in 2018 identified 18 high-risk states with a total population of over 60 million. In these areas, low immunization coverage put large numbers of people at risk.

Preventive mass vaccination campaigns in 2018 reached nearly 29 million people, while 7.8 million people were vaccinated in reactive campaigns in 2017/18. Efforts have also been made to develop yellow fever laboratory capacity, with the country hoping to expand its network from four to seven sites and to establish a Regional Reference Laboratory; currently, all cases are confirmed by the Regional Reference Laboratory in Dakar, Senegal.

Current challenges include ongoing vaccine shortages, and delays between detection and confirmation of cases. Surveillance and laboratory services are often affected by resourcing and materials shortages. The control programme also faces many operational challenges, including insecurity.

Moving forward, multiple actions are being taken to strengthen the outbreak response. These include upgrades to laboratory capacity, repurposing of polio assets, support for a national centre for disease control, further Gavi-supported preventive mass vaccination campaigns in 2019–21 and strengthening of the immunization programme through the NERICC initiative (see page xx).

Discussions noted that yellow fever spanned different areas of interest – including health emergencies and global health security as well as immunization – and the importance of ensuring joint and coordinated responses was stressed. It was also suggested that yellow fever had not been sufficiently prioritized in the past, and that the EYE initiative was beginning to galvanize action.

It was argued that it was important to understand whether low coverage rates reflect issues related to immunization programmes or more specifically to yellow fever vaccination, with the situation likely to differ from country to country. The potential to link measles and yellow fever vaccination campaigns was noted, as well as to use campaigns to improve national immunization programmes and coverage, as recommended by WHO. Although this presents practical challenges, the experience of several countries suggests it can be achieved.

It was noted that poor past coverage, plus factors such as migration and urbanization, creates pockets of vulnerable populations in high-risk areas, including migrants and mineworkers. It was also suggested that serosurveys could be used to provide a more accurate picture of vaccine coverage, although their significant cost is an obstacle to their widespread use.

The importance of developing national surveillance and laboratory capacity was stressed, including clarity on the capabilities and performance standards required of laboratories and Regional Reference Laboratories so countries have a clear developmental roadmap. The need to consider surveillance within a wider context was also highlighted. For example, through One Health partnerships, monitoring of additional hosts such as primates and of vectors could also contribute to surveillance activities.

Additional areas of discussion included the degree of community engagement in yellow fever-related activities, as well as the potential contribution of vector control to outbreak prevention and control.

The research on fractional dosing was seen as providing vital data. It was recognized that data on the long-term effects of fractional dosing were limited, so any introduction into national immunization programmes might be premature. However, with limited supplies of vaccine, plus projected future shortfalls and little surge capacity, there could be a case for greater use of fractional dosing, for example in catch-up campaigns targeting vulnerable populations in high-risk areas. Collecting more data on long-term protection, as well as on fractional vaccine use in children under 2 and people living with HIV, should also be a global priority.

It was also noted that the term ‘fractional dosing’ was potentially misleading. Due to variation between different products, vaccine dosing varies, so ‘fractional volume’ would be a more appropriate term. In addition, use of the term fractional dosing could undermine community confidence in vaccination, despite the evidence of effective protection. Terms such as ‘appropriate’ or ‘efficient’ dosing might be preferred.

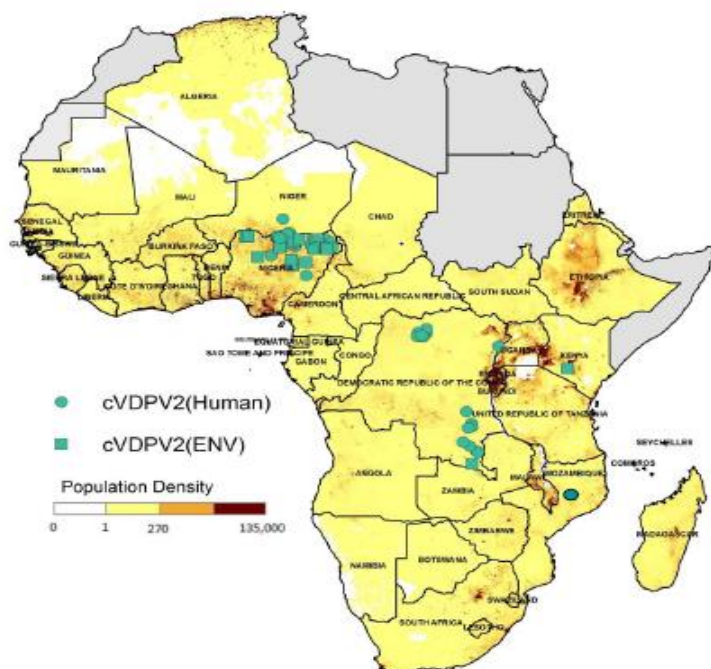
POLIO

Polio eradication in the African Region: progress towards certification

Ticha Johnson, WHO

Africa continues to edge closer to eradication of wild poliovirus. The last confirmed case of wild poliovirus was detected in northern Nigeria in August 2016, and extensive efforts have been undertaken in a challenging environment around Lake Chad to immunize local populations.

However, a spate of cVDPV outbreaks in the region is a significant cause for concern. During 2018, 63 human cases and 40 positive environmental samples were detected across several countries. Control efforts have faced multiple challenges, including low levels of population immunity, a declining number of districts hitting coverage targets and a growing number of silent districts, a lack of country commitment, and practical difficulties associated with areas of challenging terrain and insecurity.



cVDPV outbreaks in the Africa Region.

Multiple subnational outbreak responses and vaccination campaigns have been organized in DRC, Nigeria and Niger, using monovalent vaccine (mOPV2). Surveillance activities have also been strengthened, including greater use of technological innovations such as GIS-enabled systems for mapping health facility visits (Integrated Supportive Supervision, ISS, and eSurv) and the AVADAR audiovisual system in remote areas. Environmental surveillance has also been extended to 22 countries, with plans for further expansion.

Work towards certification of laboratory containment has also progressed. Phase 1 has been completed, although updates are due from countries that have been using mOPV2 in cVDPV responses. In all, 40 countries have submitted documentation to the African Regional Certification Commission (ARCC), seven are pending and one is due to resubmit. South Africa is the sole site planning to be a polio essential facility holding wild poliovirus samples, and will be supported by ARCC in its application.

Future priorities include continuing efforts to interrupt transmission in the Lake Chad area and in countries affected by cVDPV, supported by increasing use of new surveillance tools. Countries will continue to be assisted in their

documentation of polio-free status, with the aim that all countries will have their documentation accepted by the ARCC by the end of 2019.

A framework for certification of polio in the African Region was endorsed at the 68th session of the WHO Regional Committee for Africa, held in Senegal in September 2018. It sets out the steps that need to be taken to ensure timely certification of polio eradication. In October 2018, the Global Commission for the Certification of Poliomyelitis Eradication (GCC) recommended a process of sequential certification of wild poliovirus eradication and confirmation of the absence of cVDPV.

cVDPV outbreak in the Horn of Africa

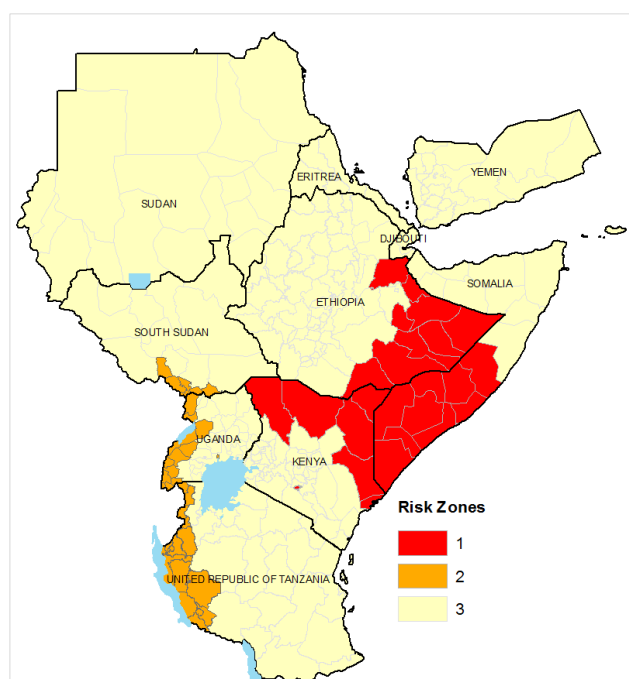
Chris Kamugisha, WHO

Multiple activities have been undertaken to control a cVDPV2 outbreak in the Horn of Africa. Centred on Somalia, the outbreak presents multiple challenges. The affected area spans WHO regions, includes highly insecure areas, and population mobility is high. Population immunity is low and there are concerns about the quality of SIAs and surveillance. A single positive environmental sample in Kenya may represent an import from further north.

Priorities in 2018 were to interrupt transmission using mOPV2 SIAs and to enhance surveillance. These additional surveillance activities identified circulating cVDPV3, necessitating use of bivalent vaccine (bOPV) in some areas.

Synchronized vaccination campaigns were organized in Somalia, Kenya and Ethiopia, achieving high coverage (although vaccination teams were not able to reach some communities owing to security concerns). Subsequent Outbreak Response Assessment (OBRA) and Technical Advisory Group (TAG) reviews noted that progress had been achieved and made a number of recommendations for further action.

The priority for phase 2 activities will be to vaccinate populations not yet reached, with a focus on inaccessible areas and special populations such as migrants and the urban poor. Further efforts will be made to enhance surveillance. Three zones have been identified, including the outbreak area, countries on the eastern border of the DRC and other countries at risk.



cVDPV risk zones in the Horn of Africa.

Further SIAs and opportunistic immunization activities will take place in zone 1, with enhanced surveillance and emphasizing cross-border collaboration. Zone 2 activities are planned to enhance preparedness, with increased surveillance and population immunity in high-risk areas and in displaced populations. Zone 3 activities will focus on risk assessment, preparedness and enhancing population immunity in high-risk areas and among special populations.

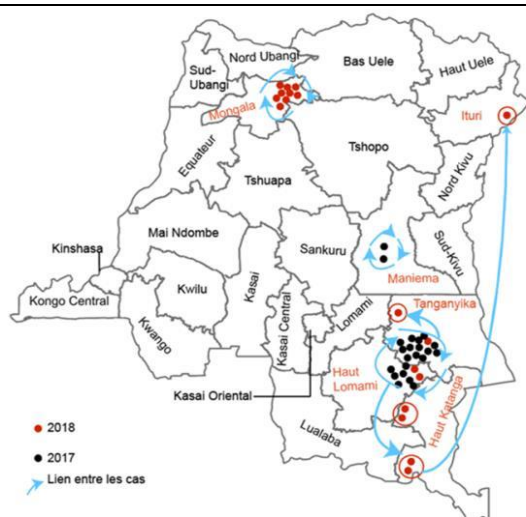
cVDPV outbreak in DR Congo: where are we now?

Guillaume Ngoie Mwamba, MoH DR Congo

The cVDPV outbreak in the DRC encompassed 42 cases in six provinces, representing four distinct outbreaks.

Transmission is thought to have been interrupted and the latest case from late 2018 is not thought to be linked to previous outbreaks.

In response to the outbreak, state governors signed the Kinshasa Declaration committing themselves to the mobilization of resources and coordination to interrupt transmission. SIAs were organized in 16 provinces over two phases, targeting a population of nearly 11 million, although activities in one area have been disrupted by the DRC's Ebola outbreak. An OBRA is planned for February 2019.



cVDPV clusters in the DRC.

Follow-up surveys identified a range of reasons for lack of vaccination, including some outright refusals and the frequent absence of children from the home during visits (potentially a form of ‘passive resistance’). Lot quality assurance sampling (LQAS) identified some improvement in coverage in phase 2 compared with phase 1.

Following these activities, two cases were detected in September 2018 and two in October 2018, unrelated to the earlier outbreaks. Further SIAs are planned for February 2019 and surveillance is being strengthened.

Lessons learned include the value of LQAS for identifying gaps in coverage and informing corrective actions, the importance of involving state governors to ensure subnational political commitment, and a strong partnership with the Ministry of Health. Challenges include the difficulties reaching insecure areas and special populations, the impact of the Ebola outbreak, and an incomplete understanding of the distribution of local settlements.

Refusal levels are a cause for concern, while weaknesses have been identified in areas such as microplanning and surveillance. Strengthening of surveillance activities and introduction of new approaches such as AVADAR and environmental surveillance will be an important focus moving forward.

Polio transition planning: update

Claudio Politi and Aschalew Dadi, WHO

A key objective of the polio transition process is to ensure that polio resources are utilized to enhance more general health services, including immunization programmes. All seven priority countries in the African Region have developed polio transition plans endorsed by Interagency Coordinating Committees (ICCs), while Nigeria is developing a business case. However, none of the transition plans has yet been implemented.

Key barriers to progress include a lack of government commitment and ownership, limited resource mobilization capacity, and a lack of clear plans of where polio assets would be housed. To catalyse action, a polio transition team has been created at WHO HQ, incorporating staff with relevant skills seconded from other departments.

The revised Global Polio Eradication Initiative (GPEI) will support polio positions in 2019. Funds will begin to be withdrawn in selected countries in 2020, followed by a further group in 2021. The ramp down in funding will continue through 2022–23, with closure by the end of 2023.

Following approval of a Strategic Action Plan on Polio Transition by the World Health Assembly in May 2018, a transition team has been established at WHO HQ. It is responsible for liaison with partners and with focal and national focal points. It has begun to undertake joint planning missions in priority countries, with representatives from multiple WHO divisions and partners such as Gavi, to finalize transition plans and to support the development of resource mobilization plans.

The team participated in a stakeholder consultation on surveillance, organized by the African Regional Office and held in Kigali. A polio stakeholder meeting involving GPEI donors and others was held in Montreux, to discuss the Strategic Action Plan on Polio Transition and challenges associated with transition. A working group has been set up to continue discussions on the preservation of essential functions over the transition period.

It was concluded that the focus on individual countries was essential, and that funding remained a key issue. The GPEI extension has created breathing space, but may be discouraging countries from progressing their transition plans. It was noted that transition needed to take account of country context, and three distinct categories of countries could be distinguished – fragile states, lower risk countries where implementation could start, and countries with strong systems that could readily take on responsibilities.

Future activities will include further country visits, provision of technical support to complete transition plans, preparation of communication and advocacy plans, and monitoring of implementation.

Discussions emphasized the critical importance of **completing polio eradication** – enormous progress has been made over the past 20 years and the ultimate goal is now within reach. Certification of polio eradication in Africa would be a huge achievement for the region. Ministers of health have identified a need for a scorecard illustrating countries' progress towards certification in the final stages of eradication and verification. RITAG was highly supportive of this advocacy tool and asked to receive regular updates on national progress towards certification.

Other expert committees have oversight of wild poliovirus eradication and cVDPV outbreak control, so RITAG felt it was inappropriate to be offering further detailed technical recommendations. However, it noted with concern the numbers of active vaccine refusals and absence of children from home during vaccination visits (which could represent a form of 'passive refusal'). Analysis of data from cVDPV campaigns could provide a clearer picture of this issue in the region and the potential need for interventions to address it. cVDPV outbreak response campaigns were also seen as a potential route for the delivery of other vaccination services, or other healthcare services or water, sanitation and hygiene interventions.

The vital role of strong national immunization programmes and surveillance in **prevention and control of cVDPV outbreaks** was repeatedly stressed. The difficulties of confirming the eradication of wild poliovirus and cVDPV circulation in inaccessible and insecure areas with limited surveillance was widely recognized. It was suggested that a specific committee might be needed to consider this specific issue.

The **slow pace of polio transition planning** was a continuing cause for concern. The GPEI extension was felt to have further discouraged countries from pressing ahead with transition planning in a timely manner. It was also felt that global eradication efforts had led countries to adopt a recipient mentality, and a new mindset was required emphasizing country ownership and national governments' responsibilities for the health of their populations. It was also noted that financial commitments to immunization could be framed as investments in the future that deliver substantial economic as well as health benefits.

RITAG suggested that countries should continue to be encouraged to proceed with polio transition planning as a matter of urgency, leveraging commitments made in the Addis Declaration. A dashboard tracking progress in transition planning and implementation, incorporating the country categorization developed by the WHO polio transition planning team, was felt to be helpful.

A crucial step was felt to be rigorously costed national business cases for sustainable transitioning that maintain essential functions and integrate polio assets to enhance national immunization programmes. The goal was not necessarily to preserve existing approaches and structures but to transfer ownership to countries, and to absorb and rationalize assets to ensure they are repurposed to meet national needs. Importantly, transitions also need to be considered within a wider national context, including health systems strengthening, emergency preparedness, and national and global health security initiatives.

MALARIA

Update on MVIP: current status and timelines

Mary Hamel, WHO

In phase III trials, the malaria vaccine RTS,S/AS01 showed modest efficacy but had the potential for high impact. In 2015 it received a positive scientific opinion from the European Medicines Agency (EMA). Subsequently, SAGE and the Malaria Policy Advisory Committee (MPAC) recommended a phased introduction in three to five countries, to gather further evidence on efficacy, safety and feasibility.

Results from a phase III pivotal trial found that a four-dose schedule provided optimal benefits, protecting against severe and cerebral malaria; a three-dose schedule protected against clinical but not severe or cerebral malaria. However, a three-dose schedule could be integrated into existing immunization or other healthcare schedules, a four-dose schedule would require a new visit to be introduced into an immunization programme.

A recent three-year follow-up at three sites after three additional years (seven years in total), at sites of differing transmission intensity, confirmed the additional protection offered by the four-dose schedule. It also found no evidence of safety signals seen in more preliminary analyses (an increased risk of meningitis and cerebral malaria) or of a rebound in malaria cases, suggesting that vaccination is protecting children through the period when they are most at risk of malaria.

Determination of efficacy can be challenging, as simply enrolling in a trial is associated with a substantial mortality benefit, owing to the quality of care provided in a trial setting. The pilot Malaria Vaccine Implementation Programme (MVIP) studies will provide key data on mortality benefits in a programmatic setting, as well as on safety and feasibility.

For the pilot implementation studies, ministries of health were invited to submit expressions of interest. Three countries – Malawi, Kenya and Ghana – were selected on the basis of a range of criteria, including presence of a strong national immunization system and malaria programme, high transmission, high mortality and prior experience with the vaccine. A joint regulatory review involving AVAREF and national regulatory agencies was undertaken, with authorization provided in May 2017.

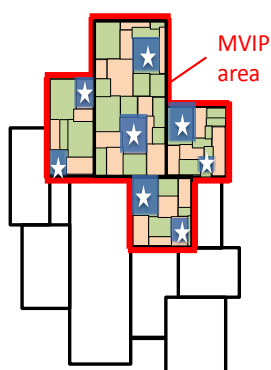
In the three countries, RTS,S/AS01 is being introduced in a selection of districts, and outcomes will be compared in those in neighbouring control districts. Ministries of health will monitor introduction as they would for any new vaccine and routine malaria monitoring will continue. In addition, an independent WHO-sponsored evaluation is being carried out, alongside a geographically separate post-licensing study sponsored by the manufacturers (GlaxoSmithKline, GSK).

The WHO-sponsored evaluation will be observational, with data collection at sentinel hospitals on meningitis, cerebral malaria and severe malaria. Community-based surveillance will be strengthened and household surveys used to assess coverage.

The GSK-led study forms part of a risk management plan agreed with the EMA. It will be carried out in four districts in each country, and will involve a prospective study of 30,000 children to monitor all medical events. In addition, a PATH-led qualitative assessment and economic analysis will examine obstacles to and enablers of implementation, and carry out a cost-effectiveness analysis.

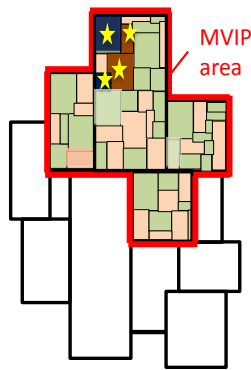
MVIP safety evaluation for RTS,S

Pilot evaluation in-patient surveillance
Focus on meningitis and cerebral malaria



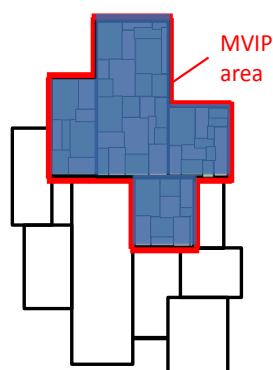
4-8 sentinel hospitals

Phase IV in-patient surveillance
Focus on meningitis, cerebral malaria and AESIs



4 sentinel hospitals
+ home visits

MoH routine PV AEFI/AESI reporting
Focus on rare and unexpected AEFI



Strengthened in all areas

Safety surveillance in the MVIP malaria vaccine implementation project.

The project also includes a data and safety monitoring board to ensure timely monitoring of data from all sources, which will liaise closely with national regulatory authorities. A further important component is an extensive stakeholder and community engagement programme, coordinated with PATH and ministries of health. The pilots are due to start at the beginning of March 2019 in Ghana and late March in Kenya and Malawi.

Vaccine introduction planning: current status, timelines, challenges and opportunities of integrating RTS,S into immunization and child health programmes

George Bonsu, MoH Ghana

Malaria is a major health challenge in Ghana. Nearly 8 million cases occurred in 2017, with 10,900 deaths; malaria is responsible for 30% of all hospital admissions. This burden remains high despite extensive use of malaria control tools, such as insecticide-treated bednets, insecticide spraying and chemoprevention during pregnancy. Ghana also has impressive immunization coverage figures, with first-year coverage exceeding 90% and MCV2 coverage of 79%.

Ghana established a Malaria Vaccine Technical Working Group in 2009 and participated in RTS,S/AS01 vaccine trials in 2009–14. It developed a technical brief in 2015–16 and its Ministry of Health communicated an expression of interest in 2016.

The national immunization programme has taken a lead role in the planning of implementation, based on approaches adopted for other new vaccine introductions. With partners, coverage will be monitored and a post-introduction evaluation will be carried out.

The pilot project was approved by the Ghanaian national regulatory authority, the Food and Drugs Authority. The schedule has been integrated with the country's vitamin A supplementation and other vaccine delivery schedules, with a new visit introduced at 7 months. Training materials have been developed, and recording and monitoring tools adapted to accommodate the new vaccine. Pharmacovigilance has been strengthened and a stakeholder engagement plan developed, including media engagement.

Challenges include the need to generate demand for all four doses, as well as communicating the unusual nature of the implementation. The complexity of the pilot has also led to some delays. The pilot is also providing an opportunity to catch up on missed vaccinations and other interventions.

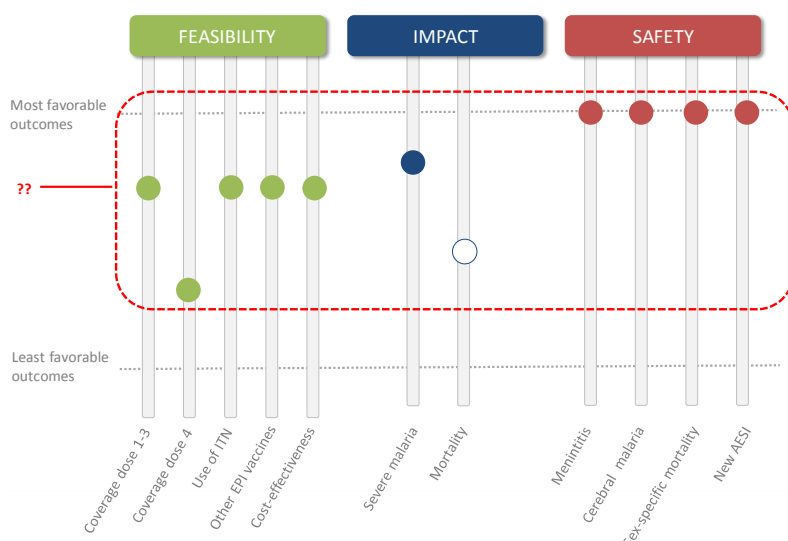
Among the lessons learned are the importance of high-level political commitment, the value of a technical working group, and the need for effective partnerships. Ethics and regulatory bodies have been engaged from an early stage, while partners have made important contributions. Detailed planning and budgeting was also carried out early in the process, based on a shared understanding of objectives.

Framework for policy decision

Mary Hamel, WHO

At the request of SAGE and MPAC, a framework for policy decisions is being developed to provide scope for emerging data to influence policy decisions, and to generate a shared understanding in advance of how MVIP data will be used to inform decision-making. A joint SAGE MPAC working group has been established, including modellers, which will report to SAGE and then to RITAG.

The framework will facilitate evidence-based decision-making and provide clarity on the use of data. This is important for programme managers, funders and for manufacturers, ensuring that supply can be matched to likely demand.



Assessment framework for the RTS,S/AS01 malaria vaccine.

The working group is considering feasibility, impact and safety, exploring scenarios in which each of these elements falls along a spectrum from most favourable to not favourable. It is applying a hierarchy in which resolution of safety signals is highest priority, followed by confirmation of impact in immunization programmes and feasibility of the fourth dose. Furthermore, initial modelling studies suggest that the impact of the fourth dose may have been overestimated – further work is being undertaken to explore this issue in collaboration with the manufacturers. Given the practical challenges associated with use of a fourth dose, it was recognized that this issue was a key one to resolve.

In discussions, it was noted that the project was associated with **strong collaborations** between national immunization programmes and national malaria control programmes, interdivisional interactions that do not always go smoothly. Documenting the factors underlying this effective collaboration could support more effective working practices in other implementation sites. Good existing relationships and embedding of national immunization programmes within wider maternal and child health programmes were seen as critical to this close working relationship.

It was noted that vaccination could be seen as an alternative to other means of malaria control, such as use of bednets. It would be important to ensure vaccine use was communicated as an **addition to rather than replacement** for these interventions. Before and after cross-sectional surveys will be used to explore impacts on such behaviours in MVIP.

It was also suggested that introduction of the vaccine might **influence caregiver behaviour in control areas**. Caregivers may seek out health facilities in which the vaccine is available, potentially affecting analyses of efficacy data or increasing the risk of stockouts. The fact that vaccination will largely be integrated into existing health facility visits may mitigate this risk, but monitoring of caregiver behaviour would be important. A further risk is that caregivers in control areas may resent not having access to the new vaccine.

The implementation project is complex and unlikely to be feasible for all new vaccine introductions. It would be important to identify the **critical policy elements**, such as communication, that are central to effective implementation.

It was also suggested that consideration should be given to how an **ethical dimension** could be incorporated into the policy framework discussions.

It was also noted that vaccine efficacy is highly dependent on **malaria transmission dynamics**. As well as integration into other vaccination or health intervention schedules, a malaria vaccine schedule will need to be sensitive to issues such as local seasonality in malaria transmission. Potentially, a tool could be developed to enable countries to assess their need for and design of a malaria vaccine schedule based on their local malaria data.

EBOLA

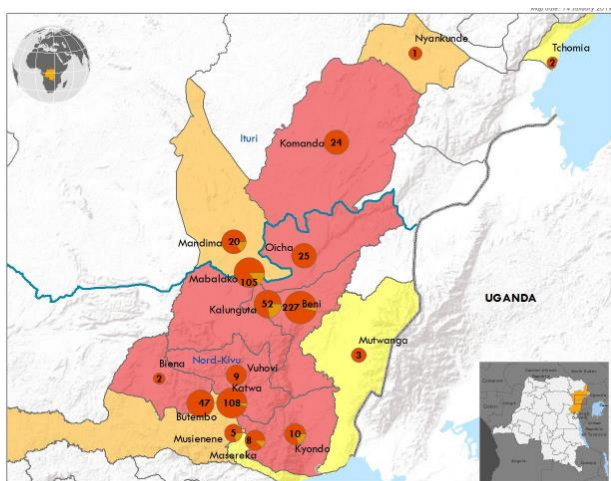
Update on Ebola virus vaccines

Ana Maria Henao-Restrepo, WHO

The Ebola outbreak that began in the DRC in 2018 is the second largest ever recorded. Disease control efforts include use of Merck's rVSVΔG-ZEBOV-GP vaccine (also known as VSV-EBOV), which was deployed in the latter stages of the 2014–16 West African Ebola outbreak.

An overarching policy framework for the globally coordinated development and evaluation of vaccines for use in emergencies is provided by the R&D Blueprint, which includes a preparedness plan and strategy for vaccine evaluation and deployment. The Ebola vaccine pipeline is relatively well-stocked with 13 products in the pipeline (although most are at an early stage of clinical evaluation). China and Russia have each licensed a locally developed vaccine, although limited clinical data are available. Of note, a prime–boost vaccine in phase III trials provides protection across a wider range of Ebola strains than VSV-EBOV.

Unlicensed developmental vaccines can be introduced in the context of clinical trials, while licensed and prequalified vaccines are typically made available in implementation studies with national regulatory authority approval. In October 2018, SAGE recommended use of the VSV-EBOV vaccine in the DRC Ebola outbreak through a compassionate use mechanism, using an agreed protocol and with adherence to GCP procedures and informed consent, and with appropriate national regulatory authority and ethical review committee approvals. As contact tracing is challenging in insecure areas, a ring vaccination strategy has been adopted around villages or clusters of cases.



Distribution of Ebola cases in the DRC.

Pregnant women are at particular risk of death from Ebola infections, but limited data are available on the safety of Ebola vaccination in this group. With effective ring vaccination, pregnant women are likely to benefit from herd immunity, and risk of transmission is primarily associated with contact with health facilities. Given the complexity of benefit–risk assessments in this group, decision-making has been entrusted to national regulatory authorities and ethical review committees.

The vaccine strategy has been deployed in North Kivu and Ituri, with the support of the DRC government and partners. More than 400 rings have been vaccinated, surrounding 90% of confirmed cases. A total of 60,000 people have been vaccinated, including 20,000 healthcare workers and frontline workers and 14,500 children and young people. Overall coverage has been in excess of 90%.

A vaccination strategy has also been developed for neighbouring countries, with more than 25,000 healthcare workers vaccinated in Uganda and vaccination plans developed for South Sudan, Rwanda and Burundi.

Key future challenges include the need to build capacity in GCP and use of Ebola vaccines in at-risk countries, as well as maintaining momentum in regulatory approval processes. SAGE has recommended that WHO work with national regulatory authorities to identify appropriate pathways for evaluation and approval of Ebola vaccines.

RITAG members commended this work, carried out under highly challenging circumstances, noting the effective collaboration between countries, WHO and partners. The exceptional commitment of healthcare workers and other frontline workers was also noted. The lead role being played by national governments was recognized, as well as the close collaboration between national immunization programmes and health emergency teams.

Discussions focused on the need to obtain more data on **vaccine use in pregnant women and infants under 1 year**. **Breastfeeding women** were felt to be a separate category in which vaccine use could be appropriate, particularly given anecdotal evidence that women may be stopping breastfeeding in order to be vaccinated.

It was argued that every effort should be made to **accelerate licensure of the VSV-EBOV vaccine** to simplify its introduction, with the recognition that further data on long-term efficacy are required. It was also important to **continue development and evaluation of additional vaccines**, to avoid supply bottlenecks and vulnerabilities and to deliver products offering longer protection or defence against a wider range of strains. SAGE is due to consider the design of trials of other vaccine candidates and a framework for product selection, although final choices on use in the field will be made at a country level.

While vaccination plans have been developed for countries neighbouring the DRC, it was suggested that advice should also be developed for **other countries at risk of importation** or likely to send healthcare workers or peacekeeping forces to affected areas.

It was also suggested that **ring vaccination should be emphasized as the optimal strategy for containment**. It is likely to represent a better use of resources than mass vaccination, and is not being used as a vaccine-sparing strategy. Given the

challenging circumstances, it is also important that lessons are learned about effective **community engagement** to inform activities in future outbreaks.

The occurrence of multiple seemingly independent clusters was noted. However, for a range of reasons – including conflict, economic insecurity and mistrust of health services – affected populations are highly dynamic, leading to the dissemination of cases. Subsequent analyses have linked cases into a much smaller number of clusters. The possibility of using new tools such as portable genome sequencers to provide real-time information on infections is being examined.

It was also stressed that, while **research in emergency situations** is vital, outbreaks should not be used opportunistically by researchers. Accepted regulatory and ethical approval mechanisms should be followed, and research projects should not interfere with emergency disease control responses. Research responses should be coordinated, led by a local public health agenda, and have strong involvement from national governments.

REGIONAL PROGRESS

Progress and challenges in improving coverage and equity in the African Region

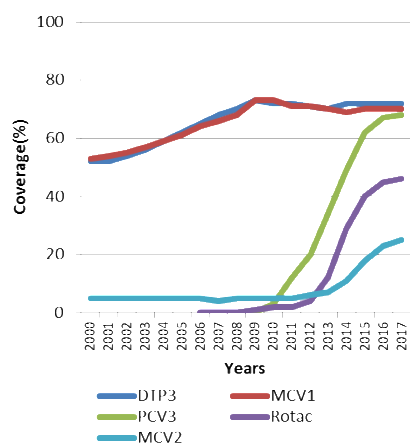
Richard Mihigo, WHO

Delivering an annual review of immunization in the region, Dr Mihigo noted some of the most notable developments of 2018. These included the launch of the Regional Office's Business Case for Immunization, outlining the approach to be taken by WHO in support of countries, as well as the development of the 'maturity grid' approach for categorizing countries, providing a framework for establishing the nature and intensity of support to be provided.

Other notable events included the launch of the WHO's 13th Global Programme of Work, identifying its 'three billion' aims – 1 billion more people with health coverage, 1 billion more people made safer, and 1 billion more lives improved by 2023 – to which immunization will make a key contribution. In addition, Gavi has launched a consultation exercise to gather input into the latest iteration of its strategy ('Gavi 5.0').

Within the region, a succession of infectious disease outbreaks has drawn attention to shortcomings in national immunization programmes, with inadequate coverage creating pockets of vulnerable under-immunized individuals.

In terms of progress towards the objectives of the Regional Strategic Plan for Immunization, DTP3 coverage continued to plateau at 72%, although encouraging progress was seen in PCV3 and MCV2 coverage levels. Moreover, due to the increasing size of birth cohorts in Africa, the actual number of children immunized has increased significantly. Inequities within countries remain a significant concern, with factors such as location (urban or rural), wealth and education all having a significant impact on coverage levels, although the exact situation differs markedly between countries. Conflicts and insecurity are also of concern in the region, contributing to the numbers of unimmunized people in the region.



Vaccine coverage trends in the Africa Region.

Work is ongoing to support the switch over to new rotavirus vaccines, following the withdrawal of RotaTaq and supply shortages with Rotarix. Although multiple countries have expressed interest in HPV immunization, vaccine shortages and practical challenges have limited its introduction. MenA vaccination has almost completely eliminated meningococcal A meningitis epidemics, and a roadmap is being developed to control all bacterial meningitis by 2030.

Looking forward, systemic issues with immunization system performance remain a major obstacle to progress. Further key issues include a lack of country ownership, governance and accountability shortcomings, frequent health emergencies, multiple population movements, and insufficient attention to demand generation. There are also broader health systems limitations whose effects on immunization are often under-recognized.

The Addis Declaration remains a key route through which national governments can be held accountable for their commitments to immunization. A presentation to the African Union in July 2019 provides an opportunity to report on progress with implementation and present a scorecard. The presentation will emphasize the importance of the new differentiated approach of country support, the importance of coordination with partners beyond health (for example through one health initiatives), and the key roles to be played by CSOs in ensuring accountability and in demand creation.

Other important future goals include emphasizing the intimate relationship between immunization and universal health coverage, primary health care, and health system strengthening, and providing input into the post-2020 global immunization strategy following the end of the Decade of Vaccines.

Urban Immunization: diagnoses and preliminary solutions - reflections from Ghana, Kenya and DR Congo

Lora Shimp, JSI

Urban populations present a major and growing challenge to national immunization programmes, as they are increasingly characterized by under-vaccinated populations. It is important to understand both the obstacles to and enablers of access to vaccination in these populations, to support the design of interventions to improve the delivery of immunization services.

A mixed methods study led by JSI and partners in Ghana, Kenya and the DRC has examined some of these obstacles and enablers. The project incorporated both a review of existing material as well as focus groups with people living in urban settlements.

The findings suggest that issues affecting take up of services are complex and context-specific. Across the sites, multiple barriers are associated with the planning and coordination of services. Additional common themes included a lack of trust in health services, concerns about the quality of services delivered, and a lack of community engagement.

Potential ways forward include the design of services that are more suited to the lives of families in urban settlements, as well as greater attention to the quality of services and the importance of interactions with health service providers. Other possible strategies include greater social engagement with communities and more effective collection and use of data.

More generally, the study highlights the potential to undertake rapid assessments of urban settlement dwellers' needs and attitudes, as a basis for refining and redesigning service delivery. A range of resources exist that could inform the design of such interventions, including the Reaching Every District (RED) guide and Tailoring Immunization Programmess (TIP), which could be rapidly adapted in partnership with communities and with other health and municipal service providers, then trialled and embedded if effective in a specific local setting. Solutions can combine both 'quick wins' to deliver short-term benefits as well as sustainable longer-term interventions.

Progress in implementation of the National Emergency Routine Immunization Coordination Centre (NERICC) plan for routine immunization and primary health care strengthening in Nigeria

Bassey Okposen Bassey, MoH Nigeria

In 2017, Nigeria launched an emergency response to improve immunization coverage, coordinated by the National Emergency Routine Immunization Coordination Centre (NERICC). The impetus for NERICC came in 2016 with the recognition that overall coverage was low (DTP coverage of 33%), that administrative data were not providing a true picture of coverage, and that coverage varied widely subnationally. In addition, take up of services was influenced by a lack of trust in health services, a lack of awareness, and concerns about the quality of immunization services. The result was large numbers of under-immunized children.

In June 2017, the Ministry of Health declared a public health emergency and NERICC was launched the following month. Its key aim was to achieve coverage of at least 80% across all age groups by 2028. Five objectives were established, including increasing detection and responses, improving accountability, enhancing coordination, improving data use and enhancing outreach services.

NERICC's plans were developed and implemented in close collaboration with partners. A prioritization exercise identified 11 very high and seven high-priority states, which have been the focus of NERICC's activities. Strategic interventions have targeted key aspects of immunization function, including programme management and coordination, service delivery, performance management and data quality, advocacy and demand generation, and mobilization of resources. Frequent LQAS have been used to provide reliable data on coverage.

A key aim has been to instill accountability at all levels. States have been encouraged to assume greater responsibility for immunization services, and individual staff members are held accountable for their performance – underperforming individuals have lost their positions. Active community engagement has also been prioritized.

A differentiated approach has been established subnationally, with different states having different planned trajectories of improvement towards the 2028 target. LQAs are also being conducted quarterly to continue to identify underlying reasons and monitor progress. Although plans are at early stages of implementation, significant improvements in coverage have been achieved and smaller discrepancies are being seen between survey and administrative data.

Implementation of the Marshall Plan in DR Congo for routine immunization strengthening

Guillaume Ngoie Mwamba, MoH DR Congo

The DRC's Marshall Plan to enhance its national immunization programme was driven by the recognition that the country had large numbers of under-immunized children, was experiencing frequent stockouts, was affected by multiple epidemics, including cVDPV, yellow fever and measles, and that funds were not available at times of need.

Development of the plan drew on five key principles. These included complementarity with wider health development strategies, a results-based approach with appropriate quantitative indicators, a bottom-up approach, and a strong focus on integration, with a specific coordination team.

A prioritization exercise considering issues such as outbreaks, stockouts and numbers of under-immunized children identified nine priority provinces. A goal has been set of increasing coverage by 15% in 18 months. Priority activities across five themes were launched in 2018, spanning areas such as coordination of financing, service delivery, distribution, and monitoring and evaluation. The plan's overall budget is US\$28m.

Discussions emphasized the key need to **promote country ownership of immunization** and domestic investment, leveraging the commitments made in the Addis Declaration. A change in mindset was needed to ensure that national governments see protection of the health of their populations as a key aspect of their stewardship role. Given known returns on investment, supporting immunization activities should be seen as an investment in future national prosperity.

As well as mapping trends in financing over time, it was also argued that **greater transparency in national budgeting** was required. It was suggested that countries should develop **disaggregated budgets** that include specific budget lines for key activities such as surveillance, data management, vaccine logistics and NITAGs, and indicate whether resources are from domestic sources or partners.

RITAG members applauded the commitment and focus demonstrated by Nigeria and DRC, and the constructive engagement with partners to develop rigorous **country-led strategies and action plans**. The development activities were also seen to illustrate the **linkages between development of national immunization systems and health systems strengthening**, the two having a reciprocal and mutually reinforcing relationship.

It was also noted that the country examples illustrate the principle of a **differentiated approach to support at a subnational level**, with countries developing approaches to target priority areas to achieve greatest impact. With

devolvement of many health activities, it was also suggested that domestic financial commitments should be considered at a subnational as well as national level.

Questions were raised about the **sustainability of emergency responses**. Both countries emphasized the importance of integration with other health systems strengthening strategies. NERICC, for example, is intended to have a three-year lifespan, after which the emergency element will be dropped, although its structures and approaches will continue. Activities will also be integrated with the health systems strengthening initiative for Nigeria recently approved by Gavi.

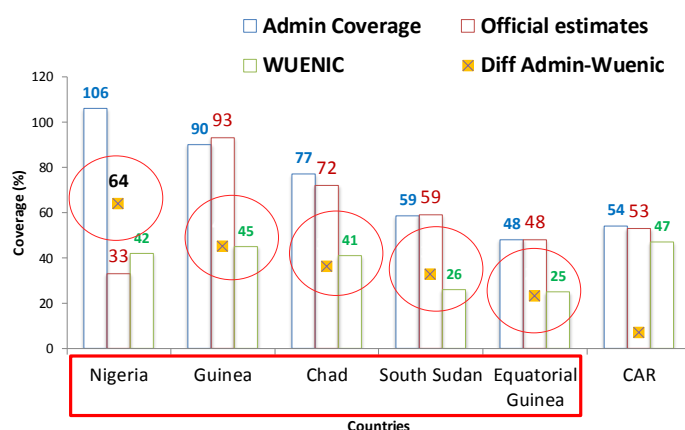
VACCINE DATA AND LOGISTICS

Progress in investments for improving data quality and use in the African Region

Alain Poy, WHO

Use of data is essential for planning and monitoring the performance of national immunization systems. Multiple types of data, particularly coverage and surveillance data, are of particular value. Data quality, management and use are therefore critical elements of national immunization programmes.

Notably, although administrative data are often used to plan and monitor immunization activities, there are frequently discrepancies between these figures and WUENIC data (WHO and UNICEF Estimates of National Immunization Coverage). In 2017, 18 countries had DTP3 coverage of greater than 80% according to both national and WUENIC data (up from 15 in 2016). Elsewhere, administrative data are generally higher than corresponding WUENIC figures, and discrepancies are typically greatest in low-coverage countries. Hence administrative data may often be overestimating coverage, and decision-making may be based on misleading data.



The difference ranges from 64 points in Nigeria to 7 points in CAR

Discrepancies between WUENIC and other estimates of vaccination coverage.

The WHO Regional Office has been working with countries to improve the quality of data collection, management, analysis and use. Data improvement plans have been developed for 20 countries, and support is being provided to strengthen information systems. New technologies are being introduced to provide additional data, adopting some of the technologies pioneered for polio surveillance. The capacity of EPI managers to make use of data is being developed, supported by new tools such as data dashboards. The Regional Office is also working with a wide range of external partners to develop new tools and improvements to IT systems.

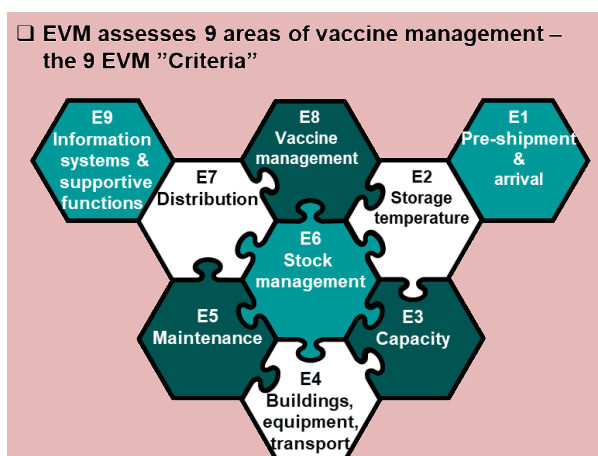
The impact of such work can be seen in countries such as Kenya, which has seen a decrease in the number of ‘data impossibilities’, such as coverage rates in excess of 100% and negative dropouts between immunization rounds. Administrative data are now also closer to WUENIC estimates.

Notably, increased data accuracy may be associated with an apparent decline in coverage. It was emphasized that accountability should be based on accuracy of data rather than coverage, to minimize the risk of inaccurate data recording or data falsification in order to deliver high coverage numbers

Progress in improving vaccine management and logistics in the African Region

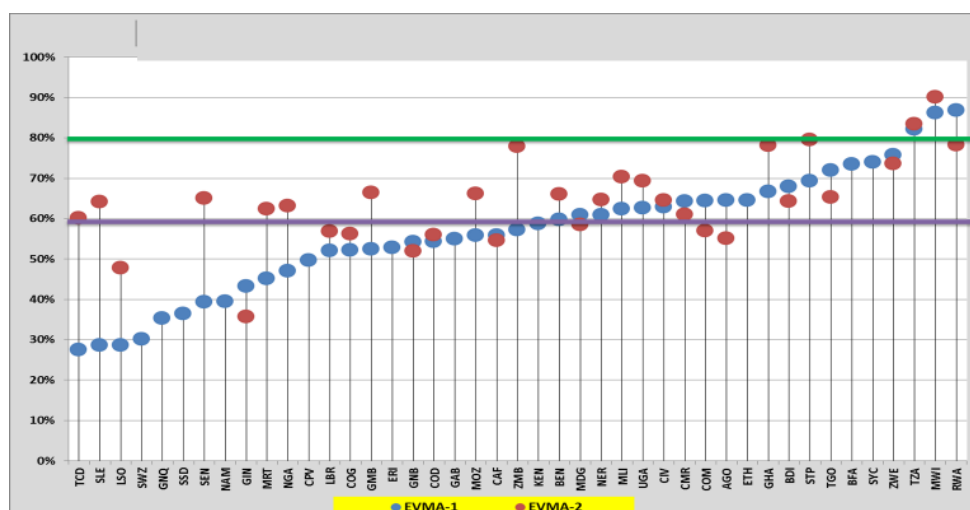
Claude Mangobo, WHO

Immunization programmes are dependent on both access to global vaccine supplies and the ability to deliver vaccines to populations. However, despite many changes in immunization programmes, the vaccine supply chain has changed little in decades. Benchmarking of national performance is based on Effective Vaccine Management criteria, which assess nine areas of vaccine management. Although some progress was achieved in the region between 2009 and 2018, there remains considerable room for improvement.



The nine criteria used in vaccine management evaluation.

Areas in particular need of improvement include analysis of temperature monitoring data, maintenance of cold chain equipment, stock management and distribution. Multiple actions could be taken to improve performance, including the development of cost-improvement plans, targeted staff training, and adherence to standard operating procedures. Improvement plans should be monitored, with a self-evaluation after two years.



Trends in vaccine management performance in countries in the Africa region.

WHO and partners are undertaking a range of initiatives to secure the global supply chain. A supply chain strategy has been developed for the period up to 2020.

National activities are beginning to bear fruit, with multiple examples of enhanced storage capacity and remodelling of supply chains to ensure quality vaccines reach delivery points. Attempts are also being made to increase efficiencies by integrating immunization and other medical supplies, although this is challenging in practice. Nevertheless, vaccine logistics remains a relatively neglected and under-resourced area.

Discussions emphasized the **critical importance of both data management and quality** and of **vaccine logistics** to immunization. The causes of inaccurate data are likely to be many and varied, and to differ between countries. As a general principle, it was argued that data accuracy should be seen as paramount, with mechanisms such as LQAS used to ensure accuracy whenever possible. Furthermore, the culture of data collection should prioritize accuracy and **avoid incentives based only on maximizing coverage** and punishments linked only to low coverage, which may encourage false reporting. Openness about coverage should be encouraged, as a basis for collaborative efforts to address the key issues affecting immunization coverage. Donors should also avoid simple performance measures that may incentivize falsification.

It was also noted that multiple **data quality initiatives** are underway, regionally and globally, emphasizing the importance of the issue. These include a data quality working group established by SAGE.

In terms of **procurement**, it was suggested that it would be helpful to revisit past recommendations on the potential for regional pooled procurement, particularly as more countries are due to graduate from Gavi support. It was also noted that lessons could be learned from countries such as Tanzania that had made progress in **integration of medical supply chains**.

MEASLES AND MATERNAL AND NEONATAL TETANUS

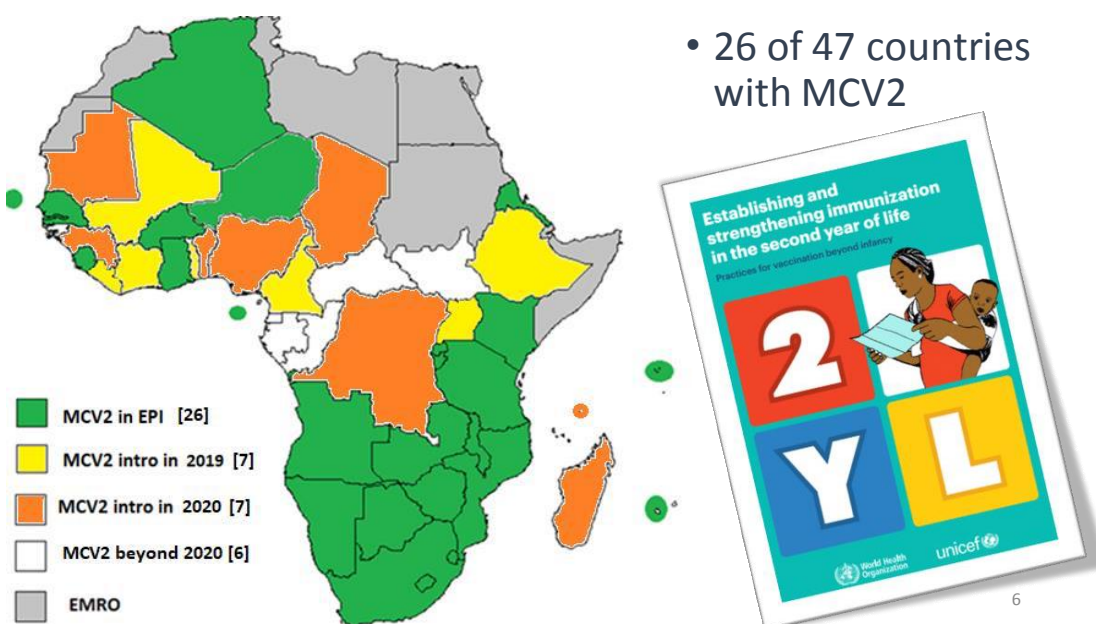
Status report on measles/rubella elimination in the African Region and plans to accelerate activities to reach 2020 measles elimination goal

Balcha Masresha, WHO

MCV1 coverage in Africa has plateaued at around 70% over the last five years, although MCV2 coverage has increased significantly since 2013. Eight countries achieved the target MCV1 coverage of 95% or higher in 2017, and a further eight achieved coverage of between 90 and 94%.

A total of 26 out of 47 countries have introduced MCV2, seven plan to do so in 2019 and seven more in 2020.

Nevertheless, dropout rates remain high, and coverage levels vary significantly subnationally. Reasons for low MCV2 coverage include insufficient political commitment and a lack of public awareness of its importance. Similarly, only eight countries have introduced DTP4 vaccination in the second year of life.



Status of MCV2 introductions.

Administrative data suggest that measles and measles/rubella campaigns routinely achieve 100% coverage. However, survey data suggest that, in reality, relatively few exceed 95% coverage (and not all countries carry out confirmatory surveys). Major campaigns have been carried out in Nigeria, achieving 88% coverage, compared with 56% in the national immunization programme. Some 40 million children were vaccinated through SIAs, 34% of whom received MCV for the first time.

Measles surveillance also remains suboptimal in the region. For the two surveillance indicators used for measles, both targets were met in 23 countries, but neither were met in nine.

Despite the plateauing of coverage, the incidence of measles and annual mortality have both continued to decline. This is particularly notable given that some large countries have yet to introduce MCV2 and known shortcomings in measles SIAs. Annual mortality has declined by 86% between 2000 and 2017, from 348,000 to 48,000 deaths. Nine countries are nearing elimination, and a further four are on track. This progress is encouraging discussions on suitable mechanisms for verification of eradication.

Nevertheless, on current trends, the 2020 measles elimination goal will not be achieved. Furthermore, the region has been affected by a number of large outbreaks, some affecting countries with relatively high coverage – evidence that measles will exploit even the smallest gaps in immunization coverage.

In November 2018, SAGE issued further guidance on measles control, defining three categories of countries and recommending control strategies for each category. However, to support operationalization of this guidance, clarification may be needed for the middle category, countries experiencing periodic outbreaks, with moderate coverage and inadequate population immunity.

Moving forward, further advocacy is required to accelerate progress towards the 2020 goals, with a particular emphasis on strengthening national immunization programmes and coverage in the second year of life. This agenda could be advanced by the setting of regional and national goals for MCV2 coverage and by developing a definition for the fully immunized child at age 2.

Measles elimination: lessons learnt and experience from SEARO

Sunil Bahl, WHO (via webex)

The South-East Asia Region encompasses a population of nearly 2 billion people in 11 countries, and an annual birth cohort of 38 million. Its regional goal is to achieve measles elimination by 2020. To date, elimination has been verified in four countries and six countries have verified rubella control.

All 11 countries have introduced MCV2 and all 11 will have introduced rubella vaccination by the end of 2019. A total of 345 million people were reached through measles SIAs in 2016–18 and more campaigns are planned for 2019. In terms of surveillance, every country has a WHO-proficient laboratory. A regional verification committee, national verification committees and framework for measles elimination have also been established.

Regional MCV1 coverage is close to 90% and MCV2 coverage has risen to nearly 80%, following a strong push since 2010 and its adoption by several large countries. The numbers of measles cases in the region have fallen significantly, from around 100,000 cases a year in the early 2000s to less than 30,000 cases in 2016 and 2017. Each country has adopted specific measures to improve national immunization programmes and optimize immunization schedules, including a strong focus on year 2.

Regional challenges include suboptimal coverage in six countries, subnational variation in coverage, and a backlog of under-immunized children and young adults. Various policy and programme barriers have been identified, and dropout is not yet monitored adequately.

A range of targeted and tailored measures are being promoted to address these challenges. SIAs are being used to enhance national immunization programmes and the regional technical advisory group and NITAGs are being mobilized to tackle the policy and programme barriers.

Much has been learnt from regional SIA, including the importance of pre-campaign readiness assessments, which inform corrective actions before campaigns are launched. Social media have been extensively mobilized to engage communities, and innovative work carried out with schools. Local immunity data have been used to establish the appropriate age

ranges for immunization, which often extend into adulthood. Staff have been recruited to manage independent monitoring. Importantly, activities have been driven by high levels of political commitment and strong engagement with partners.

First Assessment			Final Assessment		
District	Operations	Communications	District	Operations	Communications
ADILABAD	Moderate	Moderate	ADILABAD	On track	On track
HYDERABAD	Critical	Critical	HYDERABAD	Moderate	Moderate
KARIMNAGAR	Moderate	Moderate	KARIMNAGAR	Moderate	Moderate
KHAMMAM	Moderate	Critical	KHAMMAM	On track	On Track
MAHABUBABAD	Moderate	Moderate	MAHABUBABAD	On track	On Track
MAHBUBNAGAR	Critical	Moderate	MAHBUBNAGAR	Moderate	On Track
MANCHERIAL	Moderate	Critical	MANCHERIAL	On track	Moderate
MEDCHAL MALKAJGIRI	Moderate	Critical	MEDCHAL MALKAJGIRI	Moderate	On Track
NALGONDA	Critical	Critical	NALGONDA	On track	On Track
RANGAREDDY	Moderate	Moderate	RANGAREDDY	On track	Moderate
SANGAREDDY	Critical	Moderate	SANGAREDDY	On Track	Moderate
WARANGAL URBAN	Moderate	On track	WARANGAL URBAN	On track	On track
STATE	Moderate	Critical	STATE	On track	On track

Preparedness assessments before measles SIAs in the South-East Asia Region.

Attention has also been given to strengthening surveillance systems and laboratory networks, and to ensuring effective emergency responses. A regional verification committee was created in 2016 and has established processes and structures defining the steps towards verification of elimination.

Measles elimination: country perspectives

Yousseuf Ahmat Annadif, MoH Chad

Chad is a country of 16.3 million people in 23 provinces. Vaccine coverage has slipped in recent years, from 84% for MCV1 in 2016 to under 70% in 2017, although WUENIC estimates suggest lower coverage (below 40%). Discrepancies are likely to reflect inaccurate data recording but also denominator uncertainty given large numbers of displaced people. Insecurity in the Lake Chad Basin area presents a particular challenge to immunization. Coverage also shows significant subnational variation.

Below-target performance reflects a number of issues. These include problems with stockouts, ineffective field visits, lack of transport, poor cold chain capabilities, insecurity and inaccessibility of some populations.

Immunization has been identified as a national priority, illustrated by a National Vaccination Forum held in March 2018 and strong support from the First Lady of Chad. Immunization budgets are being increased, with support from a range of partners. A variety of approaches have been adopted in 2017 and 2018 to increase coverage, including use of the missed opportunities approach, targeting of special groups and population sites such as nomadic and urban populations, and introduction of new packages of vaccines.

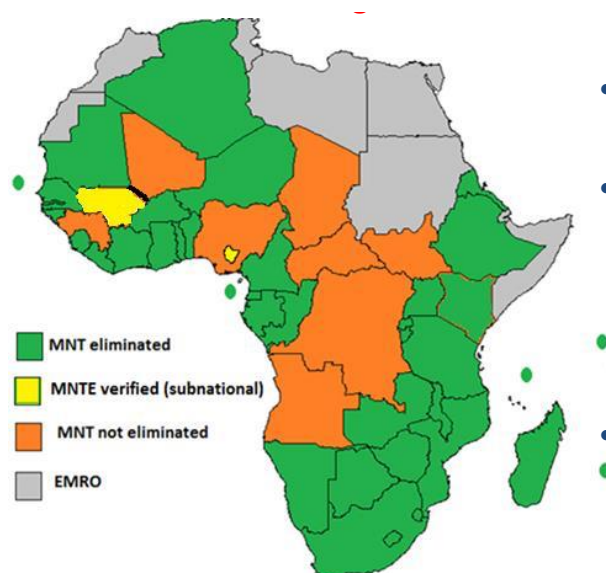
Governance and leadership have been central to this renewed vigour, particularly the commitment of the head of state. Technical and financial partners also provide key regular input. Efforts are being made to improve data quality and accuracy as well as surveillance coverage.

The country was affected by a large measles outbreak in 2018, illustrating the importance of continuing these improvement efforts. Further campaigns are planned for 2019 alongside strengthening of the national immunization programme, and the country is due to introduce MCV2 in 2020.

Status report on maternal and neonatal tetanus elimination in the African Region

Richard Luce, WHO

Elimination of maternal and neonatal tetanus by 2020 is one of the objectives of the Regional Strategic Plan for Immunization. As at March 2018, 45 out of 59 at-risk countries globally had achieved elimination. Eight out of the 14 remaining countries were in the African Region.



Status of maternal and neonatal tetanus elimination (MNTE) in the Africa Region.

In 2017, 43% of reported cases of maternal and neonatal tetanus were in the African Region (reported cases probably greatly underestimate the total disease burden). Protection at birth, an indicator that includes vaccination as well as other interventions that prevent infection, has risen from 60% to 80% since 2000, although coverage varies widely across the region.

Between 2014 and 2017, 13.3 million women of reproductive age were reached by tetanus toxoid (TT) SIAs in high-risk districts in nine countries. SIAs were not completed in several countries owing to security challenges and funding shortfalls.

In 2017, new recommendations for a six-dose schedule starting at six weeks of age were issued. A long-standing recommendation is for countries to switch from TT to tetanus–diphtheria (Td) vaccination, although fewer than half the countries have done so to date. The slow transition may reflect the lack of an active push to discourage TT use, insufficient awareness of the benefits of a diphtheria booster, and the need for evidence of cost-effectiveness (although the price differential is small). Additional guidance on transition was issued in June 2018, and withdrawal of UNICEF funding for TT should accelerate this transition.

Key global activities include a meeting in November 2018 to discuss the of maternal and neonatal tetanus elimination business case. This identified US\$200m as the sum required to achieve elimination, although commitments to date have totalled just US\$21.6m, so a sizeable funding gap remains. The figure includes US\$55m for use of compact pre-filled auto-disable (Uniject) devices, which was not approved by the Gavi Policy and Programme Committee.

With many countries having achieved elimination, sustaining these gains is also a high priority. Maternal and neonatal tetanus elimination sustainability guidelines have been developed and a planning workshop was held with 19 countries in August 2018.

Mali and Nigeria have adopted a state-by-state approach to elimination, and individual states and regions have achieved elimination in each country. Other countries that have yet to achieve elimination have activities planned, and it is anticipated that four further countries and additional states and regions in Mali and Nigeria will secure elimination status by 2020. However, progress in South Sudan and the Central African Republic is significantly slower.

Key challenges include insecurity and the fragility of some countries' health systems, as well as the relatively small pool of donors engaged in maternal and neonatal tetanus elimination. Countries also have multiple competing health priorities, while limited human resources are available to drive forward elimination. Future actions include finalization of remaining countries' elimination plans, integration of maternal and neonatal tetanus elimination activities into wider reproductive, maternal and child health service delivery, and encouraging more countries to adopt the six-dose policy.

In discussions, the **key role played by partners** in regional efforts to control measles was acknowledged, particularly the US CDC. With the regional 2020 target looking likely to be missed, there was much debate on whether a new **elimination target date** should be set. While this might aid planning, it could also discourage countries from energetically pursuing elimination by 2020.

It was suggested that **advocacy linked to the Addis Declaration** should stress the importance of controlling measles. Specific **regional and national targets for MCV2 coverage** could also help to galvanize action, as could a new definition for a **'fully immunized child at age 2'** including MCV2.

It was noted that much could be learned from SEARO's significant progress, particularly in its effective use of SIAs, for example through extensive **pre-campaign planning and preparedness assessment**. The need to ensure that SIAs also **enhance national immunization programmes** was reiterated. It was also argued that countries should decide on the **age range and geographic coverage of SIAs** based on local epidemiological data, rather than being driven by donor policies.

For maternal and neonatal tetanus elimination, it was noted that progress needed to be monitored carefully, particularly given maternal and neonatal tetanus's status as an infection predominantly affecting the poor and women. The narrowness of funding sources was acknowledged to be a significant issue, and it was also acknowledged that global support for auto-disable technology would not be forthcoming.

The importance of integrating maternal and neonatal tetanus control with reproductive, maternal and child health services was stressed. It was also suggested that opportunities might exist to link HPV vaccination to the last Td booster,

potentially extending vaccination to boys as well as girls (which, as well as delivering health benefits to boys, might help to address falsehoods linked to vaccination just of girls).

DEMAND

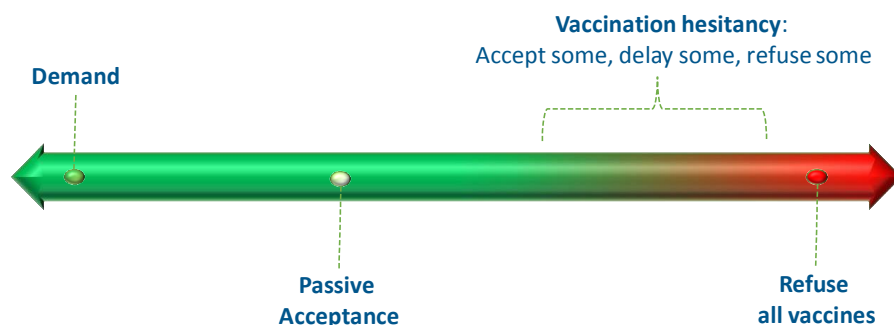
Community demand for immunization: proven and promising approaches

Robb Butler, UNICEF

Vaccination acceptance and demand are increasingly seen as central to the success of national immunization programmes, even if the full extent of hesitancy, and whether it is on the rise, is not yet clear. A move towards demand-driven immunization is a central tenet of the Regional Strategic Plan for Immunization.

A caregivers' journey to immunization is complex, subject to multiple influences, and affected by many different enablers and barriers. It is essential to understand key 'demand determinants' that have influence on this journey, so barriers can be lowered and enablers promoted. It is also important to note the distinction between an intention to act and the action itself, as there are often disconnects between knowledge and action. This has important implications for the nature and targeting of messages, both of which need to be based on an understanding and segmentation of audiences.

Vaccination behaviour can be seen as falling on a continuum from active demand, through passive acceptance, hesitancy and outright refusal (generally still rare). Consultations suggest that the reasons for not choosing vaccination vary widely, and are often not simply due to lack of knowledge. People's experience of vaccine services, for example, has a major impact on the likelihood of return visits to health facilities. Such studies emphasize the need to build trust, reduce practical and psychological barriers, tailor services to user needs, and to use interventions that help to turn intentions into actions.



The spectrum of vaccination demand.

Hesitancy can be considered within the context of the '3Cs' – complacency (of caregivers, healthcare workers and politicians), convenience (for caregivers) and confidence (trust in healthcare workers and immunization systems more generally). Passive acceptance is commonplace, but may often reflect copying behaviours linked to social norms. Although this may generate good coverage, passive acceptance is vulnerable to external shocks that rapidly shift social norms – as illustrated by national outbreaks of hesitancy in which coverage has plummeted and taken years to recover.

Greater resilience to external shocks can be achieved by shifting passive acceptance towards active demand – broadly defined as seeking of services, advocating for immunization services and actively promoting immunization. Although

there have been many attempts at demand creation, few have been well documented and there is limited evidence on which to base recommendations. Importantly, however, it is essential to consider local context to tailor activities, considering reasons for lack of vaccination (barriers) as well as for being vaccinated (enablers).

Panel Discussion and RITAG Q&A

Moderator: Niklas Danielsson, UNICEF

Launching the discussion, panel member **Joseph Okeibunor** (WHO) noted that multiple factors affect people's vaccination behaviour. These are highly contextual and subject to change over time. Research and listening to people is needed to generate a clearer picture of these factors. He argued that social scientists have a key role to play in ensuring that the right questions are asked in the right ways in such studies, so that reliable evidence on attitudes and behaviour is generated.

Sue Goldstein (Priceless) noted that community engagement has tended to be framed in a western context, with a strong emphasis on the individual and less on more collective cultural norms typical of Asia and Africa. Storytelling and participation are deeply rooted aspects of African culture. She also suggested that it was important to learn from the engagement approaches adopted by the polio programme in Afghanistan and Pakistan, and to prioritize listening to communities. Involving frontline workers was crucial, providing an opportunity to change not only how they are perceived by others but also how they perceive themselves.

Charles Shey Wiysonge (South African Cochrane Centre) noted that service delivery issues represented a major cause of vaccine hesitancy in many settings. He argued that it was important to tackle the quality of services to reduce barriers to vaccination, and that local data were important to shape interventions. Most research in this area to date has been carried out in high-income countries and may be of limited relevance in the African Region.

Whether vaccine hesitancy is on the increase was much debated. SAGE's vaccine hesitancy working group recently concluded that it was hard to judge with any certainty. Reasons for hesitancy can be highly localized and can now generate a lot of attention. While active resistance to vaccination may always have existed, and may still be rare, new tools such as social media provide a route through which negative views can gain much greater exposure very rapidly. In addition, several vaccine-preventable diseases are now rare, so the 'fear factor' may have declined and concerns about the possible harms of vaccination become more significant.

It was also noted that CSOs had a potentially critical role to play in demand activities, and that some have the expertise to undertake systematic community consultation (CSOs include academic institutions). It was suggested that other fields of medicine, such as maternal health, might hold lessons for the design of respectful high-quality services – and that quality needs to be understood from a caregivers' point of view. An additional suggestion was that lessons could be learned from the corporate sector, which places great emphasis on customer engagement and incentivization of staff.

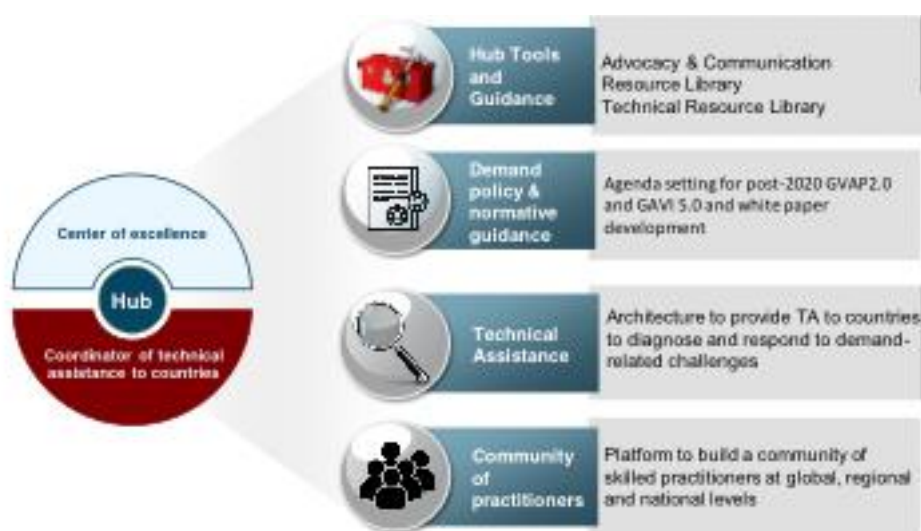
It was felt to be important to have a good understanding of the demand creation activities being undertaken in the region, and evidence of their impact, to inform future activities. However, it was questioned whether national immunization programmes had the expertise or capacity to integrate this aspect into their work.

It was argued that it was important to have high-quality data on hesitancy, and to track attitudes and behaviour over time. Investing in demand generation was seen as critical to hesitancy prevention, to create resilient populations that are not swung by misinformation or unnecessary alarms. Nevertheless, it was argued that the capacity to develop and implement demand generation strategies was currently limited in the region. Although more needs to be done, it is important that activities are based on best practices and supported by strong evidence.

Consolidating guidance, aligning and harmonizing efforts to generate acceptance and demand

Robb Butler, UNICEF

UNICEF and multiple partners² have formed a collaboration to develop a global vaccine acceptance and demand hub. The impetus for the initiative was the fragmented nature of the technical assistance being offered by the various partners. The vision was therefore to create a single knowledge repository for high-quality demand-related materials, to help align and harmonize the technical support provided. It will include practical tools and policy guidance, and provide a platform for a demand-related community of practice.



Overview of the global vaccine acceptance and demand hub.

Consultation exercises with multiple stakeholders are being used to shape the vision, scope and functionality of the resource. This includes engagement with additional providers of technical assistance as well as CSOs and communities themselves. Terms of reference have now been endorsed across all partners.

Alongside this work, a white paper is being developed spelling out challenges and a vision for demand generation over the next decade. This will be published in time to feed into discussions on the global post-2020 immunization strategy.

Long-term goals for the field include the need to adopt a more strategic approach to demand generation, to demonstrate its value, to integrate demand activities into routine practice, to raise the visibility of demand as a key aspect of immunization systems, and to ensure integrated support is available through the demand hub.

² WHO, CDC, Bill and Melinda Gates Foundation, Gavi, Gavi CSO Constituency, International Federation of Red Cross and Red Crescent Societies, and JSI.

Use of IHR monitoring and evaluation framework and IDSR strategy for strategic planning to secure health security in Africa

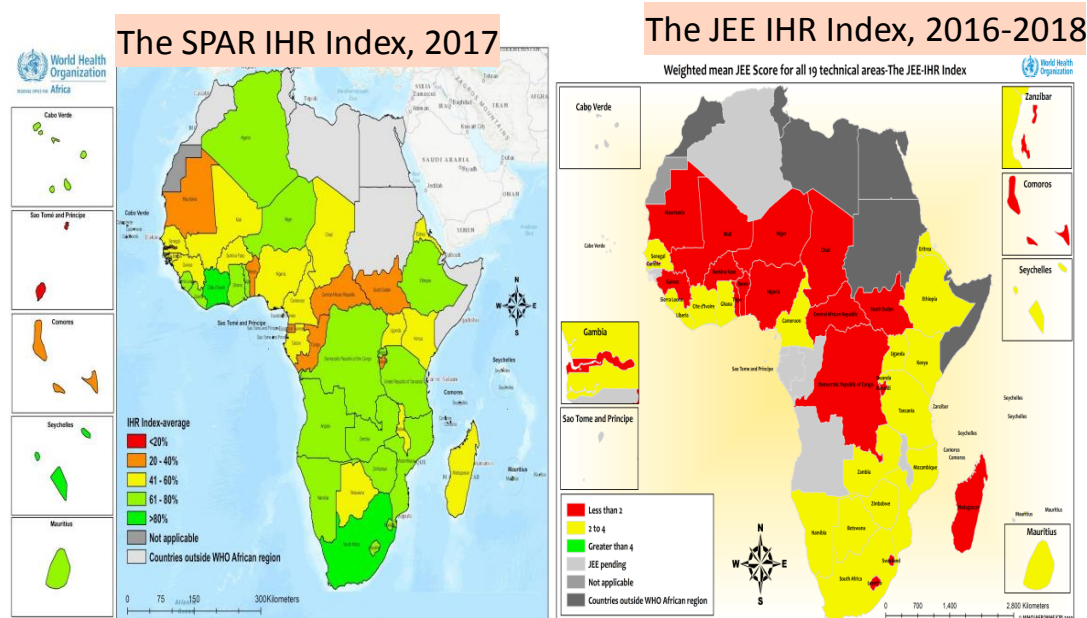
Ambrose Talisuna, WHO

The 2014–16 Ebola outbreak catalysed renewed interest in global health security, and use of mechanisms such as IHR and Integrated Disease Surveillance and Response (IDSR) to protect it. The Building Health Security beyond Ebola meeting held in Cape Town in 2015 stressed the importance of preparedness and the roles of national, regional and global stakeholders. Africa is central to such discussions – it experiences an average of three acute public health events a week, dominated by infectious diseases such as cholera, viral haemorrhagic fevers and measles. Since the drivers of health emergencies span multiple sectors, an interdisciplinary approach is essential.

The Cape Town meeting identified global leadership priorities for WHO, actions for partners and commitments required of countries. IHR provide a global framework for preventing and responding to all public health threats, legally binding on countries. There are strong synergies between health system strengthening and development of IHR core competencies.

Monitoring IHR capabilities has four components: self-assessments, after-action reviews, simulation exercises and voluntary joint external evaluations (JEEs). In the African region, all 47 countries have undertaken self-assessments and 39 have undergone JEEs. Covering the general areas of ‘prevent’, ‘detect’ and ‘respond’, both self-assessments and JEEs generate scores (from 1–5) for key aspects of IHR capability. Notably, comparisons of self-assessment and JEE scores generally identify significant over-scoring in the former.

For most criteria, IHR scores as judged by JEEs are suboptimal. Notably, across 19 technical areas, immunization is the area that scores highest across the region as a whole. Nevertheless, the evaluations suggest countries in the region have a long way to go to develop their IHR competencies. In 2018, according to JEE criteria, no country in the region has the full set of required IHR capacities.

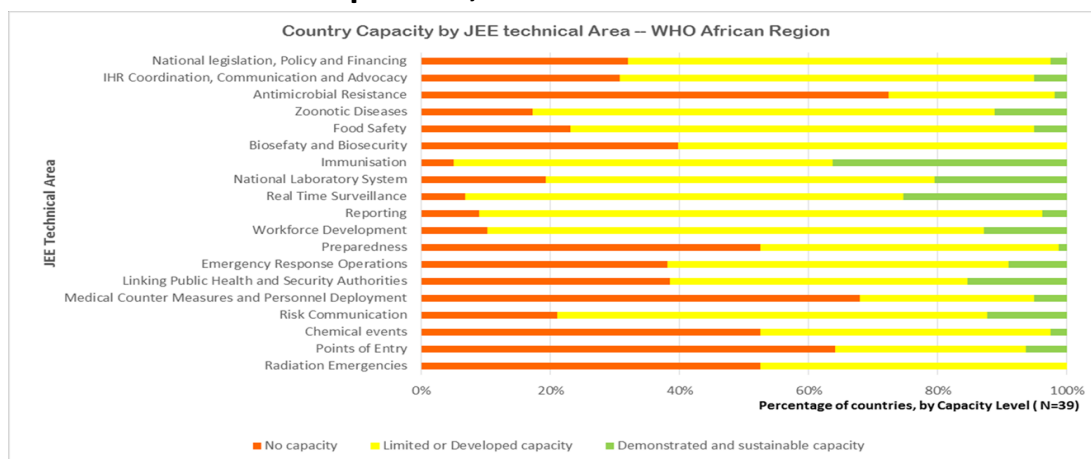


2018:Based on JEE data, no African country has the required IHR capacities

A comparison of self-assessments and JEE assessments.

JEEs are used as the basis of national actions plans for health security, which have been developed by 21 countries in the region; 11 are being developed and two more are planned. A new costing tool has been developed to identify the resource requirements associated with national actions plans.

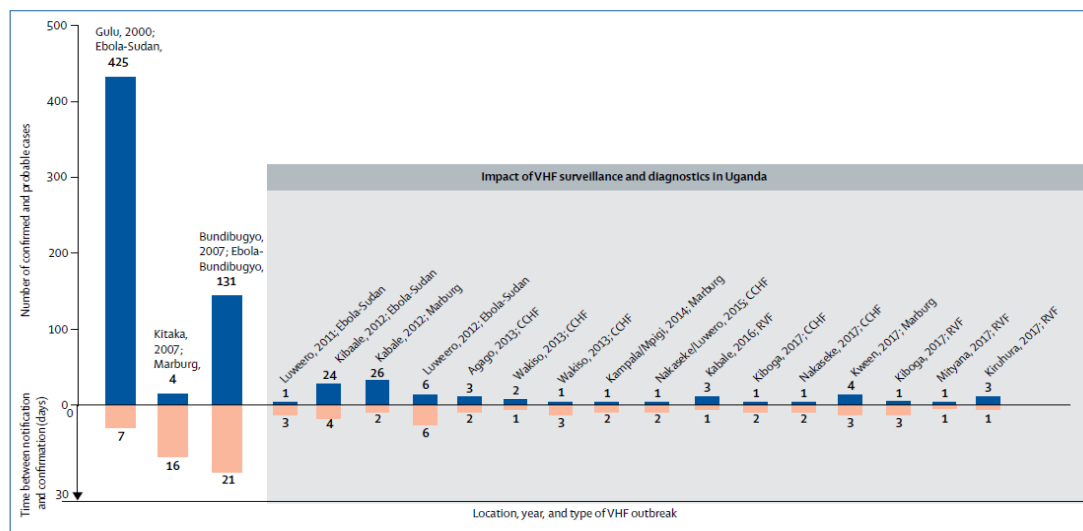
IHR Capacities, 19 JEE technical areas



IHR capacities across 19 technical areas.

The IDSR concept was developed in the 1990s. Technical guidelines and performance indicators have been developed to support event-based and indicator-based surveillance. They have been adopted in 44 countries, but only 40% have activities at peripheral health facilities.

The experience of Uganda illustrates the major impact such activities can have. The country is affected by regular haemorrhagic fever outbreaks, but since the introduction of event-based surveillance, the impact of such outbreaks has been dramatically reduced. Although zoonotic transmission cannot yet be prevented, prompt detection and containment can limit its impact³.



Reduction in haemorrhagic fever outbreak size following introduction of surveillance.

VPD surveillance and laboratory networks in the African region - current status

Balcha Masresha, WHO

Surveillance is critical to the success of national immunization programmes. Although vaccination coverage is used as the key indicator of immunization system performance, what truly matter are impacts on disease burden. Accurate understanding of infections can verify the attainment of targets but also guide the timing and nature of SIAs and shape outbreak responses.

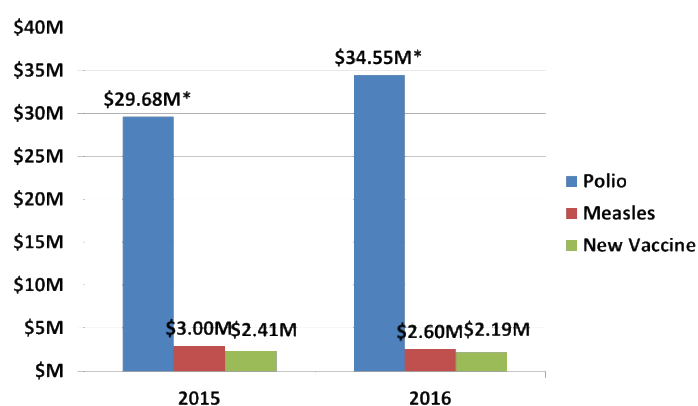
In the midterm review of the Global Vaccine Action Plan, most indicators were off-track. Notably, four key indicators require surveillance data. Furthermore, surveillance is explicitly referenced as a core commitment in the Addis Declaration.

Disease surveillance is either case-based (active seeking of infections), based on weekly or monthly reporting, or sentinel site surveillance. Case-based surveillance, exemplified by polio and infections targeted for elimination, is an intensive exercise in which every case matters. Sustainability is likely to be challenging, although digital technologies are opening up new opportunities to detect and investigate suspected cases. Sentinel surveillance, applied to infections such as rubella, rotavirus and meningitis, generally requires specialist centres and use of sophisticated diagnostic techniques. Africa currently has 32 such sentinel sites as well as three Regional Reference Laboratories for paediatric bacterial meningitis and two Regional Reference Laboratories for rotavirus.

³ Shoemaker TR *et al.* Impact of enhanced viral haemorrhagic fever surveillance on outbreak detection and response in Uganda. *Lancet Infect Dis.* 2018;18(4):373–375.

An infrastructure of laboratory networks provides critical information on disease trends, vaccine impact and detection of outbreaks. They can undertake tasks such as strain characterization to distinguish local and imported cases and shed light on routes of transmission. The regional polio laboratory network covers 16 virology laboratories in 15 countries, and often also undertakes work on other viral infections. The measles, rubella and yellow fever serological laboratory network encompasses 49 laboratories in 44 countries and three Regional Reference Laboratories.

Although figures are hard to come by, an analysis of funding suggests that the vast majority of financial support for surveillance is for polio surveillance, and nearly half is directed to just one country, Nigeria. An analysis of immunization programme data suggests that 60% of funding comes from WHO and just 11% from government sources – implying that countries are spending just US\$1 per citizen on surveillance every year.



Contribution of polio funding to surveillance expenditure.

Shifting ownership of surveillance from WHO to countries is therefore a key challenge. Other major issues include the need to ensure sustained and reliable funding to avoid stockouts of consumables, the need to track additional infections as new vaccines become available, integration of systems that have typically been developed independently, and absorption of new technologies, such as mhealth and rapid point-of-care diagnostics.

Conceptual framework for vaccine-preventable disease surveillance in Africa 2019-2030

Benoit Derudder, Deloitte

Given that surveillance in the region is so dependent on polio funding, RITAG has been concerned that the withdrawal of polio funding could compromise vital surveillance activities. It requested that the Regional Office develop an investment case for surveillance that could mobilize resources to cover any funding gaps. Subsequent consultations identified a more general need for a document that provided a foundation for longer-term investments in surveillance.

The ultimate goal is for countries to become autonomous in the financing and management of surveillance systems. While surveillance is critical to immunization, it is also an integral aspect of global health security and IHR, requiring a coordinated and cross-sectoral approach to its strategic development.

Guided by the Regional Office, Deloitte undertook an extensive consultation exercise with stakeholders including member states, agencies, WHO and external experts. It went on to develop a surveillance value report covering five areas – a situational analysis, a categorization of countries according to the maturity of their surveillance systems, value-

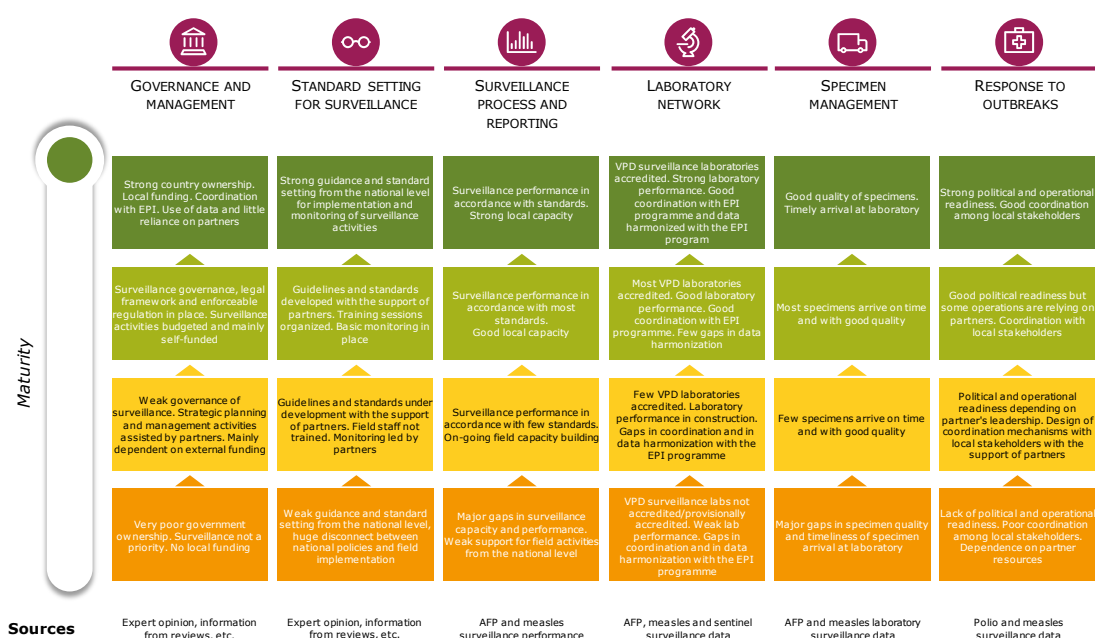
added activities that could be built on surveillance platforms to maximize their impact, and new technologies and innovations.

The report identifies a range of key challenges facing surveillance in the region. These include fragmented systems and silo-ed funding, insufficient public financing, minimal community-based surveillance, high staff turnover, and practical issues such as transportation of samples. These challenges will grow as the number of infections requiring surveillance grows – from six in 2000, to 18 now and 22 or more by 2030.

Surveillance data also provide a foundation on which other important activities could be built, to enhance monitoring, planning and budgeting, and improve the efficiency of immunization programmes. Although technological advances are hard to predict, tools such as rapid diagnostics, low-cost genome sequencing and geotagged data could have a significant future impact on surveillance.

To categorize countries' surveillance capabilities, the project defined six core components of surveillance systems, and four levels of capability within each of these components. Each country in the region was then graded for each component, and an overall maturity score calculated. Eight category 1 countries require the most intensive support to develop their surveillance capabilities, while nine category 4 countries require targeted support. The ultimate aim is to ensure 80% of countries are at category 4 by 2030.

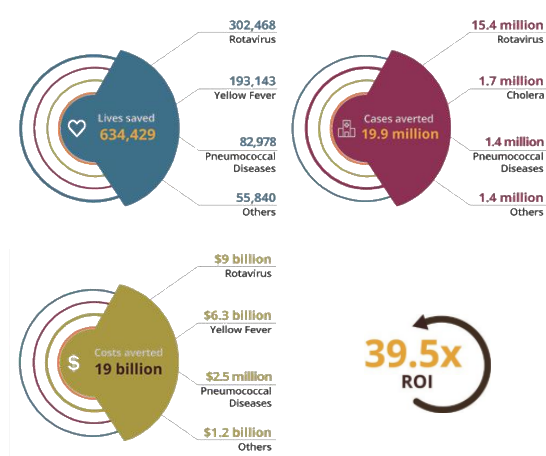
A "Surveillance Maturity Grid" was developed for each component. Level 1 refers to low maturity. Level 4 refers to the highest level of maturity



A maturity grid developed to grade national surveillance capacities.

Resourcing of surveillance can be seen as a long-term investment with the potential to deliver significant returns. By preventing and controlling outbreaks, surveillance could save an estimated 600,000 lives and avert US\$19bn in costs, delivering a 39.5-fold return on investment. Furthermore, surveillance is a critical aspect of national health security.

Outbreaks can have huge economic impact and disrupt public health systems – leading to additional mortality on the same scale as deaths directly linked to an outbreak. Nevertheless, the economic analyses are based on limited data and a range of assumptions. Further work is required to translate regional figures to the national level and to develop a true investment case for surveillance.



Projected return on investment for surveillance.

Discussions emphasized the **critical importance of surveillance**. It was felt that a change in mindset was needed, to ensure that surveillance was not seen as a WHO responsibility but was **owned by countries**. Leveraging the commitment made in the Addis Declaration, this view needed to be stressed in the July 2019 progress report to heads of state.

Furthermore, high-level advocacy needed to present an **integrated case for surveillance**, reflecting its criticality to national and global health security as well as immunization.

It was also recognised that there was an urgent need to **build surveillance capacities** in the region, to meet IHR obligations and to support immunization programmes. It was acknowledged that this presented a range of challenges, including the need to move away from vertical disease-oriented systems to more integrated and flexible models able to respond to new vaccine introductions and emerging infections. **Capacity building and skills development** would be a further major challenge, extending beyond laboratory functions and training programmes. Integrated models should also embrace **community-based surveillance**, a further challenge to capacity building, and how best to leverage CSOs. **Data management** was also suggested to be a key area for future investment and for inclusion in capacity development strategies. Overall, therefore, the design and implementation of integrated national and international surveillance presented a major challenge.

It was also suggested that the surveillance value report should include reference to other key **regional and global initiatives relevant to surveillance**. These include national public health institutes, which the African Union and Africa CDC envisage as having a key interest in surveillance. An opportunity may also exist to link surveillance for vaccine-preventable diseases to other strategically important surveillance activities, for example of disease vectors and antimicrobial resistance.

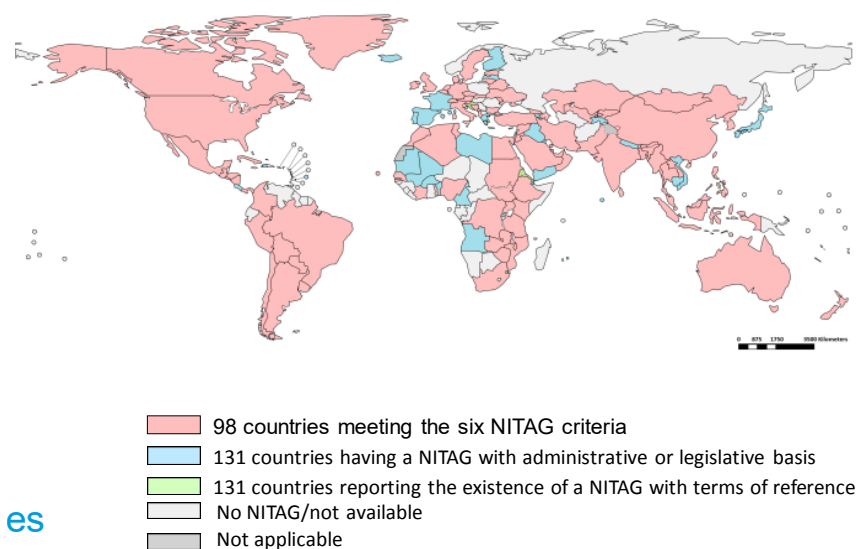
Globally, through the work of WHO and partners, updated surveillance standards were published in 2018, and a comprehensive vaccine-preventable disease surveillance strategy is being developed. In addition, a Gates Foundation-funded project is addressing fragmentation, developing an integrated information platform for managing both immunization and surveillance data.

Global strategy for NITAG support

Joachim Hombach, WHO

The Global Vaccine Action Plan identified two indicators of country ownership – domestic investment in immunization and establishment of a NITAG. The key function of NITAGs is to provide independent evidence-based advice to ministries of health and national immunization systems, acting as a conduit for global and regional technical recommendations from SAGE, technical advisory groups and RITAGs, and providing an upward channel of communication to national and global levels.

The target set in the Global Vaccine Action Plan was for all countries to have a NITAG by 2020. Good progress has been made, with 131 countries having NITAGs by the end of 2017, 98 of which fulfill six process indicators. The April 2017 SAGE meeting made a number of recommendations related to NITAGs to expand their role to include optimal use of vaccines as well as new vaccines, actions to build their capacity, and to set up of a Global NITAG Network and NITAG Reference Centre.



Global NITAG distribution.

The South East Asia Region has played an active role in the development of NITAGs, while the Region of the Americas has addressed the issue of small Caribbean Island states by creating subregional NITAGs. A similar model may be introduced for small Pacific Island states.

Recently WHO has taken on responsibility for the Global NITAG Network, which provides a forum through which NITAG representatives from LMICs and high-income countries can meet and exchange information and experience, share best practices and interact with donors. WHO has also assumed responsibility for the NITAG Resource Centre, a web-based 'one-stop' shop of NITAG resources, although further investment is required for it to achieve its full potential.

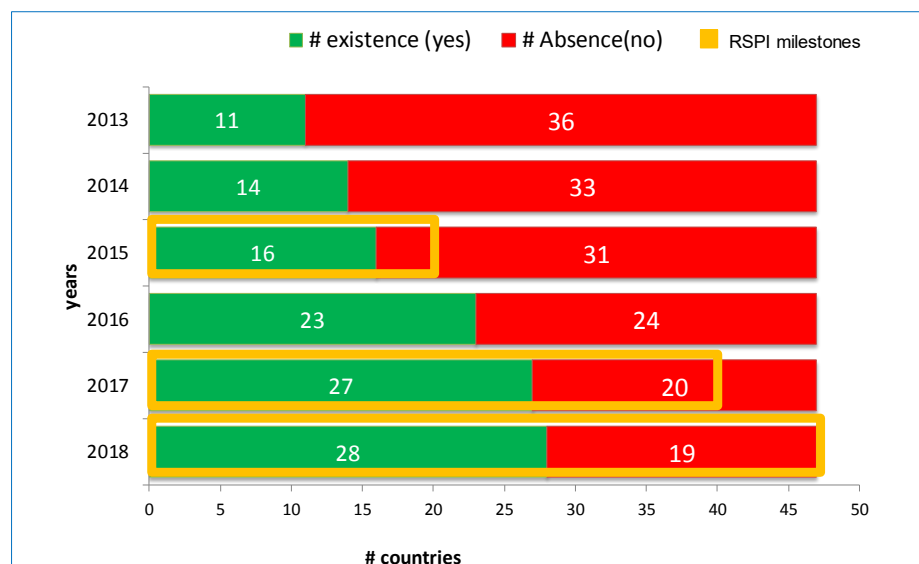
Other recent initiatives include a twinning model, encouraging North–South and South–South collaborations to support newly formed NITAGs, while discussions have been held on possible regional hubs that could provide tailored regional support. Possible additional evaluation criteria are also being considered, based on the quality of recommendations and integration of NITAG recommendations into national decision-making processes.

NITAGs can be seen as an innovative mechanism for integrating evidence-based approaches into national health policymaking. They are therefore a key national asset, the importance of which will grow as new and more costly vaccines become available. Relatively small investments at national, regional and global levels could help to further embed them in national decision making and ensure they achieve their full potential.

Progress and challenges in establishing NITAGs in the African Region

Julien Kabore, WHO

Establishing and strengthening NITAGs are specific priorities within the Regional Strategic Plan for Immunization as well as the Global Vaccine Action Plan. Although significant progress has been made, the region is currently off-track to meet its 2020 targets. By 2018, 28 countries had established NITAGs, against a target of 47, and the pace of introduction has markedly slowed in recent years. In 2017, 15 NITAGs complied with the six process criteria.



Status of NITAGs in the African Region.

Several NITAGs have undertaken self-assessment (using the SIVAC tool) or external evaluations. These evaluations examine functionality, including structural viability and functional capacity, quality, including technical expertise, access to training opportunities and access to external expertise, and integration, including relationships with local health authorities. Nine countries have undertaken self-assessments and five have undergone external evaluation.

To support regional activities, the Regional Office organized an orientation workshop in 2015, which stimulated several countries to set up a NITAG immediately. In 2018, training of consultants was organized to provide a resource to help countries establish a NITAG. Various other support activities have been organized with partners to build NITAG capacities, and staff are being recruited to extend these activities in 2019.

Challenges include the sharing and implementation of recommendations, lack of funding, a lack of visibility and clarity of roles (for example, some confusion with the role of Interagency Coordinating Committees). There are also issues with the inadequate use of information resources, lack of collaboration, a lack of competency to make recommendations in certain areas. Possible ways forward include greater advocacy to raise awareness of NITAGs and their roles, more emphasis on the use of resources and collaboration, potentially through a regional hub for capacity building or twinning/mentoring between well-established and immature NITAGs, a greater emphasis on raising resourcing for NITAGs, and development of decision-making capabilities.

Role of NITAGs in support of decision-making process

Ouattara Siguifota Coulibaly Germaine, Vice-President, Cote d'Ivoire NITAG, Belete Tafesse, MoH Ethiopia (representing the NITAG Chair), Jahit Sacarlal, Chair, Mozambique NITAG

The **Cote D'Ivoire** NITAG (CNEIV-CI) was established in 2009. It has 17 members, plus nine *ex officio* members and three liaison members. It meets at least four times a year. Its key roles are to provide advice and information to the ministry of health on optimal vaccination strategies and scientific developments in vaccination.

The NITAG responds to requests from the ministry of health. Having analysed the request, it establishes a working group of committee members and other experts which develops a draft opinion or recommendation. This is reviewed by the NITAG before being presented to the ministry of health. It aims to provide short and digestible reports to the ministry. Recommendations have covered areas such as introduction of HPV, hepB birth dose, pneumococcal, meningococcal and influenza vaccination and age of rotavirus vaccination.

Challenges include the availability of some members for meetings and a shortage of resources. Going forward, it aims to recruit new member, review its governing documents, and secure additional resources. Activities in 2019 include a survey on participation of the private sector in immunization, training for NITAG members in anthropological evaluation of immunization, and working with additional technical and financial partners.

The NITAG in **Ethiopia** (E-NITAG) was established in 2016 to provide advice to the national immunization programme. It responds to requests from the ministry of health, reviewing globally relevant documentation and SAGE and RITAG recommendations as well as any relevant local information. It then adapts recommendations to fit the local context.

It has provided advice on national multiyear plans, the national Gavi investment strategy, and on the introduction of multiple vaccines, including HPV, hepB birth dose and yellow fever, as well as measles control plans and age of MCV2 vaccination.

Challenges include ensuring the committee's breadth of expertise, limited contact with the national immunization programme, and a shortage of resources for activities such as systematic reviews. Plans for 2019 include at least two meetings on measles SIAs, and MR, yellow fever, HepB and meningococcal A vaccine introductions.

The NITAG in **Mozambique** (CoPI) was set up in 2011. Its chair and a member of the secretariat undertook a three-month evaluation exercise in 2018 using the standard NITAG evaluation tool. As a result, it updates some of its terms of reference, working procedures and workplans, in preparation for an external evaluation.

Up to the end of 2018, the NITAG had made 29 recommendations, 17 of which were implemented fully or in part, seven of which are in progress and five have yet to be implemented. Recommendations have covered introduction of vaccine introductions including rotavirus, IPV, MCV2, MR and HPV, as well as areas such as pharmacovigilance, logistics and cold chain capabilities, measles vaccination and use of cholera vaccination.

Challenges include limited funding for some NITAG activities, limited secretariat support, keeping members engaged, developing clear and concrete recommendations, and training.

Discussions noted the considerable progress that had been in the establishment of NITAGs in the region, but concern was also expressed that the rate of new introductions had slowed markedly and needed close monitoring. NITAGs were felt to be crucial aspects of national immunization ecosystems, with a vital role to play as a source of independent expert advice to support evidence-based immunization policy-making. While the six process indicators have performed a useful function in the set up phase, additional function-focused indicators were also thought to be required. These could be based on areas such as having a clear recommendation-development and evidence-assessment process and use of recommendations by national immunization programmes.

NITAGs should therefore be seen as national assets, with ring-fenced funding included in comprehensive multiyear plans. Countries should also ensure that NITAGs receive sufficient secretariat support to function effectively. A glossary describing committees relevant to immunization, such as ICCs, as well as relationships between them, could help to clarify roles and responsibilities.

Ensuring that NITAGs had sufficient breadth of expertise, ideally including areas such as the social sciences and health economics, was seen as an important issue. Local academic institutions were seen as key resources that NITAGs could draw upon. Potentially, the WHO Regional Office could offer advice on sources of expertise if they were not available locally. For countries that currently lack NITAGs and may not have the expertise in-country to cover all their functions, there was little appetite for subregional NITAGs, as too many issues were felt to be country-specific. Collaboration between NITAGs in nearby countries was felt to be a more promising alternative.

**18TH MEETING
OF THE EUROPEAN
TECHNICAL ADVISORY GROUP
OF EXPERTS ON IMMUNIZATION
(ETAGE)**

**12–13 November 2018
Copenhagen, Denmark**



Abstract

The 18th meeting of the European Technical Advisory Group of Experts on Immunization (ETAGE) took place in Copenhagen Denmark on 12 –13 November 2018 to review and discuss immunization activities and developments in the WHO European Region and provide advice to the WHO Regional Office on appropriate activities. Advice and guidance from ETAGE were sought on school entry vaccination checks, vaccination of healthcare workers and vaccination of pregnant women. Also discussed were the response to challenges faced in middle-income countries lacking donor support, cervical cancer elimination and the contribution of human papillomavirus (HPV) vaccination, hepatitis B control, strengthening the capacities and opportunities for collaboration of national immunization technical advisory groups (NITAGs), and addressing challenges to vaccination uptake among migrants, particularly urban migrants.

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Abbreviations

CDC	US Centers for Disease Control and Prevention
ECDC	European Centre for Disease Prevention and Control
ETAGE	European Technical Advisory Group of Experts on Immunization
EVAP	European Vaccine Action Plan 2015-2020
GNN	Global NITAG Network
GVAP	Global Vaccine Action Plan
HCW	healthcare worker
HPV	human papillomavirus
JRF	WHO/UNICEF Joint Reporting Form
MIC	middle-income country
NITAG	National Immunization Technical Advisory Group
RNN	Regional NITAG Network
SAGE	Strategic Advisory Group of Experts on Immunization
TIP	Tailoring Immunization Programmes
UNICEF	United Nations Children's Fund
VPI	Vaccine-preventable Diseases and Immunization Programme of the WHO Regional Office for Europe
WHA	World Health Assembly

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Executive summary

The 18th meeting of the European Technical Advisory Group of Experts on Immunization (ETAGE) was held on 12–13 November 2018 in Copenhagen, Denmark to review and discuss immunization activities and developments in the WHO European Region and provide advice to the WHO Regional Office for Europe (Regional Office) on appropriate actions.

Advice and guidance from ETAGE were sought on school entry vaccination checks, vaccination of healthcare workers, vaccination of pregnant women and strengthening and collaboration with national immunization technical advisory groups (NITAGs). Also discussed were the response to challenges faced in middle-income countries (MICs) lacking donor support, cervical cancer elimination and the contribution of vaccination against human papillomavirus (HPV), hepatitis B control, and addressing challenges to vaccination uptake among migrants, particularly urban migrants.

Among its conclusions and recommendations, ETAGE urged action to support the checking of children's immunization status at the time of primary school entry so that parents can be informed of any missed vaccination, and opportunities presented for easy access to catch-up immunization as appropriate. ETAGE recommended vaccination of healthcare workers (HCW), including medical students, and encouraged research to understand the attitudes of HCWs towards immunization better. ETAGE also recommended increased support for vaccination of pregnant women, women considering having children and those who have recently delivered. This includes rubella vaccination for women prior to conception, and, depending on local epidemiological evidence and priorities, may also include influenza and available pertussis vaccines. ETAGE fully endorsed the strategy of identifying regional focus areas and encouraged joint action between MICs with no donor support, while also acknowledging considerable challenges to strengthening and sustaining immunization services in these countries.

Introduction

ETAGE meets annually to review the progress of the Vaccine-preventable Diseases and Immunization Programme (VPI) towards the European Regional disease prevention goals. The 18th meeting of ETAGE was conducted on 12–13 November 2018 in Copenhagen, Denmark. Professor Adam Finn (ETAGE chair) chaired the meeting; Dr Ray Sanders was rapporteur.

The objectives of the meeting were to request advice and guidance from ETAGE on the following key topics and issues:

- school entry vaccination checks;
- vaccination of HCWs;
- vaccination of pregnant women.

Opportunity was taken to brief ETAGE members on the following topics and issues:

- response to challenges faced in MICs with no donor support;
- NITAG strengthening and collaboration;
- cervical cancer elimination and contribution of HPV vaccination;
- update from the ETAGE Working Group on hepatitis B control;
- addressing vaccination uptake challenges among urban migrants.

Opening remarks

The meeting was opened on behalf of the WHO Regional Office by Dr Nedret Emiroglu, Director of Programme Management, Director of the Division of Health Emergencies and Communicable Diseases. Dr Emiroglu shared information on recent changes to the management structure of the VPI team and on the planned appointment of a new Programme Manager for VPI. She also shared Member States' favourable response to the European Vaccine Action Plan (EVAP) midterm review presented at the recent Regional Committee meeting in Rome, Italy and expressed the need now to turn political commitment into practical actions.

Feedback from the recent SAGE meeting

Dr Joachim Hombach (WHO headquarters) presented highlights from a meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization held in Geneva, Switzerland on 23-25 October 2018. Following its review of the Global Vaccine Action Plan (GVAP), SAGE recommended that countries, regions and global immunization partners commit to developing an integrated post-2020 global immunization strategy. GVAP priorities need to be adapted to reflect the changing contexts and lessons learned, and should drive immunization activities until the end of the Decade of Vaccines (2011–2020). SAGE also recommended that research into immunization should be enhanced and expanded. Several steps have been taken towards developing a post-2020 global immunization strategy and it was announced that the strategy should be discussed at the World Health Assembly (WHA) in 2020.

SAGE received a partner report from GAVI, which placed added emphasis on the importance of close alignment of GAVI activities and vaccine investment strategy with WHO policy. SAGE also received a report from the PREVENT initiative, funded by the Wellcome Trust, engaged in providing pregnant women with vaccines to protect against outbreaks and epidemics. PREVENT is developing a roadmap for the inclusion of the interests of pregnant women in the development and deployment of vaccines against emerging pathogens. SAGE members welcomed the initiative, which is timely with regard to current research efforts to develop vaccines against emerging infectious diseases and projects aimed at standardizing the reporting of pregnancy outcomes.

A measles and rubella situation update revealed a resurgence of measles in all WHO regions except the South-east Asian and Western Pacific regions, with loss of elimination status in the Americas (Venezuela) and a major increase in reported cases in the European Region. Reflecting current concerns the WHO Director General will report to the WHA in 2020 “on the epidemiological aspects and feasibility of, and potential resource requirements for, measles and rubella eradication”. SAGE stressed that the vaccination campaigns are resource intensive and not sustainable, emphasizing the need for them to be linked to efforts to improve routine immunization. New guidance is being issued on identification of measles and rubella immunity gaps together with strategies to increase population immunity using a Continuous Quality Improvement approach.

SAGE welcomed the WHO Director General's multi-stakeholder launch in May 2018 of a “Call for Action Toward Cervical Cancer Elimination”, noted the progress being made with the introduction of HPV vaccines into immunization schedules but also noted that only 31% of MICs and 12% of lower-income countries had introduced HPV vaccination to date. While the WHO-recommended 2-dose schedule targeted at girls aged 9-14 years remains valid, the need for further research on vaccination schedules and comparative effectiveness was stressed. Concerns were expressed over short- to mid-term vaccine supply constraints and the need for a globally equitable vaccine allocation mechanism.

A review of the lessons learned from recent diphtheria outbreaks has demonstrated the need for improved quantity and quality of data on vaccination coverage, population size and disease surveillance at both national and sub-national levels, together with increased laboratory capacity for disease surveillance. The WHO Immunization Information System is being established to improve globally available data, and expanding collaborations with other stakeholders and United Nations agencies are investigating opportunities for better use of existing data at country level.

Discussion

While there are some very good examples of the successful introduction of HPV vaccine in the European Region, there remain questions over how best to use a vaccine that is currently in limited global supply. This is of particular concern as more countries (including in the European Region) move towards inclusion of boys in the vaccine target population. There are currently only two global producers of HPV vaccines, producing three different vaccines, with the potential for two additional vaccines in the pipeline. SAGE noted the equivalence of the currently licensed vaccines in relation to the cervical cancer elimination effort.

Update on the work of VPI

Dr Siddhartha Datta (VPI) provided an overview of recent VPI activities and achievements. The European Vaccine Action Plan 2015–2020 (EVAP) midterm review showed that only three of the six EVAP goals were on track (sustaining polio-free status; evidence-based decision making for introduction of new vaccines; achieving financial sustainability for immunization), that the status of one (control of hepatitis B) required validation, that one (meeting vaccination coverage targets) was at risk, and that one (elimination of measles and rubella) had not been achieved.

While overall regional vaccination coverage remained steady at 92-94% from 2014 to 2017, the number of Member States achieving coverage of $\geq 95\%$ declined from 36 to 32, and the number with national coverage at $< 90\%$ increased from 4 to 8 over the same time period. The suboptimal vaccination coverage at local level makes several countries in the Region prone to disease outbreaks, as demonstrated by the very large number of children and adults infected with measles in the first 8 months of 2018.

Immunization inequalities remain a concern in the Region with several MICs lagging behind high-income countries in the provision of immunization services. Vaccine stock-out events, due to vaccine supply shortages and procurement delays, also disproportionately affect MICs. The Middle-income Country Roadmap was developed to improve health and health security through immunization.

VPI's Accelerated Disease Control Team has continued its work on sustaining polio-free status and has provided global leadership in a number of areas including development of a global polio certification risk **assessment** tool. The Immunization and Surveillance Data Team is developing a web-based immunization data validation tool, has supported introduction of paediatric diarrhoea surveillance, and established measles/rubella elimination country profiles. The Immunization Demand Team has provided leadership in behavioural insights research related to immunization, including thorough support of several Tailoring Immunization Programmes (TIP) projects and development of a new edition of the TIP guide. The Team has updated guidance documents on facing vocal vaccine deniers, responding to a crisis in vaccine confidence and responding to questions on HPV vaccination, supported Region-wide advocacy events such as European Immunization Week. The Immunization System Strengthening Team has focussed programmatic support on ensuring financial sustainability in GAVI transition countries and reducing inequity of immunization services for urban migrants in GAVI support countries. The team has also continued to

support NITAG strengthening efforts, contributed to the WHO initiative Market Information for Access to Vaccines and supported development of national guidelines on adverse events following immunization (AEFI) surveillance assessment.

Session 1. School entry vaccination checks

Dr Siddhartha Datta, supported by ETAGE members Dr Ole Wichman and Dr Roman Prymula, provided a presentation on the relevance of encouraging school entry vaccination checks. In its endorsement of the Midterm Review of the Measles/Rubella Global Strategic Plan 2012-2020, SAGE noted that high contact rates after school entry and immunity gaps in school-age children together are a strong driver of disease transmission and recommended that all countries institute school entry checks for immunization status. The WHO position paper on measles (2017) recommended that children should be screened for measles vaccination history at the time of school entry, and those lacking evidence of receipt of two doses should be vaccinated. This is also an opportunity to check for receipt of other vaccines, and school-based vaccinations have proven to be an effective strategy in many countries for achieving high coverage and preventing outbreaks of vaccine-preventable diseases.

VPI recently conducted a scoping review of immunization checks at school entry and practices of school-based vaccination in the WHO European Region based on information provided by 46 Member States in the annual WHO/United Nations Children's Fund (UNICEF) Joint Reporting Form (JRF). According to the data provided, 19 Member States have 'mandatory' requirements for proof of vaccination at school entry, although no standard definition of what constitutes a 'mandatory' requirement currently exists. While the WHO European Region is diverse and health and education policy and practices vary between countries, primary school entry for all countries is between 5 and 7 years of age. Forty-five countries administer the second dose of measles-containing vaccine slightly before, or at the same time as, school entry. While school policies can differ and resources for health-related activities vary, the generally high enrolment rates make school-entry vaccination checks and school-based immunization potentially workable options in the Region. The JRF data provided little insight into how and why policies are implemented and no information on the results of specific policies. Currently available findings of operational research on the effectiveness of school-entry vaccination checks are heavily focused on the United States of America. There is therefore a need to document school vaccination mandates and best practices from high-, middle- and low-income countries in the European Region.

Discussion

ETAGE recognized the complexities of this issue but also acknowledged the value of conducting administrative vaccination checks on child entry to primary education. These checks not only provide an opportunity to collect immunization data, but also opportunities to promote and provide vaccination. While strongly supporting school-entry checks and school vaccination programmes, ETAGE was not in a position to recommend these checks and services be made mandatory, in part because there is currently no accepted standard definition of what would constitute a 'mandatory' requirement.

Many Member States do carry out school-entry checks and provide school vaccination services, but further operations research is required to document how this is being implemented, the outcomes, and lessons learned. Given the complexities involved it is unlikely that a single system will be

appropriate for all countries, but better documentation on what is currently being done could be used to develop broad guidelines based on a best practices approach.

Session 2. Vaccination of healthcare workers (HCW)

Dr Patrick O'Connor (VPI), supported by ETAGE Members Dr Antonietta Filia and Dr Federico Martinon-Torres, provided a presentation on vaccination for HCWs. The risk of vaccine-preventable diseases, particularly measles at present, in healthcare settings remains a serious concern and nosocomial infection puts both HCWs and patients at risk of severe morbidity and mortality. WHO recommends countries develop national policies for vaccination of HCWs and SAGE has recommended that verification of measles and rubella vaccination and/or immunity in HCWs be introduced into standard infection control guidelines. It is now pertinent to ask whether the Regional Office should develop standards on HCW immunization practice, and if so, which partners should be involved in the process of development and how those partners can best advocate for the vaccination of HCWs.

Discussion

While WHO has recommended vaccination of HCWs on an antigen-by-antigen basis, there has been no systematic discussion on standards and practices for HCW immunization. It is also recognized that there is no standard definition of a 'healthcare worker'; the term covers a very broad range of professions and occupations and has different connotations in different countries. While it is generally understood that susceptible HCWs can potentially play a significant role in transmission of vaccine-preventable diseases to patients and the community, very little conclusive data are available on the impact they have on transmission. Impact is most likely dependent on the specific disease and level of HCW-patient contact. An exception to this is measles: a body of evidence on the important role HCWs can play in nosocomial transmission is being established, and it may be possible to use the example of measles to drive development of broad standards for HCW vaccination.

While many Member States have policies in place for vaccination of HCWs, often on a voluntary basis, implementation of these policies is not adequately monitored and is believed often to be incomplete. These policies generally result from occupational health recommendations, aimed at protecting HCWs, and may not be compatible with managing public health risks and requirements. Also, HCWs' roles in promoting and providing vaccination to their patients and in their communities also needs to be stressed, particularly during outbreaks and epidemics. Available information suggests that a significant proportion of HCWs do not accept vaccination and a better understanding of the barriers to their acceptance of vaccines is needed.

Session 3. Vaccination of pregnant women

Dr Mark Muscat (VPI) provided an overview of and ETAGE members Adam Finn and Alenka Kraigher led a discussion on the current SAGE recommendations on vaccination of pregnant women and the rationale for developing a strategy for Member States to adopt this strategy. WHO has published position papers in which vaccination against pertussis, influenza, diphtheria and tetanus during pregnancy is encouraged, to provide immunity for mothers and their infants. Despite the SAGE recommendations there is little easily available information on routine maternal vaccination in the Region, and there are currently no Regional recommendations on this. VPI requested ETAGE to

consider its role in advocating for and supporting Member States to ensure that the SAGE recommendations for vaccinations in pregnancy are reflected in national vaccination schedules.

Discussion

ETAGE recognized the significant health benefits of immunizing women during pregnancy and the available evidence base demonstrating these benefits. Greater efforts are needed, however, to collect and collate this evidence at regional level and to share the data and conclusions with Member States. Discussions on maternal immunization tend to be antigen-specific because different antigens offer different benefits to the mother and the child, and risks from infection change over the period of gestation and during the neonatal period.

The role of ETAGE is to encourage NITAGs to investigate potential benefits of maternal immunization for their countries and make evidence-based proposals based on existing national immunization services, identified gaps in immunity or services and national vaccine use and safety legislation. Maternal immunization is a rapidly developing field and NITAGs need to be aware of the latest developments and available information to make the best-informed decisions. There is also a need to identify key personnel to lead the programme and develop national training materials. It will also be necessary to reach out to relevant HCWs to understand the barriers to acceptance of maternal immunization, as these will not be the same in all countries, and to develop locally-relevant responses.

Session 4. Update on NITAG strengthening and collaboration

Dr Luidmila Mosina (VPI) provided an overview of activities undertaken by the Secretariat to strengthen NITAGs and increase NITAG collaboration. As of October 2018, 48 of the 53 Member States in the Region had established NITAGs including 18 of the 21 MICs. In 2017, based on available data, 36 of the 47 NITAGs met all six process indicators for functionality of their NITAGs. The Regional Office conducted evaluations of NITAGs in MICs using a standardized evaluation tool. The evaluations revealed that many of the newly established NITAGs continue to face challenges, including in establishing a process for the development of NITAG recommendations, improving the quality of NITAG recommendations and reports, and lack of formalization of communication with national government authorities. To support NITAGs in building capacity, a standardized set of training materials has been developed. The materials include sets of presentations for a 4-day training workshop, simulation exercises and descriptions of best practices. Training materials were piloted in a WHO regional training workshop in May 2018. A Regional NITAG network (RNN) has been proposed to facilitate and strengthen collaboration and information sharing between NITAGs, but implementation of the network has been delayed due to lack of available funding.

Discussion

There are currently two European Union funded projects aimed at supporting collaboration between NITAGs. One is an extension of the European Centre for Disease Prevention and Control (ECDC) VENICE projects aimed at establishing a network of NITAGs within the European Union, the second is a European Commission-funded project exploring the possibilities for collaboration between NITAGs, including some NITAGs from outside of the European Union. Both of these projects are at an early stage of development.

While this topic was presented for information only, ETAGE requested a full review and discussion of programmatic issues at its next meeting. Links between the WHO Euro team and ETAGE and the ECDC initiative are also being established.

Session 5. VPI response to challenges faced in MICs with no donor support

Dr Niyazi Cakmak (VPI) provided a presentation on the VPI response to challenges faced by MICs. In light of increased international attention on restricted access to vaccines in MICs and at the request of SAGE, in June 2014 WHO convened a MIC Task Force to develop a coordinated strategy and plan of action. The proposed MIC Strategy focuses on four main areas: 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; iv) improving access to timely and affordable supply.

The Regional Office conducted a regional analysis of country performance and a pilot in-country assessment to determine the situation in the Region and to refine the menu of regional focus areas to address challenges faced by MICs with no donor support. This analysis demonstrated that immunization programme performance of the MICs with no donor support, in terms of protecting individuals against more vaccine-preventable diseases, and elimination of measles and rubella, is significantly below that of other country groups in the Region and far from achieving EVAP targets set for 2020. A pilot in-country assessment, conducted in Romania, validated the relevance of the global strategy and identified regional focus areas to address the challenges.

In response to the findings, VPI plans to further prioritize countries in greatest need of support and obtain commitment from priority countries to respond to identified challenges through collaborative work with WHO and international partners. A five-year immunization framework (roadmap) is being developed to provide support to national immunization programmes in accessing affordable vaccines, strengthening decision making, improving financial sustainability, addressing concerns over vaccine hesitancy and ensuring equitable access to immunization services.

Discussion

Start-up funding for development of the roadmap has been received from the United States Centres of Disease Control and Prevention (US CDC), but with increasing international interest in supporting MICs it is expected that partner diversity will increase. The complexities of harmonizing and aligning country requirements for vaccines to establish joint procurement systems are well recognized, but despite reluctance on the part of some countries to share information on vaccine prices, there is general interest in joint procurement and the potential benefits it can bring. ETAGE looked forward to receiving further information during future meetings.

Session 6. Cervical cancer elimination and contribution of HPV vaccination

Cervical cancer is the second most common cause of cancer deaths in women after breast cancer, and the fifth most common cause of death in women in the WHO European Region. The majority of these deaths occur in low- and middle-income countries. There are proven strategies to address cervical cancer, including vaccination to prevent HPV infection, and this is embedded in the targets

and indicators of the WHO Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2013-2020. The WHO-recommended primary target population for HPV vaccination is girls aged 9–14 years.

Thirty-six Member States in the Region have introduced HPV vaccine into routine schedules, but coverage varies from 20-80%. The greatest challenges to accelerating HPV vaccine introduction will be faced in the MICs without donor support. The vaccines available are expensive and there are currently global vaccine supply constraints. Despite evidence to the contrary, fears over vaccine safety continue to arise, and further efforts are needed in supporting national immunization programmes to respond to and manage scares around HPV vaccine.

Discussion

ETAGE recognizes the multiple challenges faced in this area. While gender-neutral vaccination policies would probably make HPV vaccination easier to promote and implement in some countries, vaccine supply constraints and the level of coverage achieved limit the effective target population. Aside from the direct benefits to boys, it was noted that modelling data suggest vaccination of boys contributes to cervical cancer elimination more in low-coverage settings than in high-coverage settings.

Session 7. Addressing vaccination uptake challenges among urban migrants

Dr Siddhartha Datta presented on existing immunization policies and practices for migrants in the Region. Ms Katrine Bach Habersaat (VPI) presented on a situation analysis of vaccination of urban migrants in Kyrgyzstan. Dr Niyazi Cakmak and Ms Aliya Kosbayeva provided the results of a vaccination coverage cluster survey among internal migrant populations of Bishkek and Osh cities in Kyrgyzstan.

A scoping review of academic and grey literature on immunization policies, vaccine delivery practices and barriers to access and utilization of immunization services by migrants and refugees found that practices vary widely in the Region. Many Member States lack policies and strategies with specific recommendations for immunization for migrants and refugees. Inbuilt administrative barriers for undocumented migrants prohibit their entitlement to free health services including immunization. Lack of financial and human resources, in particular cultural mediators and/or interpreters, act as barriers to implementation of national immunization policies and limit systematic collection and evaluation of data for corrective actions. Socioeconomic, sociocultural and educational issues of migrants and refugees influence access to available immunization services in the host countries. The review also found evidence that various targeted locally tailored interventions were successful in improving the uptake of immunization services among migrants and refugees.

A TIP project was conducted in Kyrgyzstan to review the current situation with regard to urban migrant vaccination. Use was made of published data and reports together with on-site visits to migrant communities. Kyrgyzstan has traditionally reported high vaccination coverage, but there has been a recent trend of declining coverage in urban areas, particularly those housing a large internally migrated population. Non-registered migrants often have limited access to health services due to knowledge barriers and misconceptions, but also to lack of opportunity to access the services. Many health workers serving urban migrants do not appear to be well-informed on the legal rights of migrants and do not consider it their role to facilitate registration of migrants.

Results of the vaccination coverage survey of children aged 12-35 months conducted in two cities in Kyrgyzstan demonstrated large differences between estimates based on parents' recall versus facility-based records, but found that access to services was generally good, with high coverage for the initial doses of vaccine but significant drop-out after that. Hesitation to receiving simultaneous injections, together with a tendency to delay vaccination, were noted.

Discussion

ETAGE was impressed by the work being done to address this challenge, but noted that the term 'migrants' may not be the most appropriate for this under-served population.

Session 8: Update from ETAGE Working Group on Hepatitis B

Pierre Van Damme, Chair of the ETAGE Working Group provided a presentation via video link on the conclusions of a meeting of the ETAGE Working Group on Hepatitis B held in October 2018 in Moscow, Russian Federation. The meeting provided an opportunity to discuss the process of monitoring progress of the Global Strategy and the European Action plan for the health sector response to viral hepatitis in the WHO European Region and present updated information on hepatitis B serosurveys conducted in the Russian Federation and proposed for Croatia. The opportunity was also taken to review validation reports submitted by Latvia and the Netherlands and to revise the validation process based on experience with reviewing these initial documents.

The Working Group conditionally validated the report of the Netherlands as evidence of achieving the Regional hepatitis B target, but urged the country to align its vaccination schedule with the WHO recommended birth-dose policy. Validation will be confirmed after receipt of the 2017 serosurvey results. In reviewing documents submitted by Latvia, the Working Group acknowledged the progress made, but noted the suboptimal screening programme and urged that screening be improved, including serosurveys of new cohorts.

The Working Group also discussed potential mechanisms to facilitate countries' participation in the validation process. In general, greater standardization of submitted documents is needed and more information on submitting standardized information should be provided to Member States. Incomplete documentation will not be accepted for review.

Discussion

Concerns were raised that few resources are available for this workstream in the Regional Office and that as the workload increases, support to countries will become unsustainable. Hepatitis B targets and their validation, reporting of birth-dose coverage and effective screening programmes will be discussed at the meeting in February 2019.

Conclusions and recommendations

School entry vaccination checks

Conclusions

- Several Member States in the Region have vaccination checks at school entry but the nature of these checks is highly heterogeneous. It would be very helpful to have more detailed information on what systems already exist, how they are implemented, how they are used and lessons learned.
- Collection of such data for all children, given appropriate permissions and/or anonymization, may have additional potential value, including informing parents of vaccination coverage in individual schools and providing public health authorities with detailed coverage data at the local level. Such checks should, where possible, be linked to easy access to catch-up immunization when required, for example in primary care or through school-based immunization services.
- While there are several levels at which checks on vaccination status could be conducted, from kindergarten/day-care entry to university entry, primary school entry checks offer an achievable goal as a minimum requirement. Additional such checks, for example at secondary school entry and at entry into higher education, may have similar value and may be feasible in some settings.
- To conduct these activities, the mandates of ministries of health and education may require review and revision to ensure that both sectors work collaboratively.
- Further operational research to reconfirm beneficial consequences of vaccination checks is required to provide information to parents/guardians, schools, family doctors and the public health system.

Recommendation

- ETAGE recommended that an administrative check of all children's immunization status be performed at the time of primary school entry in order to inform the parents of the child's potential vulnerability to preventable infections at a time of increased likelihood of exposure. In this context, the value of, and need to, protect their own child as well as other children should be noted.

Vaccination of healthcare workers (HCW)

Conclusions

- There is no single concise definition of HCW as the term covers a broad range of professions and work activities, and professional exposure to risk varies from very low to very high. The definition of the target HCW group needs to be developed as per risk assessment for each specific vaccine.
- WHO has published a series of position papers which provide recommendations on vaccination of HCWs on an antigen-by-antigen basis.

- There is a variable body of evidence available on the increased risk of infection in HCWs and the role they play in the transmission of vaccine-preventable infections. The example of measles could drive the development of standards and requirements for vaccination of HCWs against a range of infectious diseases.
- In addition to the occupational health benefits of direct risk reduction for individuals who may be at enhanced risk of exposure to vaccine-preventable infections by virtue of their work, vaccination of HCWs also has the potential to enhance strategies to reduce hospital-acquired infections and should therefore be seen as part of wider infection control efforts. Cooperation between occupational health and infection control teams with regard to the immunization programme is likely to be highly beneficial.
- For certain infections, particularly in the context of outbreaks and epidemics, HCW immunization may contribute to sustaining effective function of healthcare services. Since HCWs can influence the behaviour of others through their knowledge and communication, enhancing their understanding and awareness of the importance of immunization may have wider benefits.
- Precise policies with respect to specific vaccines will vary with local epidemiology and priorities and, in some cases, may focus on specific groups of HCWs whose patients are at especially high risk.
- There is an urgent need to gain a more comprehensive understanding of the nature and extent of barriers to HCW vaccination, including attitudes to vaccination, existence of knowledge gaps and effective delivery.

Recommendations

- ETAGE recommended that NITAGs and immunization programmes consider the merits of offering targeted immunization to HCWs with patient contact including medical students..
- ETAGE also emphasized the importance of relevant local research to understand the attitudes of HCWs towards immunization and urged Member States to collect accurate data on coverage and disease burden and thus achieve effective strategies.

Maternal immunization around childbirth

Conclusions

- Evidence is available for the safety and effectiveness of a limited range of vaccines used during pregnancy. It is likely that additional vaccines to protect the infant postnatally will become available alongside new evidence concerning vaccines already in use, so that policies should be kept under regular review.
- The critical importance of collecting data on background adverse event rates and enhancing vaccine safety surveillance was emphasized.
- The importance of full engagement with HCWs who are the primary source of advice for pregnant women (most commonly obstetricians or midwives) was emphasized. Such colleagues' advice should be sought in programme planning and they should have training on the value and potential impact and safety of maternal vaccine programmes.

- Maternal immunization could leverage the recent WHO antenatal care guidelines that call for eight visits during pregnancy and could be used as an opportunity to collaborate with the maternal health programmes by defining and delivering a package of interventions at each visit, which includes the relevant vaccines, in addition to the other required interventions at those visits.

Recommendation

- ETAGE recommended that NITAGs and national immunization programmes consider the benefits of offering appropriate vaccines in pregnancy as well as to women considering having children and those who have recently delivered. Such local recommendations should be governed by local epidemiological evidence and priorities, but may include influenza and available pertussis vaccines, which generally contain other antigens, including tetanus and diphtheria, which may be valuable in some settings. The value of rubella vaccination (usually as MMR) for women prior to conceiving should also be borne in mind.

NITAG strengthening and collaboration

Conclusions

- ETAGE acknowledged the substantial progress that continues to be made in the Region in establishing NITAGs and strengthening their capacities in the face of the currently limited human and financial resources available through the WHO Regional Office.
- The Global NITAG Network (GNN) is now established, with a steering committee nominated and membership growing. NITAGs in the European Region are strongly encouraged to participate in this network.
- ETAGE endorsed proposals for a Regional NITAG Network (RNN) to be established and noted the continuing efforts made by the WHO Secretariat to raise funding for implementation of the Network.
- ETAGE noted the development of two synergistic European Commission/ECDC projects to stimulate and support collaboration between NITAGs and strengthen NITAG capabilities. ETAGE looked forward to hearing of the positive outcomes from these projects in future meetings.

Response to challenges faced in MICs with no donor support

Conclusions

- ETAGE acknowledged the considerable body of work performed by the WHO Regional Office in conducting a regional analysis of country performance and piloting an in-country assessment of the challenges faced by these countries.
- While fully endorsing the strategy of identifying regional focus areas and encouraging joint action between Member States, ETAGE acknowledged the considerable challenges to strengthening and sustaining immunization services in these countries.
- Prioritization of countries in greatest need, development of the roadmap for south-eastern European countries and mobilization of resources for implementation of action plans are all positive steps and ETAGE looked forward to receiving reports of further progress in future.

Cervical cancer elimination and contribution of HPV vaccination

Conclusions

- ETAGE recognised and supports the role WHO can play in coordinating a coherent response to achieving elimination of cervical cancer through development of national elimination plans that build upon current cancer prevention and control strategies implemented through existing services.
- It was recognized that there remain a number of unresolved technical challenges, including the effectiveness of single dose HPV vaccine schedules, inclusion of males into the vaccination target population, global vaccine supply constraints and ongoing public concerns over vaccine safety and acceptance.

Addressing vaccination challenges among (urban) migrants

Conclusion

- Recognising the complexities surrounding this important challenge to vaccination in the Region, ETAGE acknowledged the quality and scope of work being conducted by the VPI team, and looked forward to receiving reports of further progress in future.

Report from the ETAGE Working Group on Hepatitis B

Conclusion

- ETAGE noted with approval the progress being made in the Region towards hepatitis B control and endorsed the work done by the ETAGE Working Group in developing and introducing a system for validation of national control achievements.

Participants

ETAGE members

Professor Adam Finn, ETAGE Chair
Professor F. Nur Baran Aksakal
Dr Antonietta Filia
Professor Alenka Kraigher
Dr Federico Martín-Torres
Professor Roman Prymula
Dr Ole Wichmann

Temporary advisors

Dr Thomas Cherian
Dr Raymond Sanders, Rapporteur
Professor Pierre Van Damme (*by Webex*), Chair of ETAGE Working Group on Hepatitis B

WHO headquarters

Dr Joachim Hombach, Senior Health Adviser

WHO Regional Office for Europe

Dr Oleg Benes, Technical Officer
Dr Niyazi Cakmak, Team Lead
Dr Paul Chenoweth, Technical Officer
Ms Danni Daniels, Technical Officer
Dr Siddhartha Datta, Team Lead a.i.
Ms Catharina de Kat, Communications, Web and Information Officer
Dr Nedret Emiroglu, Director of Programme Management, Director of the Division of Health Emergencies and Communicable Diseases
Ms Natasha Allen Grue, Programme Assistant
Ms Katrine Bach Habersaat, Technical Officer
Dr Shahin Huseynov, Technical Officer
Dr Aliya Kosbayeva, Technical Officer
Dr Liudmila Mosina, Technical Officer
Dr Mark Muscat, Technical Officer
Ms Siff Malue Nielsen, Consultant
Dr Patrick O'Connor, Team Lead
Mr Simarjit Singh, Technical Officer

The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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World Health Organization Regional Office for Europe

UN City, Marmorvej 51, DK-2100 Copenhagen Ø, Denmark

Tel: +45 45 33 70 00 Fax: +45 45 33 70 01

Email: eurocontact@who.int

Website: www.euro.who.int

Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC) recommendations September 2018

Theme 1: Research to minimize barriers and improve coverage of vaccines currently in use

Session 1: Global vaccine acceptance and demand

Introduction

The IVIR-AC working group on Vaccine Acceptance and Demand, which was established in March 2018, presented their draft terms of reference for review and a draft

Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC): recommandations, septembre 2018

Thème 1: Recherche visant à réduire au minimum les obstacles et à améliorer la couverture des vaccins actuellement utilisés

Session 1: Acceptation et demande de vaccins dans le monde

Introduction

Le groupe de travail de l'IVIR-AC sur l'acceptation et la demande de vaccins, créé en mars 2018, a présenté son projet de mandat pour examen et un projet de cadre générique des parties

generic IVIR-AC stakeholder framework for vaccine acceptance and demand. In addition, South Africa presented a project protocol based on the IVIR-AC stakeholder framework to address essential features of acceptance and demand to test the generic approach of IVIR-AC for human papillomavirus (HPV) and other vaccination programmes. A draft dashboard for HPV was presented, containing information on population demographics, the national cervical cancer screening programme, the HPV burden and prevalence, vaccination and the impact of vaccination, as a tool to guide national decision-makers in policy and monitoring.

RECOMMENDATIONS

Terms of reference of the IVIR-AC working group

- The Committee agreed on the terms of reference presented and proposed that the working group: 1) map current knowledge to determine priority research questions to fill gaps; and 2) establish a model of the determinants of vaccine decision-making, based on published literature.
- The Committee proposed that IVIR-AC encourage behavioural modelling based on behavioural economics, incorporating psychological, cultural and other drivers of health behaviour change. IVIR-AC is in a good position to provide input on such studies, given the diversity of disciplines represented on the Committee (such as modellers, economists, social scientists, anthropologists, psychologists, epidemiologists and managers in the Expanded Programme on Immunization (EPI)).
- Ensure linkage with other projects and partnerships with stakeholders active in this area.

IVIR-AC Framework on vaccine acceptance and demand

- Considerations of equity should be emphasized to acknowledge that coverage problems are most acute in the populations that are most difficult to reach (e.g. school vaccination programmes that miss children who do not attend school or who have dropped out).
- The Framework should explicitly acknowledge differences in contexts and settings (e.g. school versus provider vaccination programmes).
- The Committee recommended that quantitative and qualitative methods for understanding decision-making be explored, at least providing a conceptual scheme of the underlying processes (e.g. behavioural choices) by which decisions are made (diagrams or computational representations), which can be used to quantify input variables.
- Explore use of the conceptual framework model to assess features of acceptance and demand and their interaction and possibly to derive input parameters for stakeholders.

prenantes de l'IVIR-AC pour l'acceptation et la demande de vaccins. En outre, l'Afrique du Sud a présenté un protocole de projet fondé sur le cadre des parties prenantes de l'IVIR-AC pour examiner les caractéristiques essentielles de l'acceptation et de la demande afin de tester l'approche générique de l'IVIR-AC pour le papillomavirus humain (PVH) et d'autres programmes de vaccination. Un projet de tableau de bord sur le PVH a été présenté, contenant des informations sur la démographie de la population, le programme national de dépistage du cancer du col de l'utérus, la charge et la prévalence du PVH, la vaccination et l'impact de la vaccination, comme outil pour guider les décideurs nationaux en matière de politique et de suivi.

RECOMMENDATIONS

Mandat du groupe de travail IVIR-AC

- Le Comité a approuvé le mandat présenté et a proposé que le groupe de travail: 1) dresse la carte des connaissances actuelles pour déterminer les questions de recherche prioritaires afin de combler les lacunes; et 2) établisse un modèle des déterminants de la prise de décisions en matière de vaccins fondé sur la littérature publiée.
- Le Comité a proposé que le groupe de travail de l'IVIR-AC encourage la modélisation comportementale fondée sur l'économie comportementale, en intégrant les facteurs psychologiques, culturels et autres qui influent sur la modification des comportements en matière de santé. L'IVIR-AC est bien placé pour contribuer à ces études étant donné la diversité des disciplines représentées au sein du Comité (modélisateurs, économistes, spécialistes en sciences sociales, anthropologues, psychologues, épidémiologistes et gestionnaires du Programme élargi de vaccination [PEV]).
- L'IVIR-AC est chargé d'assurer le lien avec d'autres projets et partenariats avec les parties prenantes actives dans ce domaine.

Cadre de l'IVIR-AC sur l'acceptation et la demande de vaccins

- Il convient de mettre l'accent sur l'équité pour reconnaître que les problèmes de couverture sont plus aigus dans les populations les plus difficiles à atteindre (par exemple les programmes de vaccination scolaire qui manquent les enfants qui ne vont pas à l'école ou qui ont quitté l'école).
- Le cadre doit reconnaître explicitement les différences de contextes et de situations (par exemple les programmes de vaccination à l'école par opposition aux programmes de vaccination des prestataires).
- Le Comité a recommandé d'explorer des méthodes quantitatives et qualitatives pour comprendre la prise de décisions, afin de parvenir au moins à un schéma conceptuel des processus sous-jacents (par exemple les choix comportementaux) par lesquels les décisions sont prises (diagrammes ou représentations algorithmiques), qui peuvent être utilisées pour quantifier les variables d'entrée.
- Il convient d'explorer l'utilisation du modèle du cadre conceptuel pour évaluer les caractéristiques de l'acceptation et de la demande et leur interaction, et dans la mesure du possible pour en tirer des paramètres d'entrée pour les parties prenantes.

Research protocol

- The Committee noted that the methods described in the protocol are not sufficient for assessing use of the IVIR-AC framework, and there is inadequate consideration of methods for testing use of the framework.
- The IVIR-AC review identified several aspects of the aims of the proposed research to inform and improve the HPV vaccination programme in South Africa that require further attention.
- Approaches for explicit testing of the framework should be explored that include the counterfactual condition.
- The acceptability of the 1st dose of HPV vaccine in the South African study was good (80% or more), which raises the question of why coverage of the 2nd dose was lower. Although it might be due to low acceptance, it might be due to a health system problem in making the 2nd dose available (e.g. lack of follow-up) or the way in which the vaccine was offered (opt-in versus opt-out, school vs. practitioner). It is recommended that the researchers determine the cause by enquiring about general vaccine acceptance and general health system issues and determine whether issues specific to the HPV vaccine (e.g. adverse events associated with the 1st dose) caused decreased uptake of the 2nd dose.
- The Committee considered that the qualitative aspects of the protocol for overcoming hesitancy were well developed but noted potential biases in the design of the study, particularly for entry into the study (e.g. parents who refuse vaccination might also be more likely to refuse participation in the study).
- The researchers could determine this in advance and include only participants who agree to take part in both rounds.

Country dashboard

- The Committee suggested that the developers of the dashboard should explicitly indicate the target users (e.g. researchers or policy-makers).
- The methods for collecting and analysing meta-data should be transparent, and the sources, quality and limitations of meta-data should be explicitly stated (e.g. indicate which data are from neighbouring countries).
- The Committee recommended that ways be found to ensure that country data are comparable, to avoid problems in measurement (e.g. influence of local culture).
- Continuous dialogue should be established with decision-makers and local immunization programme staff about their information needs.
- A balance between iterative use and cost should be considered in optimizing use of the dashboard.

Protocole de recherche

- Le Comité a noté que les méthodes décrites dans le protocole ne sont pas suffisantes pour évaluer l'utilisation du cadre de l'IVIR-AC et qu'il n'est pas suffisamment tenu compte des méthodes pour tester l'utilisation du cadre.
- L'examen de l'IVIR-AC a identifié plusieurs points dans les objectifs de la recherche proposée pour éclairer et améliorer le programme de vaccination contre le PVH en Afrique du Sud qui nécessitent une attention particulière.
- Il conviendrait d'explorer des approches pour la mise à l'essai explicite du cadre, y compris la condition contrefactuelle.
- L'acceptabilité de la 1^{ère} dose de vaccin anti-PVH dans l'étude sud-africaine était bonne (80% ou plus), ce qui soulève la question de savoir pourquoi la couverture de la 2^e dose était moindre. Bien qu'une mauvaise acceptation puisse en être la cause, cela peut aussi provenir d'un problème de système de santé dans la mise à disposition de la 2^e dose (par exemple une absence de suivi) ou de la manière dont le vaccin a été proposé (option d'acceptation / option de refus, école / praticien). Il est recommandé que les chercheurs en déterminent la cause en s'enquérant de l'acceptation générale du vaccin et des problèmes du système de santé, et déterminent si les problèmes propres au vaccin anti-PVH (par exemple les effets indésirables associés à la 1^{ère} dose) ont entraîné une diminution du recours à la 2^e dose.
- Le Comité a estimé que les aspects qualitatifs du protocole visant à résoudre le problème des hésitations étaient bien développés, mais a noté des biais potentiels dans la conception de l'étude, en particulier dans le recrutement (par exemple les parents qui refusent la vaccination pourraient aussi être davantage susceptibles de refuser de participer à l'étude).
- Les chercheurs pourraient anticiper cela et n'inclure que les personnes qui acceptent de participer aux deux tournées de vaccination.

Tableau de bord des pays

- Le Comité a suggéré que les concepteurs du tableau de bord indiquent explicitement les utilisateurs cibles (par exemple les chercheurs ou les décideurs).
- Les méthodes de collecte et d'analyse des métadonnées doivent être transparentes et les sources, la qualité et les limites des métadonnées doivent être explicitement indiquées (par exemple indiquer quelles données proviennent de pays voisins).
- Le Comité a recommandé de trouver des moyens d'assurer la comparabilité des données nationales afin d'éviter les problèmes de mesure (par exemple l'influence de la culture locale).
- Un dialogue permanent doit être établi avec les décideurs et le personnel local des programmes de vaccination au sujet de leurs besoins d'information.
- Un équilibre entre l'utilisation itérative et le coût doit être envisagé pour optimiser l'utilisation du tableau de bord.

Session 2: Model comparison for cervical cancer elimination

Introduction

In response to the global call for action to eliminate cervical cancer by the Director-General of WHO in May 2018, a model comparison was undertaken to inform cervical cancer elimination thresholds and strategies for global cervical cancer elimination. The mathematical models used in the comparison study were presented as well as the collaborative work to compare them. The evidence generated by the epidemiological and economic modelling studies will have informed the decisions of the WHO Strategic Advisory Group of Experts (SAGE) on immunization in October 2018.

IVIR-AC was requested to review the mathematical models and the collaborative comparison to address the following questions:

- Did the Committee have any concern about the methods in the models used in the comparison?
- Did the Committee consider that the process, methods and interpretation of the collaborative model comparison for defining cervical cancer elimination thresholds and strategies towards global cervical cancer elimination are valid?

RECOMMENDATIONS

Overall recommendations

IVIR-AC found that the models used (i.e. Policy-1, Harvard, HPV-ADVISE and Spectrum) are well established and well suited for the purpose of the study and that the model comparison was well conducted. In order that the results can be used for policy-making, IVIR-AC would like more emphasis on the public health impact of interventions over time, the financial resources required, the implications for health systems and the incremental cost-effectiveness of each intervention, which should inform development of evidence-based thresholds for defining elimination.

Assessment of mathematical models

- Although none of the models was originally designed to predict very low cancer incidence targets in the future, all the models used in the comparison are well established and well known for application in vaccine and screening studies in many high-income and low- and middle-income countries (LMICs).
- The criteria for selecting the models are transparent and appropriate. Only individual or hybrid models were included, and each modelling group is willing and able to contribute time to conducting analyses. The Committee was impressed by the amount and the quality of the work already done in a relatively short time.
- For the purpose of the comparison, the models were individually calibrated and validated to a sufficient variety of end-points and in a sufficient range of countries.

Session 2: Comparaison de modèles pour l'élimination du cancer du col de l'utérus

Introduction

En réponse à l'appel mondial lancé par le Directeur général de l'OMS en mai 2018 pour l'élimination du cancer du col de l'utérus, une comparaison de modèles a été entreprise afin de définir des seuils pour l'élimination du cancer du col et des stratégies d'élimination au niveau mondial. Les modèles mathématiques utilisés dans l'étude comparative ont été présentés ainsi que le travail collaboratif entrepris pour les comparer. Les données probantes issues des études de modélisation épidémiologique et économique ont éclairé les décisions du Groupe stratégique consultatif d'experts de l'OMS (SAGE) sur la vaccination en octobre 2018.

On a demandé à l'IVIR-AC d'examiner les modèles mathématiques et la comparaison collaborative pour répondre aux questions suivantes:

- Le Comité a-t-il des réserves au sujet des méthodes utilisées dans les modèles employés pour la comparaison?
- Le Comité considère-t-il que le processus, les méthodes et l'interprétation de la comparaison collaborative des modèles pour définir les seuils de l'élimination du cancer du col de l'utérus et les stratégies d'élimination au niveau mondial sont valables?

RECOMMANDATIONS

Recommandations globales

L'IVIR-AC a constaté que les modèles utilisés (Policy-1, Harvard, HPV-ADVISE et Spectrum) sont bien établis et bien adaptés aux fins de l'étude et que la comparaison des modèles a été bien menée. Pour que les résultats puissent servir à l'élaboration des politiques, l'IVIR-AC souhaiterait que l'on mette davantage l'accent sur l'impact des interventions sur la santé publique au fil du temps, les ressources financières requises, les répercussions sur les systèmes de santé et le rapport coût-efficacité progressif de chaque intervention, ce qui devrait permettre d'élaborer des seuils fondés sur des données probantes pour définir l'élimination.

Évaluation des modèles mathématiques

- Bien qu'aucun des modèles n'ait été conçu à l'origine pour prédire des cibles très faibles d'incidence du cancer dans le futur, tous les modèles utilisés dans la comparaison sont bien établis et bien connus pour leur application dans les études de vaccination et de dépistage dans de nombreux pays à revenu élevé et à revenu faible et intermédiaire.
- Les critères de sélection des modèles sont transparents et appropriés. Seuls des modèles individuels ou hybrides ont été inclus, et chaque groupe de modélisation est disposé et capable de consacrer du temps aux analyses. Le Comité a été impressionné par la quantité et la qualité du travail déjà accompli en relativement peu de temps.
- Aux fins de la comparaison, les modèles ont été calibrés et validés individuellement en fonction de critères d'évaluation suffisamment variés et dans un nombre adéquat de pays.

- The vaccination and screening strategies are varied, specific and usually pragmatic enough for potential implementation in any country.
- The models are sufficiently distinct and compatible to determine uncertainty in estimates of whether short- and long-term intervention impacts can be obtained and, if so, when the impacts could be expected with feasible combined screening and vaccination strategies.
- It would be instructive to estimate and display not only the total impact of the intervention packages but also the effect of each component (e.g. direct and indirect protection by the vaccine and screening and treatment) and how the impacts vary over time. This could be done by HPV type.
- It is reassuring that, although the models have substantially different structures and set-ups, they produce broadly similar estimates of the evolving impact of various strategies over time.
- Recognizing that the purpose of model comparison is to understand the key drivers of results (i.e. transparency in disease dynamics and processes), the Committee considered that harmonization, differences in parameterization, structural similarities and differences between the models should be transparently communicated.
- As a longer-term research agenda, if possible, more work should be done under assumptions of heterogeneity in geographical location or sexual network contact structure or both. It is likely that the long-term equilibrium that is achievable is directly related to the degree of heterogeneity. Ideally, HPV modellers should communicate with modellers of HIV infection and other sexually transmitted diseases to develop data and methods to address such heterogeneity.
- Les stratégies de vaccination et de dépistage sont variées, spécifiques et généralement suffisamment pragmatiques pour pouvoir être appliquées dans n'importe quel pays.
- Les modèles sont suffisamment distincts et compatibles pour déterminer l'incertitude des estimations quant à la possibilité d'obtenir des impacts d'intervention à court et à long terme et, dans l'affirmative, déterminer à quel moment on peut s'attendre à un impact avec des stratégies de dépistage et de vaccination combinées réalisables.
- Il serait instructif d'estimer et de montrer non seulement l'impact total des ensembles d'interventions, mais aussi l'effet de chaque composante (par exemple la protection directe et indirecte par le vaccin, le dépistage et le traitement) et comment ces effets évoluent avec le temps. Cela pourrait être fait par type de PVH.
- Il est rassurant de constater que, bien que les modèles aient des structures et des configurations sensiblement différentes, ils produisent des estimations globalement similaires de l'impact évolutif de diverses stratégies au fil du temps.
- Reconnaissant que l'objectif de la comparaison des modèles est de comprendre les principaux moteurs des résultats (c'est-à-dire la transparence de la dynamique et des processus de la maladie), le Comité a estimé que l'harmonisation, les différences de paramétrage, les similitudes et les différences structurelles entre les modèles devraient être communiquées de manière transparente.
- Dans le cadre d'un programme de recherche à plus long terme, il faudrait, dans la mesure du possible, travailler davantage en tenant compte de l'hétérogénéité de l'emplacement géographique ou de la structure des contacts du réseau sexuel ou des deux. Il est probable que l'équilibre à long terme recherché est directement lié au degré d'hétérogénéité. Dans l'idéal, les modélisateurs du PVH devraient communiquer avec les modélisateurs de l'infection à VIH et d'autres maladies sexuellement transmissibles pour élaborer des données et des méthodes permettant de remédier à cette hétérogénéité.

Collaborative model comparison

- The Committee acknowledged that the modellers responded to the questions of whether cervical cancer elimination is feasible and whether the strategies for achieving global cervical cancer elimination are suitable. However, the Committee considered it more important to determine the gains at different milestones (e.g. 2030, 2045 or 2060), recognizing that vaccinated cohorts grow and become adults who are (or are not) protected against cervical cancer.
- IVIR-AC considered that the thresholds for elimination should not be defined before modelling but in the light of evidence from modelling on the feasibility, cost-effectiveness, financial resources required, health systems implications and public health impact of different options.
- The Committee indicated that focusing on arbitrary long-term elimination targets will under-emphasize the most important public health impacts – massive reductions in cervical cancer cases and mortality – whether or not such targets are formally reached in the distant future.

Comparaison collaborative des modèles

- Le Comité a reconnu que les modélisateurs ont répondu à la question de savoir si l'élimination du cancer du col de l'utérus était réalisable et si les stratégies d'élimination mondiale du cancer du col étaient appropriées. Toutefois, le Comité a jugé plus important de déterminer les gains à différentes étapes (par exemple 2030, 2045 ou 2060), en reconnaissant que les cohortes vaccinées grandissent et deviennent des adultes qui sont (ou ne sont pas) protégés contre le cancer du col de l'utérus.
- L'IVIR-AC a estimé que les seuils de l'élimination ne devraient pas être définis avant la modélisation, mais à la lumière des résultats de la modélisation sur la faisabilité, le rapport coût-efficacité, les ressources financières nécessaires, les répercussions sur les systèmes de santé et l'impact des différentes options sur la santé publique.
- Le Comité a indiqué que le fait de se concentrer sur des cibles arbitraires d'élimination à long terme conduira à sous-estimer les effets les plus importants sur la santé publique – réduction massive des cas de cancer du col de l'utérus et de la mortalité associée. À que ces cibles soient officiellement atteintes ou non dans un avenir lointain.

- The Committee expressed concern about the use of the term “elimination” and suggested an alternative term, such as “massive reductions in disease” or “advanced control of disease”.
- The time frame of up to 100 years to reach thresholds may give rise to concern about the public health significance of the conclusions. Demonstration of the percentage decrease in cases accumulated at different times might be preferable, as it will provide highly useful information about the impact of different strategies over time. The percentage decrease could be presented as a complement to results showing whether a specific strategy reduces cancer incidence below the defined low threshold in the distant future.
- Aside from cancer incidence, intermediate outcomes should be considered, such as the incidence of pre-cancerous lesions and prevalence of infection.
- The Committee suggested revision of the concept of threshold targets in light of the model results (e.g. proportionate reduction instead of absolute incidence). It is paradoxical that the same countries that are unable to meet the arbitrary thresholds will benefit most in terms of reduced numbers of cases.
- One of the planned next steps, the economic analysis, should focus on the marginal costs and marginal benefits over time, both with and without discounting.
 - The marginal benefits should include the percentages of cases and deaths averted, life-years gained and DALYs averted from cervical cancer and other cancers.
 - In terms of marginal costs, care should be taken to document the most influential time-dependent, scale-specific costs of setting up and maintaining screening and of scaling up and maintaining high vaccination coverage. Consideration should also be given to the changing costs of vaccines, screening and cancer treatment over time and to the opportunity costs to local health systems of undertaking cervical cancer control campaigns (e.g. diversion of human and physical resources to campaigns rather than routine tasks).
- Le Comité s’est déclaré préoccupé par l’emploi du terme «élimination» et a suggéré un autre terme, tel que «réduction massive de la maladie» ou «maîtrise avancée de la maladie».
- L’échéance pour atteindre les seuils, qui peut aller jusqu’à 100 ans, peut donner lieu à des préoccupations quant à la signification des conclusions pour la santé publique. Il serait peut-être préférable de démontrer la diminution en pourcentage du nombre de cas accumulés à différents moments, car elle fournira des renseignements très utiles sur l’impact des différentes stratégies au fil du temps. Cette diminution en pourcentage pourrait être présentée comme complémentaire aux résultats montrant si une stratégie donnée ramène l’incidence du cancer en dessous du seuil bas défini dans un avenir lointain.
- Outre l’incidence du cancer, il faut tenir compte des résultats intermédiaires, comme l’incidence des lésions précancéreuses et la prévalence de l’infection.
- Le Comité a suggéré de réviser le concept de seuils cibles à la lumière des résultats de la modélisation (par exemple la réduction proportionnelle plutôt que l’incidence absolue). Il est paradoxal que les pays qui ne sont pas en mesure d’atteindre les seuils arbitraires en tireront le plus grand bénéfice en termes de réduction du nombre de cas.
- L’une des prochaines étapes prévues, l’analyse économique, devrait porter sur les coûts marginaux et les avantages marginaux dans le temps, avec et sans décote.
 - Les avantages marginaux doivent inclure les pourcentages de cas et de décès évités, les années de vie gagnées et les années de vie ajustées sur l’incapacité évitées du cancer du col utérin et d’autres cancers.
 - En termes de coûts marginaux, il faut veiller à documenter les coûts qui ont le plus d’impact en fonction du temps et de l’échelle liés à la mise en place et au maintien du dépistage et à l’extension et au maintien d’une couverture vaccinale élevée. Il convient également de tenir compte de l’évolution des coûts des vaccins, du dépistage et du traitement du cancer au fil du temps, ainsi que du manque à gagner pour les systèmes de santé locaux liés aux campagnes de lutte contre le cancer du col (par exemple le détournement des ressources humaines et matérielles vers des campagnes plutôt que vers des tâches de routine).

Theme 2: Research to evaluate the impact of vaccines currently in use

Session 3: Total system effectiveness (TSE)

Introduction

In response to IVIR-AC recommendations in March 2018, the TSE project was revised. IVIR-AC’s assessment of the methods and tools used to support country-level uptake of vaccines and/or research and development decisions were requested.

RECOMMENDATIONS

- IVIR-AC expressed appreciation for the work on TSE. In particular, it commended the team for

Thème 2: Recherche pour évaluer l’impact des vaccins actuellement utilisés

Session 3: Efficacité totale du système (ETS)

Introduction

En réponse aux recommandations de l’IVIR-AC en mars 2018, le projet ETS a été révisé. Il a été demandé à l’IVIR-AC d’évaluer les méthodes et les outils utilisés pour soutenir l’adoption des vaccins et/ou les décisions en matière de recherche et développement au niveau national.

RECOMMANDATIONS

- L’IVIR-AC s’est félicité des travaux réalisés sur l’ETS. En particulier, il a félicité l’équipe d’avoir radicalement rema-

having radically redesigned the platform on the basis of feedback from country pilot studies and partners.

- The excellent flexibility of the new TSE interface allows countries to use self-defined criteria. However, TSE should be aligned with and ideally embedded into other priority-setting initiatives in countries, such as efforts to strengthen health technology assessments and national immunization technical advisory committees, to avoid duplication of efforts in countries, such as priority-setting initiatives led by WHO, the World Bank and the International Decision Support Initiative.
- There is a need to ensure that TSE actually provides useful market signals to vaccine developers, including developers of vaccines targeted to LMICs, in view of the long time (>10 years) required to develop a new vaccine. It would be useful to get input from vaccine developers on the characteristics of TSE that would be most helpful to them in deciding whether to develop and market vaccines.
- The term “TSE” suggests inclusion of elements other than vaccines and immunization and should therefore be reconsidered. The Committee suggests “immunization-related health technology assessment” and “evidence-based decision-making for priority-setting of vaccines and immunization programmes”.

Session 4: Measles–rubella investment case and intervals between supplementary immunization activities (SIAs)

Introduction

In March 2018, IVIR-AC formed a measles–rubella working group to assess modelling for the measles eradication investment case and the timing of SIAs. They reviewed the KidRisk model, which was used to assess elimination goals that had already been reviewed by IVIR-AC’s predecessor, Quantitative Immunization and Vaccine-related Research Advisory Committee, in October 2011, September 2012 and November 2013.

After the 2011–2013 reviews, it was suggested that the model be revised and resubmitted to IVIR-AC; however, it has not been reviewed by IVIR-AC since 2013. During the past few months, it was reviewed by the IVIR-AC measles–rubella working group, which concluded that further details would have to be clarified before it could recommend that the work be used to inform global policy.

After the IVIR-AC meeting in March 2018, an update was provided on the optimal intervals between SIAs to achieve immunity in populations, avoid measles outbreaks and make progress towards regional elimination of measles.

RECOMMENDATIONS

Investment case

- IVIR-AC agreed with the conclusions of the Committee’s working group on measles and rubella.

nié la plate-forme sur la base des observations issues des études pilotes nationales et des partenaires.

- L’excellente flexibilité de la nouvelle interface ETS permet aux pays d’utiliser des critères personnalisés. Toutefois, l’ETS devrait être aligné sur d’autres initiatives d’établissement des priorités dans les pays, et idéalement intégrées à celles-ci, par exemple en renforçant l’évaluation des technologies de la santé et les comités consultatifs techniques nationaux sur la vaccination, afin d’éviter le chevauchement des efforts dans les pays, comme les initiatives d’établissement des priorités menées par l’OMS, la Banque mondiale et l’International Decision Support Initiative.
- Il est nécessaire de s’assurer que l’ETS fournit effectivement des signaux de marché utiles aux développeurs de vaccins, y compris les développeurs de vaccins destinés aux pays à revenu faible et intermédiaire, compte tenu du temps long (>10 ans) nécessaire pour développer un nouveau vaccin. Il serait utile d’obtenir l’avis des développeurs de vaccins sur les caractéristiques de l’ETS qui leur seraient les plus utiles pour décider de développer et de commercialiser des vaccins ou non.
- Le terme «ETS» suggère l’inclusion d’éléments autres que les vaccins et la vaccination et devrait donc être reconsidéré. Le Comité suggère «évaluation des technologies de la santé liées à la vaccination» et «prise de décisions fondées sur des données probantes pour l’établissement des priorités en matière de vaccins et de programmes de vaccination».

Session 4: Argumentaire d’investissement dans la lutte contre la rougeole et la rubéole et intervalles entre les activités de vaccination supplémentaire (AVS)

Introduction

En mars 2018, l’IVIR-AC a constitué un groupe de travail sur la rougeole et la rubéole pour évaluer la modélisation de l’argumentaire d’investissement dans l’éradication de la rougeole et le calendrier des AVS. Le groupe a examiné le modèle KidRisk, qui a servi à évaluer les objectifs d’élimination déjà revus par le Comité consultatif sur la vaccination quantitative et la recherche liée aux vaccins, prédécesseur de l’IVIR-AC, en octobre 2011, septembre 2012 et novembre 2013.

Après les revues de 2011–2013, il a été suggéré que le modèle soit révisé et soumis de nouveau à l’IVIR-AC; toutefois, il n’a pas été examiné par le Comité depuis 2013. Au cours des derniers mois, le groupe de travail de l’IVIR-AC sur la rougeole et la rubéole a étudié le modèle et a conclu qu’il faudrait clarifier certains détails avant de pouvoir recommander l’utilisation de ces travaux pour éclairer la politique mondiale.

Après la réunion de l’IVIR-AC en mars 2018, une mise à jour a été fournie sur les intervalles optimaux entre les AVS pour que les populations soient immunisées, pour éviter les épidémies de rougeole et pour progresser vers l’élimination régionale de la rougeole.

RECOMMANDATIONS

Argumentaire d’investissement

- L’IVIR-AC a souscrit aux conclusions du groupe de travail du Comité sur la rougeole et la rubéole.

- It is important to measure the impact of measles and rubella elimination activities on the overall immunization system, including, for example, strengthening vaccination in the 2nd year of life and implementing school entry checks for not only measles and rubella but also all recommended antigens and providing those vaccines to children that require them.
- IVIR-AC supported the suggestion that another group model the impact of the elimination programme in order to address some of the concerns about the current model, potentially using innovative modelling approaches, to generate greater confidence in the results.

Intervals between SIAs

- IVIR-AC was impressed with the quality of the work presented on estimating intervals between SIAs, the potential impact of various methods and the analysis of the strengths and weaknesses of the models used.
- IVIR-AC emphasized that the models should indicate when both national and subnational SIAs should be conducted.
- For future modelling, IVIR-AC suggested that interruption of transmission, defined as at least 1 year with no sustained indigenous transmission, is a critical outcome to be considered with regard to SIA intervals and frequency.
- IVIR-AC made several recommendations on the need for and performance of SIAs in routine immunization programmes:
 - A need for SIAs indicates failure of the routine immunization programme to achieve the level of immunity required to interrupt transmission. As SIAs may disrupt both routine immunization systems and overall health systems, the impact of SIAs on these systems should be documented. Therefore, protocols should be developed to support programme managers in assessing the positive and negative impacts or opportunity costs of SIAs on overall systems, as previously recommended by IVIR-AC.
 - If an outbreak occurs after SIAs, it is important to investigate whether the cases are primarily due to accumulation in susceptible people born since the last SIA (i.e. an SIA is required earlier than predicted) or to a problem in implementation and coverage of previous SIAs. The latter may require follow-up SIAs that include older age groups. Outbreak investigations and better surveillance are required to identify and measure causes of vaccination gaps.
 - Although SIAs are needed now, the ultimate goal is routine vaccination systems that induce adequate population immunity to interrupt transmission, making SIAs unnecessary.

- Il est important de mesurer l'impact des activités d'élimination de la rougeole et de la rubéole sur l'ensemble du système de vaccination, y compris, par exemple, le renforcement de la vaccination au cours de la 2^e année de vie et la mise en œuvre de contrôles à l'entrée à l'école, non seulement pour la rougeole et la rubéole mais aussi pour tous les antigènes recommandés, et l'administration de ces vaccins aux enfants qui en ont besoin.
- L'IVIR-AC a appuyé la suggestion d'une modélisation de l'impact du programme d'élimination par un autre groupe afin de répondre à certaines des préoccupations suscitées par le modèle actuel, en utilisant éventuellement des méthodes de modélisation novatrices, de manière à accroître la confiance dans les résultats.

Intervalle entre les AVS

- L'IVIR-AC a été impressionné par la qualité du travail présenté sur l'estimation des intervalles entre les AVS, l'impact potentiel des différentes méthodes et l'analyse des forces et faiblesses des modèles utilisés.
- L'IVIR-AC a souligné que les modèles devraient indiquer quand les AVS nationales et infranationales doivent être menées.
- Pour la modélisation future, l'IVIR-AC a suggéré que l'interruption de la transmission, définie comme l'absence de transmission autochtone persistante pendant au moins 1 an, est un résultat essentiel à prendre en compte dans la détermination des intervalles et de la fréquence des AVS.
- L'IVIR-AC a formulé plusieurs recommandations sur la nécessité des AVS dans les programmes de vaccination systématique et sur leurs résultats:
 - Le besoin d'AVS indique que le programme de vaccination systématique n'a pas permis d'atteindre le niveau d'immunité requis pour interrompre la transmission. Comme les AVS peuvent perturber à la fois les systèmes de vaccination systématique et les systèmes de santé en général, l'impact des AVS sur ces systèmes devrait être documenté. Il faudrait donc élaborer des protocoles pour aider les gestionnaires de programme à évaluer les incidences positives et négatives ou le manque à gagner des AVS sur l'ensemble des systèmes, comme l'IVIR-AC l'avait recommandé.
 - Si une épidémie survient après une AVS, il est important de déterminer si les cas sont principalement dus à une accumulation chez des personnes sensibles nées depuis la dernière AVS (c.-à-d. qu'une AVS est requise plus tôt que prévu) ou à un problème dans la mise en œuvre et la couverture des AVS antérieures. Ces dernières peuvent nécessiter des AVS de suivi qui incluent des tranches d'âge plus âgées. Des enquêtes sur les épidémies et une meilleure surveillance sont nécessaires pour identifier et mesurer les causes des lacunes en matière de vaccination.
 - Bien que les AVS soient nécessaires maintenant, l'objectif ultime est de parvenir à des systèmes de vaccination systématique qui induisent une immunité suffisante de la population pour interrompre la transmission, rendant les AVS inutiles.

Session 5: WHO guide on typhoid vaccine cost-effectiveness

Introduction

The availability of new Vi-tetanus toxoid conjugate vaccines against typhoid is likely to increase the demand for evaluation of cost-effectiveness and affordability, to inform national vaccination strategies. Currently, there are few economic evaluations of typhoid vaccination, and a wide range of methods was used in the available studies. IVIR-AC was asked to comment on draft guidelines for economic evaluation of typhoid vaccination.

RECOMMENDATIONS

- The Committee proposed that the similarities and differences between typhoid vaccine-specific and general guidelines for economic evaluation be clearly articulated.
- A number of elements critical to conducting economic evaluations of typhoid vaccination should be explained further, including:
 - the use of dynamic modelling to evaluate the impact of chronic carriage;
 - specification of essential unknowns and uncertainties (e.g. duration of vaccine protection);
 - consideration of broader impacts, such as reduction of antimicrobial resistance and equity; and
 - a description of “current practice” and health system constraints, such as the delivery platforms used (routine versus campaign delivery) and use of routine health services.
- The document would be clearer if:
 - equations and diagrams were used to illustrate different modelling approaches;
 - it advocated for rigorous model parametrization and quantification of uncertainty;
 - it advocated for modelling of discrete entities when possible;
 - it stressed out-of-sample validity and mentioned cross-validation as desirable; and
 - it indicated consistency with WHO’s general guidelines on economic evaluation of vaccination programmes and where it adds further detail to those guidelines.

Session 6: Multi-model comparison guidelines

Introduction

In May 2016, evaluation of a systematic review of vaccine-related model comparisons, which was presented to IVIR-AC, indicated that the process and technical procedures for comparing mathematical models should be standardized. A meeting was held in June 2018 in London, hosted by the London School of Hygiene and

Session 5: Guide de l’OMS sur le rapport coût-efficacité des vaccins antityphoïdiques

Introduction

La disponibilité de nouveaux vaccins conjugués contenant l’anatoxine Vi-tétanique contre la typhoïde est susceptible d’accroître la demande d’évaluation du rapport coût-efficacité et de l’accessibilité financière, afin de guider les stratégies nationales de vaccination. Actuellement, il existe peu d’évaluations économiques de la vaccination antityphoïdique, et un large éventail de méthodes a été utilisé dans les études disponibles. Il a été demandé à l’IVIR-AC de commenter le projet de lignes directrices pour l’évaluation économique de la vaccination antityphoïdique.

RECOMMANDATIONS

- Le Comité a proposé que les similitudes et les différences entre les lignes directrices spécifiques au vaccin antityphoïdique et les lignes directrices générales pour l’évaluation économique soient clairement énoncées.
- Un certain nombre d’éléments essentiels à la réalisation d’évaluations économiques de la vaccination contre la typhoïde devraient être expliqués plus en détail, notamment:
 - l’utilisation de la modélisation dynamique pour évaluer l’impact du portage chronique;
 - la spécification des inconnues et des incertitudes essentielles (par exemple la durée de la protection vaccinale);
- la prise en compte d’effets plus étendus, tels que la réduction de la résistance aux antimicrobiens et l’équité; et
- une description des «pratiques actuelles» et des contraintes du système de santé, telles que les plateformes de prestation utilisées (prestation systématique par opposition à prestation lors de campagnes de vaccination) et l’utilisation des services de santé courants.
- Le document serait plus clair si:
 - des formules et des diagrammes étaient utilisés pour illustrer différentes approches de modélisation;
 - il préconisait une paramétrisation rigoureuse des modèles et une quantification de l’incertitude;
 - il préconisait la modélisation d’entités discrètes dans la mesure du possible;
 - il soulignait la validité hors échantillon et mentionnait la validation croisée comme il est souhaitable de le faire; et
 - il était conforme aux lignes directrices générales de l’OMS sur l’évaluation économique des programmes de vaccination et ajoutait des précisions à ces lignes directrices.

Session 6: Lignes directrices pour la comparaison de plusieurs modèles

Introduction

En mai 2016, l’évaluation d’une revue systématique des comparaisons de modèles liés au vaccin, qui a été présenté à l’IVIR-AC, indiquait que le processus et les procédures techniques pour comparer les modèles mathématiques devraient être standardisés. Une réunion s’est tenue en juin 2018 à Londres, accueillie par la London School of Hygiene and Tropical Medicine, afin

Tropical Medicine, to learn from other comparisons of infectious disease models and to prepare guidelines for comparisons of models. A first draft of the guidelines was presented to IVIR-AC for feedback.

RECOMMENDATIONS

- The Committee endorsed the processes established for development of the guidelines for comparing models.
- The document should emphasize that the purpose of model comparisons is to provide the best possible input to policy-making. Model comparisons are only one aspect of the process, which also includes data-sharing, conveying a sense of ownership of the model to decision-makers and communicating results. The whole process might better be referred to as “meta-modelling”.
- Early in multi-modelling, there should be discussion and explicit agreement on the mechanisms represented in the models, such as the dynamics of disease transmission from person to person, the natural history of disease and disease expression and the efficacy of available treatments.
- Each modelling group should be free to represent and parameterize these processes as it sees fit, but agreement on shared processes would allow sharper analysis of differences in outcomes.
- To facilitate comparisons, each model should be described in several ways, ideally in words, diagrams, equations and computer code.
- A valuable “by-product” of model comparisons to support decisions is identification of critical gaps in scientific knowledge and in data availability that prevent robust, valid conclusions (e.g. value of information analyses). These gaps should be identified and presented to decision-makers so that they might invest in new research and data collection to advance future decision-making.
- IVIR-AC recommended that the guidelines for model comparisons:
 - include recommendations on the description of models, including how structures differ;
 - recommend use of different types of model (with different structures);
 - indicate what to do if model outputs differ; and
 - recommend use of intermediate outputs (e.g. infection) in addition to final outputs (e.g. disease).

Theme 3: Research to improve methods for monitoring immunization programmes

Session 7: Data for risk analysis

Introduction

An unexpected worldwide surge in outbreaks of diphtheria in the past few years, coupled with a global shortage

de tirer des enseignements d'autres comparaisons de modèles de maladies infectieuses et de préparer des lignes directrices pour la comparaison de modèles. Une première ébauche des lignes directrices a été présentée à l'IVIR-AC pour commentaires.

RECOMMANDATIONS

- Le Comité a approuvé les processus établis pour l'élaboration des lignes directrices relatives à la comparaison des modèles.
- Le document devrait souligner que l'objectif de la comparaison de modèles est d'apporter la meilleure contribution possible à l'élaboration des politiques. La comparaison de modèles n'est qu'un aspect du processus, qui comprend également le partage des données, la transmission d'un sentiment d'appropriation du modèle aux décideurs et la communication des résultats. L'ensemble du processus pourrait plutôt être appelé «méta-modélisation».
- Au début de la modélisation multiple, il faut discuter et s'entendre explicitement sur les mécanismes représentés dans les modèles, comme la dynamique de la transmission de la maladie d'une personne à l'autre, l'histoire naturelle de la maladie et son expression et l'efficacité des traitements disponibles.
- Chaque groupe de modélisation devrait être libre de représenter et de paramétrer ces processus comme bon lui semble, mais un accord sur les processus partagés permettrait une analyse plus précise des différences dans les résultats.
- Pour faciliter les comparaisons, chaque modèle devrait être décrit de plusieurs façons, idéalement par des mots, des diagrammes, des formules et du code informatique.
- Un «sous-produit» précieux de la comparaison de modèles pour appuyer les décisions est l'identification des lacunes critiques dans les connaissances scientifiques et la disponibilité des données qui empêchent de tirer des conclusions solides et valables (par exemple la valeur des analyses de l'information). Ces lacunes doivent être identifiées et présentées aux décideurs afin qu'ils puissent investir dans de nouveaux travaux de recherche et collecte de données pour faire avancer les décisions futures.
- L'IVIR-AC recommande que les lignes directrices pour la comparaison de modèles:
 - incluent des recommandations sur la description des modèles, y compris la façon dont les structures diffèrent;
 - recommandent l'utilisation de différents types de modèles (avec des structures différentes);
 - indiquent ce qu'il faut faire si les résultats des modèles diffèrent; et
 - recommandent l'utilisation de résultats intermédiaires (par exemple l'infection) en plus des résultats finaux (la maladie).

Thème 3: Recherche pour améliorer les méthodes de suivi des programmes de vaccination

Session 7: Données pour l'analyse des risques

Introduction

Une résurgence mondiale inattendue de flambées épidémiques de diphtérie au cours des dernières années, conjuguée à une

of diphtheria antitoxin (DAT), highlighted the urgency of understanding where outbreaks might occur in the future. An MS Excel® tool developed by the Centers for Disease Control and Prevention in the USA and WHO was presented to IVIR-AC for review. The purpose of the tool is to predict the level of risk for a diphtheria outbreak by country in order to inform vaccination policy to prevent future epidemics and thus the demand for DAT, providing manufacturers with an appropriate timeline and quantity for production.

Researchers at the University of Pittsburgh (USA) introduced “Project Tycho – Data for Health” for making data usable for decisions in countries.

RECOMMENDATIONS

Pragmatic tool to identify immunization gaps

- IVIR-AC recognized the value of a diphtheria risk survey form for guiding EPI managers in high-burden countries.
- More experience in maintaining the currency of data and the experience of programme managers in using these graded criteria-based assessments of risk to guide vaccination priorities will further improve the survey methods and their effective use.
- The correlation between predictions and outcomes and continued improvement of the tool should be assessed continuously.
- As the work proceeds, more sophisticated analytical methods for weighting should be considered to improve the usefulness of the survey data. These methods could be used to determine the weights given to different criteria, without further complicating the tool currently used by programme managers.
- The risk model for diphtheria outbreaks could be considered a template for other diseases.

Vaccine decision information systems

- Notwithstanding needs for better data on vaccines and populations, the compilations of existing data at various levels of granularity are a welcome addition to the available resources.
- Current work on a database of findable, accessible, interoperable and re-usable (“FAIR”) data is encouraged. How these data might be used to guide research and programmes in global, national and local health systems will benefit from further consideration and refinement as the work proceeds. ■

pénurie mondiale d'antitoxines diphtériques, a mis en lumière l'urgence de comprendre où les flambées épidémiques pourraient se produire dans le futur. Un outil MS Excel® mis au point par les *Centers for Disease Control and Prevention* aux États-Unis et l'OMS a été présenté à l'IVIR-AC pour examen. La finalité de cet outil est de prédire le niveau de risque d'une épidémie de diphtérie par pays afin d'éclairer la politique de vaccination pour prévenir de futures épidémies et donc la demande d'antitoxine diphtérique, en indiquant aux fabricants un calendrier et un volume appropriés de production.

Des chercheurs de l'Université de Pittsburgh (États-Unis) ont introduit le «Project Tycho – Data for Health» pour rendre les données utilisables aux fins des décisions dans les pays.

RECOMMANDATIONS

Outil pragmatique pour identifier les lacunes en matière de vaccination

- L'IVIR-AC a reconnu la valeur d'un formulaire d'enquête sur le risque de diphtérie pour guider les gestionnaires du PEV dans les pays à forte charge de morbidité.
- Une plus grande expérience de la mise à jour des données et l'expérience des administrateurs de programme dans l'utilisation de ces évaluations des risques gradées fondées sur des critères pour guider les priorités en matière de vaccination permettront d'améliorer encore les méthodes d'enquête et leur utilisation concrète.
- La corrélation entre les prévisions et les résultats et l'amélioration continue de l'outil devrait être évaluée en permanence.
- Au fur et à mesure de l'avancement des travaux, des méthodes analytiques plus sophistiquées de pondération devraient être envisagées afin d'améliorer l'utilité des données de l'enquête. Ces méthodes pourraient être utilisées pour déterminer les pondérations accordées aux différents critères, sans compliquer davantage l'outil actuellement utilisé par les administrateurs de programme.
- Le modèle de risque pour les épidémies de diphtérie pourrait être considéré comme un modèle pour d'autres maladies.

Systèmes d'information pour les décisions en matière de vaccins

- Malgré la nécessité de disposer de meilleures données sur les vaccins et les populations, les compilations de données existantes à différents niveaux de granularité constituent un complément utile aux ressources disponibles.
- Les travaux en cours sur une base de données d'informations trouvables, accessibles, interopérables et réutilisables («FAIR») sont encouragés. La manière dont ces données pourraient être utilisées pour orienter la recherche et les programmes dans les systèmes de santé mondiaux, nationaux et locaux bénéficiera d'un examen et d'une mise au point plus approfondis au fur et à mesure de l'avancement des travaux. ■

Executive Summary

Material included in the Yellow Book

1. Executive Summary of the report of the WG
2. Report of the SAGE Working Group on Quality and Use of Immunization and Surveillance Data”
 - Annexes and references included on the SharePoint
 - Sections include:
 - 1) Introduction and Methods
 - 2) Landscape of immunization and surveillance data availability, quality, use and guidance for countries
 - 3) Governance: Leadership, Policies, and Standards to Maximize the Data Quality and Use
 - 4) People: Building Workforce Capacity in the Generation and Use of Immunization Data
 - 5) Tools: Information Systems and the Risks and Benefits of Novel Approaches
 - 6) Assessment and Improvement Planning: Data Use for Continuous Quality Improvement
 - 7) Evidence gaps and research agenda
 - 8) Moving Forward
 - 9) Proposed recommendations
 - Sections 3-6 include a box with Key Messages at the beginning and conclusion at the end
 - Section 9 proposes recommendations and indicates for which level (country, regional, global) and links to the section of the report that contains the evidence
3. Immunization Data: Evidence for Action (IDEA) Precis of the “Realist Review of What Works to Improve Data Use for Immunization Evidence from low- and middle-income countries” (PATH/PAHO)

Supplemental material on the SharePoint

- All annexes to the Report: literature reviews, case studies, white papers and full list of references

Purpose of session: summarize major WG findings for each one of its 6 terms of reference, present a way forward and proposed recommendations

Target outcomes: SAGE to consider and endorse WG recommendations

Specific questions for SAGE: for SAGE to discuss major recommendations i.e., queries for direction.

Background

Concerns about the quality and use of immunization and vaccine-preventable disease (VPD) surveillance data have been highlighted on the global agenda –including by the SAGE – for more than two decades. The demand for accurate data and their use in programme management and decision-making has only increased as countries strive to meet the ambitious vaccination coverage and disease elimination goals of the Global Vaccine Action Plan (GVAP). These agreed upon goals require new, more precise and finer types of measurements than have often been used in many low- and middle-income countries. Improved information systems and data quality will also be critical to measuring progress in achieving the Sustainable Development Goals (SDGs) and Universal Health Coverage (UHC), such as improvements in equity of service delivery and in reaching under-served, marginalized, and migrant populations.

Recent efforts by countries and immunization partners to improve immunization-related data have resulted in successes in a number of countries. However, poor quality and under use of data remain a persistent problem in many, affecting the ability of countries and partners to monitor progress against the GVAP and other global goals as well as to support optimal changes to immunization programmes. In fact, SAGE assessment reports of GVAP implementation stated that poor data quality was impeding programme improvement, and recommended that improving data quality should be a top priority for national immunization programmes.

As a concrete measure to address this ongoing problem, the SAGE Working Group (WG) on the Quality and Use of Global Immunization and Surveillance Data was established in August 2017. Its mandate was to:

- Review current practices in the collection, use and impact of national, regional and global immunization and surveillance data, as well as data quality and gaps in data collected;
- Review existing guidance and standards for immunization programme monitoring and VPD surveillance and identify gaps;
- Review and assess the current ‘state’ of immunization and VPD-surveillance data quality at country and global level;
- Examine the factors limiting the quality and use of both immunization and VPD surveillance;
- Examine the effectiveness of various interventions to improve data access, quality and use; and
- Identify gaps in knowledge to inform a research agenda around data quality and use, and to propose recommendations for action.

Methods and definitions

A series of landscape analyses (involving key informant interviews and document reviews), literature reviews, country case studies and data analyses (data triangulation exercises) was conducted by the WG, consultants and partners to fulfill the terms of reference of the WG and prepare this report. Detailed reports for many of these reviews and analyses can be found in the Annexes, along with full versions of the case studies.

The WG used a definition of data quality as *data that are accurate, precise, relevant, complete and timely enough for the intended purpose (or “fit-for-purpose”)*, such as to monitor programme performance, support efficient programme management or provide evidence for decision-making. The structure of the report presents the current landscape and is based on a simplified theory of change, which identifies five the pillars – Governance, People, Tools, and Processes for Continuous Quality Improvement, and Evidence required to produce data that are available, fit-for-purpose and used for action.

Major findings and key points

The availability, quality and use of immunization and surveillance data, data-related guidance and assessment methods

There is a considerable amount and variety of immunization and surveillance-related data available nationally, regionally, and globally, though the data are not always accessible to those that need them the most. However, when evaluated, the quality of these data is still often poor, especially in low- and middle-income countries, with inaccuracies in denominators used to calculate immunization coverage or disease incidence rates being particularly pronounced. The WHO-UNICEF Joint Reporting Form (JRF) and WHO-UNICEF estimates of national immunization coverage (WUENIC) remain key sources of immunization data available internationally. There is also increased demand for the collection of disaggregated data for immunization and VPD surveillance (e.g., subnational; individual-level) to support achieving program objectives. The new global electronic platforms and strategies, including the WHO Immunization Information System (WIISE) (which will include an e-JRF), the WHO Immunization Data Handbook and related Immunization Monitoring Academy and the global Comprehensive VPD Surveillance Strategy, should help improve the quality and use of immunization and surveillance data.

In recent years, a plethora of global and regional guidance documents and standards have been developed to address issues related to monitoring, data quality and use. However, awareness of these tools among people working in immunization and VPD surveillance and their ability to find and access these tools needs to improve. In addition, the review found a continued lack of practical guidance and tools for a number of technical areas. Tools for countries to assess data quality – such as the Data Quality Self-assessment (DQS) and Data Quality Review (DQR) tools – have improved over the years and have had a positive impact on country ownership and interest in making data improvements in a number of countries, with some evidence of positive impact as well on data quality and use. More work is needed to define a common lexicon of definitions around data and a standard set of indicators to measure data quality and use, as part of comprehensive programme monitoring.

Governance related to immunization and VPD surveillance data and information systems

Having strong policies and mechanisms in place that govern all key aspects of data generation and use is important to develop immunization and VPD surveillance information systems that produce high-quality, credible data that are useful to monitor programmes, to keep them accountable for their performance, and inform policy decisions. Coordination and collaboration between different units dealing with data (e.g., immunization programme, labs, surveillance units), between partners and the government, as well as across the entire health care system is crucial to establish efficient, harmonized information systems, and to avoid systems that are fragmented and duplicative. Strong leadership within national governments and the political will to improve data quality — even if it initially leads to lower reported performance — are also critical to ensure the sufficient resources, key policies and regulations, and development of a “data use culture” needed for improvements. Also key is the establishment of national standards governing all stages of data generation and use, and having policies and mechanisms in place for sharing data both within countries (e.g., data from the private sector and NGOs/CSOs) and internationally, while also taking issues of privacy and confidentiality into account.

Building the capacity of the health workforce in data generation and use

The lack of skills among health workers in data collection, analysis, interpretation and use, as well as a lack of capacity-building in this area, are key factors limiting the quality of immunization and VPD surveillance data. This report recognizes that data quality at all levels ultimately depends on the quality of data collection at the health facility level, and thus data quality interventions, including capacity-building and creating an enabling environment, must specifically target the local level. In addition, data-related activities often compete with clinical duties for health workers' time, thus impacting the quality, completeness and timeliness of reporting. Improving this situation requires a multi-pronged approach — including pre-service and in-service training, with regular reinforcement through supportive supervision, and feedback — as well as dedicated time for data-related tasks taking into consideration in workforce planning.

The reviews found that current pre-service training programmes often do not adequately prepare health workers to carry out data-related tasks, even in high-income countries, nor has most in-service training around data had a major impact in improving the skills and practices of health workers. Governments therefore need to make a dedicated effort to provide continuous and effective competency-based training on the generation and use of health data, based on the data-related responsibilities required at all levels of the health system. The WG has developed a framework that defines the roles and responsibilities of health workers in collecting, analyzing and using immunization data from the facility to the global level in order to assist countries in planning their capacity-building activities related to immunization data and information systems.

The role of technological innovations in improving data quality and use and their limitations

Health workers need user-friendly tools (either paper or electronic) that make their jobs easier and more efficient. Recent advances in information and communication technology (ICT) have led to a multitude of innovative tools developed with the aim of improving data quality, availability and use. Immunization information systems are currently immunization-specific tools or part of an integrated health management information system, such as DHIS2, and challenges with both approaches exist. Innovative “e-Health” tools used in immunization and disease surveillance programmes range from electronic immunization registries (EIRs) to decision-support tools (such as dashboards), mobile technologies to enable real-time data collection, reporting and monitoring; geospatial-based tools (e.g., GIS) and predictive analytics to improve coverage and population estimates.

While there is evidence that some of these tools improve data quality and use, many — with the exception of electronic information systems, such as DHIS2 and some EIRs — never get rolled out nationally, nor thoroughly evaluated. Some innovations have failed because they ignored country context, user requirements, and issues of interoperability with existing systems. This highlights the fact that technology solutions are not a magic bullet for solving all data problems, but rather the successful use and scale-up of these innovations depends to a large extent on other key elements being in place, including a skilled and motivated workforce, strong governance, sustainable financing, adequate infrastructure, such as computers and connectivity, and clear operating procedures and processes. Global guidance is also needed on how and when to scale up innovations to ensure a sustained, long-term benefit on data quality and use.

Use of immunization and surveillance data for continuous quality improvement

There is evidence to suggest that improving the quality of immunization and VPD surveillance data on a periodic basis can only go so far, and that using a continuous quality improvement (CQI) approach has the potential for greater and longer-lasting improvements. This approach should start with an assessment of the

root causes of poor data quality extending down to the lowest level of the health system. Limited evidence also indicates that increasing the use of data can improve data quality, though not necessarily the other way round. However, gaps in data use and data use capacity abound at all levels.

Solutions proposed as part of a continuous quality improvement approach include a shift from periodic data quality assessments to routine monitoring of data quality, including automated data validation checks and analyses on electronic information systems; and the better use of existing, under-utilized data, such as surveillance, rapid coverage monitoring, and vaccine supply data, to create a fuller picture of programme performance. They also include the “triangulation” of data to synthesize evidence across different data sources to address relevant questions for program planning and decision-making (e.g., checking data quality, prioritizing areas for intervention, estimating coverage/denominator, evaluating program impact/effectiveness). Such data triangulation analyses should be the default for public health analysis.

In line with the goals of improving equity of services across populations and geographic areas, better measures, tools and indicators need to be developed to monitor equity on a regular basis. Similarly, current methods for measuring and estimating vaccination coverage must be adjusted to accommodate the shift towards a life-course vaccination approach. Methods for improving estimates of target populations, including dealing with migration, remain among the needs that are most critically felt at the local programme level.

Gaps in evidence and the research agenda and recommendations

This report identifies and maps out gaps in evidence and knowledge concerning key aspects affecting the quality and use of immunization and VPD surveillance data and proposes a research agenda based on these gaps, structured according to the pillars for improving data quality and use. In general, the Working Group found a need for more robust evaluation of the impact of various data quality and use interventions (e.g., tools, capacity building approaches), their cost-effectiveness, and their impact on staff time and efficiencies.

In Chapter 9 of the report, the Working Group has outlined specific recommendations for countries (national and subnational), regional and global levels under the following headers:

1. Embed monitoring of data quality into global, regional and country monitoring of immunization and VPD surveillance performance;
2. Increase workforce capacity and capability for data quality and use, starting at the lowest level where data collection occurs;
3. Take actions to improve the accuracy of immunization programme targets (denominators);
4. Enhance use of existing data at all levels for tailored action, including immunization programme planning, management, and decision-making;
5. Adopt a data-driven continuous quality improvement (CQI) approach as part of health system strengthening at all levels;
6. Strengthen governance around piloting and implementation of new information, communication, and technology (ICT) tools for immunization and surveillance data collection and use;
7. Improve data sharing and knowledge management across areas and organizations (e.g., private sector) for improved transparency and efficiency; and
8. WHO and UNICEF to strengthen global reporting and monitoring of immunization and surveillance data through a periodic needs assessment and revision process.

Report of the SAGE Working Group on Quality and Use of Immunization and Surveillance Data

April 2019

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List of Abbreviations

AEFI	Adverse events following immunization
AFP	Acute flaccid paralysis
AFR	African Region (WHO)
AMR	American Region (WHO)
CDC	Centers for Disease Control and Prevention (U.S.)
cMYP	Comprehensive multi-year plan
CQI	Continuous quality improvement
CSO	Civil society organization
DHS	Demographic Health Survey
DHIS2	District Health Information System 2
DIP	Data immunization plan
DIT	Data improvement team
DTP	Diphtheria-tetanus-pertussis
DTPCV	Diphtheria-tetanus-pertussis containing vaccine
DQA	Data quality audit
DQR	Data quality review
DQRC	Data quality record card
DQS	Data quality self-assessment
DVDMT	District vaccination data management tool
ECDC	European Centers for Disease Control
EHR	Electronic health record
EIR	Electronic immunization registry
EMR	Eastern Mediterranean region (WHO)
EPI	Expanded Programme on Immunization
EUR	European region (WHO)
GCC	Global Certification Commission
GIS	Geographic information system
GPEI	Global Polio Eradication Initiative
GVAP	Global Vaccine Action Plan
HBR	Home-based record
HIS	Health information system
HIV	Human immunodeficiency virus
HMIS	Health management information system
ICT	Information and communication technology
IDSR	Integrated disease surveillance and response
IHME	Institute for Health Metrics and Evaluation
IIS	Immunization information system
JRF	WHO/UNICEF Joint reporting form [for immunization data]

JSI	John Snow, Inc.
LGA	Local government area
LIC	Low-income country
LMIC	Low- and middle-income country
LMIS	Logistics management information system
MCV	Measles-containing vaccine
MICS	Multiple Indicator Cluster Survey
MLM	Middle-Level Management (training course)
MNT	Maternal and neonatal tetanus
NCC	National Certification Committee
NGO	Non-government organization
NITAG	National immunization technical advisory group
NT	Neonatal tetanus
NVC	National verification committee
OPV	Oral polio vaccine
PAB	Protection at birth (against tetanus)
PAHO	Pan American Health Organization
POLIS	Polio Information System
RCC	Regional certification commission
RI	Routine immunization
SAGE	Strategic Advisory Group of Experts (on immunization)
SDG	Sustainable development goals
SEAR	Southeast Asia region (WHO)
SMS	Short message service
TB	Tuberculosis
TORs	Terms of reference
TT	Tetanus toxoid
TTCV	Tetanus toxoid containing vaccine
UHC	Universal health coverage
UNICEF	United Nations Children's Fund
V3P	Vaccine Product, Price and Procurement
VF	Verification factor
VPD	Vaccine-preventable disease
WG	Working group
WHO	World Health Organization
WIISE	WHO Immunization Information System
WPR	Western Pacific Region (WHO)
WUENIC	WHO-UNICEF estimates of national immunization coverage
YF	Yellow fever

1. Introduction and Methods

1.1 Background

With the aim of supporting the planning and monitoring of national immunization programmes, the World Health Organization (WHO) and partners encourage countries to collect Expanded Programme on Immunization (EPI) data, including data on vaccine coverage, vaccine-preventable disease (VPD) surveillance, human resources, financing, vaccine and supply chain, service delivery, and safety.

Concerns about the quality of EPI data have been highlighted on the global agenda for more than two decades. In 1998, the Strategic Advisory Group of Experts (SAGE) reviewed analysis of officially reported vaccination coverage data¹ for 217 countries and territories that revealed many issues with internal consistency (20% of countries with >10% difference from one year to next; 15% of countries with >5% difference in vaccine doses given at same age) and lack of concordance with data obtained from other sources (17% of countries with >10% difference) during the period of 1991 to 1996 (1). Accordingly, SAGE recommended that the EPI intensify efforts and add resources to improve the quality and validation of national immunization data in the overall context of national health information systems strengthening (1). These recommendations eventually led to the development of the annual WHO and UNICEF estimates of national immunization coverage (WUENIC) for every country, based on a systematic analysis of data from various sources (2).

In 2007, WHO and partners published the Global Framework for Immunization Monitoring and Surveillance (GFIMS) that defined the necessary types of data and components for health systems to monitor and evaluate immunization programmes (3). In 2011, to enhance country ownership, monitoring and accountability of immunization service delivery under the Global Vaccine Action Plan (GVAP) (2011-2020), SAGE recommended efforts to improve the quality of national and subnational coverage and surveillance data (4). At this time, SAGE acknowledged the important role of the WUENIC estimates, but advised caution in interpreting coverage estimates for performance-based financing. The SAGE also recommended that WHO work towards improving coverage survey methods, developing guidelines for using biomarkers to validate vaccination coverage (e.g., serosurveys), and supporting countries to improve use of surveillance data for monitoring immunization programme performance and decision-making (4). SAGE assessment reports of GVAP implementation in 2013 and 2014 stated that poor data quality was impeding programme improvement, and recommended that improving data quality should be the number one priority for national immunization programmes (5).

Countries and immunization partners have made a number of efforts in recent years to improve the availability, quality, and use of immunization-related data. In 2015, SAGE highlighted that data quality improvement efforts were a major contributing factor in significant program gains achieved in several countries (5). And, in 2017, the Gavi Alliance established a “Strategic Focus Area” in immunization, surveillance, and safety data (“data SFA”) to allow for synchronized investments by countries and partners in data improvements (Box 1.1) (6).

However, data quality challenges continue to affect monitoring of GVAP, as well as progress in achieving the Sustainable Development Goals (SDGs) and Universal Health Coverage (UHC). Within the last few years, issues with data quality and use have been highlighted in most disease-specific presentations to SAGE (e.g., polio, measles, tetanus, diphtheria). In the 2016 GVAP mid-term assessment, SAGE also highlighted the need to improve VPD surveillance capacity and EPI data quality (5).

These ongoing concerns lead to the establishment of the SAGE Working Group (WG) on the Quality and Use of Global Immunization and Surveillance Data in August 2017. The WG terms of reference are shown in Box 1.2 (7). A *Global Framework to Strengthen Immunization and Surveillance Data for Decision-Making* was developed and reviewed by partners and the SAGE Data WG during the Data Partners Meeting in Cascais during 23–25 October 2017 (8) ([Annex 1](#)). A Post-2020 GVAP plan is currently under development, and the findings of this WG are relevant for informing data-related strategies in the plan (9).

¹ Bacillus Calmette–Guérin (BCG), 3rd dose of diphtheria-tetanus-pertussis (DTP3), hepatitis B, measles, 3rd dose of oral poliovirus (OPV3), 2nd or subsequent dose of tetanus toxoid (TT2+), and yellow fever vaccines.

Box 1.1. Major Immunization Data Partners and Initiatives

Major Immunization Data Partners

WHO — standards, immunization and surveillance data reporting, partner coordination

UNICEF — immunization and surveillance data reporting, logistics and stock management, digital health

Gavi, the Vaccine Alliance — funding for new vaccine introduction, health systems strengthening, targeted country assistance, partner projects on data quality and use through the data Strategic Focus Area (SFA)

Bill & Melinda Gates Foundation (BMGF) — funding and technical support for immunization and surveillance data quality and use

U.S. Centers for Disease Control and Prevention (CDC) — technical support for surveillance, workforce capacity, and evidence generation

European Centers for Disease Control (ECDC) — Immunization information systems and surveillance

PATH — digital health, evaluation of new interventions

John Snow Inc. (JSI) — capacity building and design of information systems and tools

Institute for Health Metrics and Evaluation (IHME) — research on disease modeling, data visualization

Major Initiatives Relevant to Immunization Data

BID Initiative (2013–2018) — an initiative led by PATH and funded by BMGF, that was designed in partnership with countries to enhance immunization and health service delivery through improved data collection, quality, and use. The BID Learning Network (BLN) was established to foster continuous learning and information sharing across countries to improve their data and decision-making.

Health Data Collaborative (HDC) — launched in 2016 as a partnership of international agencies, governments, philanthropies, and academics with the goal of strengthening country health information systems to meet the challenge of monitoring the health-related Sustainable Development Goals and boost the development of robust, sustainable national health monitoring systems.

Data Strategic Focus Area (SFA) — established by the Gavi Alliance in 2017 to allow for synchronized investments by countries and partners to improve immunization, surveillance, and safety data.

Box 1.2. Terms of Reference for the SAGE Data Working Group

1. Take stock of data availability and determine if there are unmet immunization monitoring and evaluation data needs at global and regional level, and suggest revisions for 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 and use at country, regional, and global level (including triangulation)
4. (a) Review evidence on factors that may cause and/or limit access to quality and use of immunization and VPD-surveillance data for decision-making at different levels
(b) Review evidence on 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.

1.2 Methods

Since its establishment in August 2017, the Data WG met during multiple teleconferences and three face-to-face meetings, including two Data Partners' Meetings (2017 and 2018). During the meetings, WG members outlined the scope of work, plans for completion, and progress, as well as had robust discussions on framing of the topic and recommendations. In addition, teleconferences with partners were conducted to orientate the WG about relevant work on the topic and related cross-cutting areas.

Data considered within the scope of this work were vaccine coverage, immunization program process indicators (e.g., vaccination sessions), vaccine supply, and VPD surveillance data.

1.2.1. Reviews and studies

A range of research methods were used to fulfill the terms of reference of the WG and develop this report. A series of landscape analyses; literature reviews; country case studies on different aspects of immunization and surveillance data and a data triangulation analysis were conducted by the WG members, consultants, or partners (see Box 1.3). It is important to recognize the significant contribution of WHO, UNICEF, Ministries of Health, and partner organizations who worked in close collaboration with the WG to complete the scope of work. Findings from their work are used throughout this report and also included as online Annexes.

Box 1.3. Studies and reviews conducted for this SAGE Data Working Group report (Annexes)

- Landscape analyses of:
 - Data availability, reporting and monitoring needs involving survey of 22 key informants (TOR1)
 - Immunization and surveillance guidance and standards, including survey of informants from six WHO Regional Offices (TOR2)
 - Data quality assessment approaches and indicators (TOR3)
 - Data triangulation use by immunization and other public health programs (TOR3)
 - Evidence gaps and research needs (TOR6)
- Literature and other reviews:
 - Immunization Data: Evidence for Action. A realist review of what works to improve data use for immunization, Evidence from low - and middle-income countries (LMICs) (TOR4b)
 - Scoping review of factors limiting quality of immunization data in LMICs (TOR4a)
 - Literature review of barriers limiting quality of and access to VPD surveillance data (TOR4a)
 - Scoping review of pre- and in-service training on immunization data in LMICs (TOR4a)
 - Literature review of novel approaches for immunization data (TOR5)
 - Literature review of novel methods for polio surveillance & applicability to other VPDs (TOR5)
- Triangulation analysis of tetanus vaccination and surveillance data (TOR3)
- Series of country case studies (various TORs)

The landscape analysis of data availability and monitoring needs involved interviews in person, by phone or by self-administered questionnaire of 22 key informants from all levels of WHO, partner agencies, ministries of health and other experts. Themes from qualitative findings were abstracted and summarized. Staff from the six WHO Regional Office were also administered a short questionnaire on available guidance and examples of the state of data use in the regions; UNICEF regions were also invited to participate. Separate landscape analyses of data quality assessment approaches and indicators, as well as data triangulation use by EPI and other health programs were also conducted. The latter was developed into a Global Framework on the Application of Public Health Data Triangulation for Immunization and Surveillance Programs, which is a joint product of the WG with WHO, UNICEF and CDC ([Annex 2](#)) (10). Evidence gaps and research needs were identified based on

review of meeting reports, background documents developed for the WG and key informant interviews; a research agenda was developed based on identified gaps.

The literature reviews included traditional reviews, as well as a “realist review” and several “scoping reviews” on key topics, including barriers to immunization and VPD surveillance data quality and use. Although differing slightly in terms of methodology,² all literature reviews included searches of electronic databases (e.g., Pubmed) to identify relevant published literature. Most also included a search of references from identified articles (“snowballing citations”), as well as consulting with experts to identify other relevant references, including from the grey literature.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology is usually used by the SAGE to critically evaluate evidence for making vaccine recommendations. However, the WG found that the present topic was not amenable to this methodology because the scope of work and questions posed to the WG were broad, and a lot of the related evidence was descriptive in nature. A majority of evidence came from the literature reviews and landscape analyses described in Box 1.3, and the published and grey literature identified therein. Published systematic reviews were used where available. Where there was a paucity of high-quality evidence, the WG employed expert opinion and consensus.

1.2.2 Relevant definitions

Vaccination coverage

Coverage is measured using one or more of the following approaches: (1) administrative-based approaches that utilize individual level vaccination registries (either paper-based or electronic immunization registries [EIRs]), or aggregated summary reports of administrative data to identify the number of vaccinated individuals, or (2) population-based household coverage surveys (11). This report primarily focuses on *administrative* vaccination coverage data since these data are readily available to programmes on a day-to-day basis. Population-based household coverage surveys are also conducted periodically to monitor vaccination coverage (e.g., every 5 years), but not everywhere and not frequently enough to provide information for regular programme management. Readers should be aware that similar data quality concerns and concurrent discussions are taking place around vaccination coverage surveys (see Chapter 2) (12, 13).

Administrative vaccination coverage requires data on a target population or the number of age-eligible children in a defined geographic area during a defined time period (the denominator), as well as data on the number of age-eligible children vaccinated (the numerator) from the same target population as the denominator. By dividing the number of age-eligible vaccinated children by the appropriate target population, programme staff are able to measure the percentage of the target population that has received a specific vaccine dose in a given geographic area during a specific time period.

VPD surveillance

These data provide vital information to help immunization programmes understand the burden and epidemiology of vaccine preventable diseases, and to assess vaccination impact, to inform programme policy and strategy. Specifically, disease surveillance helps establish the VPD burden, thus providing evidence for vaccine introduction, refinement of vaccination schedules and targeting vaccination campaigns. It also helps identify immunity gaps and unreached populations; enables the programme to monitor progress towards disease eradication, elimination and/or control goals; facilitates rapid detection and response to disease events of public health concern; facilitates documentation of short- and long-term effects of vaccination on disease burden and epidemiology, thereby monitoring programme effectiveness and impact; and enables detection of shifts in types or sub-types of organisms causing disease (14).

² A realist review is where the question of interest includes how and why complex social interventions work in certain situations, rather than assume they either do or do not work at all. A scoping review is a type of research synthesis that aims to 'map the literature on a particular topic or research area and provide an opportunity to identify key concepts; gaps in the research; and types and sources of evidence to inform practice, policymaking, and research. For more information on types of reviews please see: <https://www.ncbi.nlm.nih.gov/pubmed/26693720>.

VPD surveillance data comes from three types of surveillance: 1) passive notification of VPDs from healthcare providers, 2) active surveillance in which public health officers review hospital or clinic discharge data for specific VPDs, or 3) sentinel site surveillance typically occurring at specialized hospitals with high clinical and laboratory capacity. VPDs on lists of notifiable diseases typically have standardized case definitions for detection and reporting to the central public health authority. VPD data are reported through aggregate summary reports or individual-level case investigation forms (“case-based” data). Some diseases have both aggregate and case-based data and may also have additional data on healthcare visits by diagnosis reported through the health information system (14).

Data quality

The definition of data quality for immunization varies but has typically been described in two ways. The first defines quality as the degree to which the data represent the truth of a given reality at a specific point in time. Using this definition, data quality would be reflected by the accuracy of the measurement relative to an absolute truth and precision of the measurement. Because the absolute truth with regard to immunization program performance and disease burden is usually impossible to know, the first definition is of limited operational use. The second defines data quality as the degree to which data are “*fit for the intended purpose*.” This definition is arguably the more operationally relevant by combining various functional aspects of data quality and usability. Operational definitions used in this report are summarized in Box 1.4.

Box 1.4. Operational definitions used in this report

- **Data:** Measurement inputs that need to be processed into actionable information before action can be taken or decisions can be made (15).
- **Data availability:** Degree to which data relevant for decision-making can be reliably accessed by relevant persons.
- **Data quality:** Degree to which data are fit for the intended purpose (*see paragraphs below*).
- **Data use:** Degree to which data are actually used for a defined purpose, e.g., program management, planning, decision-making.
- **Culture of data use:** The customs, dispositions, and behaviors of a particular group or organization to support and encourage the use of evidence, including facts, figures, and statistics, to inform their decision-making (16).
- **Data triangulation:** An approach for critical synthesis of existing data from two or more data sources to address relevant questions for program planning and decision-making ([Annex 2](#)).

For the purpose of this report, the **WG further defined quality data as accurate, precise, relevant, complete, and timely enough for intended purpose** (Box 1.5). This was based on adaptation of a scheme by Bloland and MacNeil (17), after review of several schemes of data quality attributes (17-19) ([Annex 3](#)). Since accuracy and precision may be hard to measure, consistency, concurrence, and integrity in the case of evaluations of secondary data quality (i.e., stored data at higher levels), can be considered as proxies for accuracy and precision. It is important to note that implicit in the definition is the fact that data quality is context-specific, and fitness for purpose may vary by place, health system level, over time, or from user to user.

WHO defines public health surveillance as “the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice (20).” Most of the routine data collected for immunization programmes could be considered surveillance data under this broad definition. In 1988, the U.S. Centers for Disease Control and Prevention (CDC) published their first *Guidelines for Evaluating Surveillance Systems*, which has been updated periodically and adapted by WHO (21-23). According to the WHO Guide to Monitoring Communicable Disease Surveillance and Response Systems (2006), “the quality of the surveillance system is defined by attributes such as completeness, timeliness, usefulness, sensitivity, positive predictive value, specificity, representativeness, simplicity, flexibility, acceptability, and reliability (23).” Since routine data is product of a data collection system, it is probably not surprising that we observe

these terms to relate to a mix of system and data quality attributes (under the above definition of data quality as “fit for purpose,” including dimensions of quality and usability).

Box 1.5. Attributes of data quality, as defined as “fit-for-purpose”

- **Accuracy** — Degree of agreement between a given measurement and the actual (or true) value.
 - **Concurrence** (proxy) — Degree of agreement between different methods intended to measure the same construct.
 - **Integrity** (proxy) — Degree to which data, once entered into the official record, are not lost, incorrectly transcribed from one record to another, or otherwise altered from the original, i.e., accuracy of stored/reported data.
- **Precision** — Degree of spread among a series of measurements that is independent of accuracy
 - **Consistency** (proxy) — Degree to which data attributes are free from contradiction and are coherent with other data in a specific context of use, e.g., over time for one indicator or across related indicators.
- **Relevancy** — Degree to which the data collected and reported reflect what is most important to support decision-making and not in excess of what is needed so as to consume scarce resources.
- **Completeness** — Degree to which all relevant data needed for decision-making are recorded and reported and therefore available for use.
- **Timeliness** — Degree to which data are current and available when needed to inform decisions.

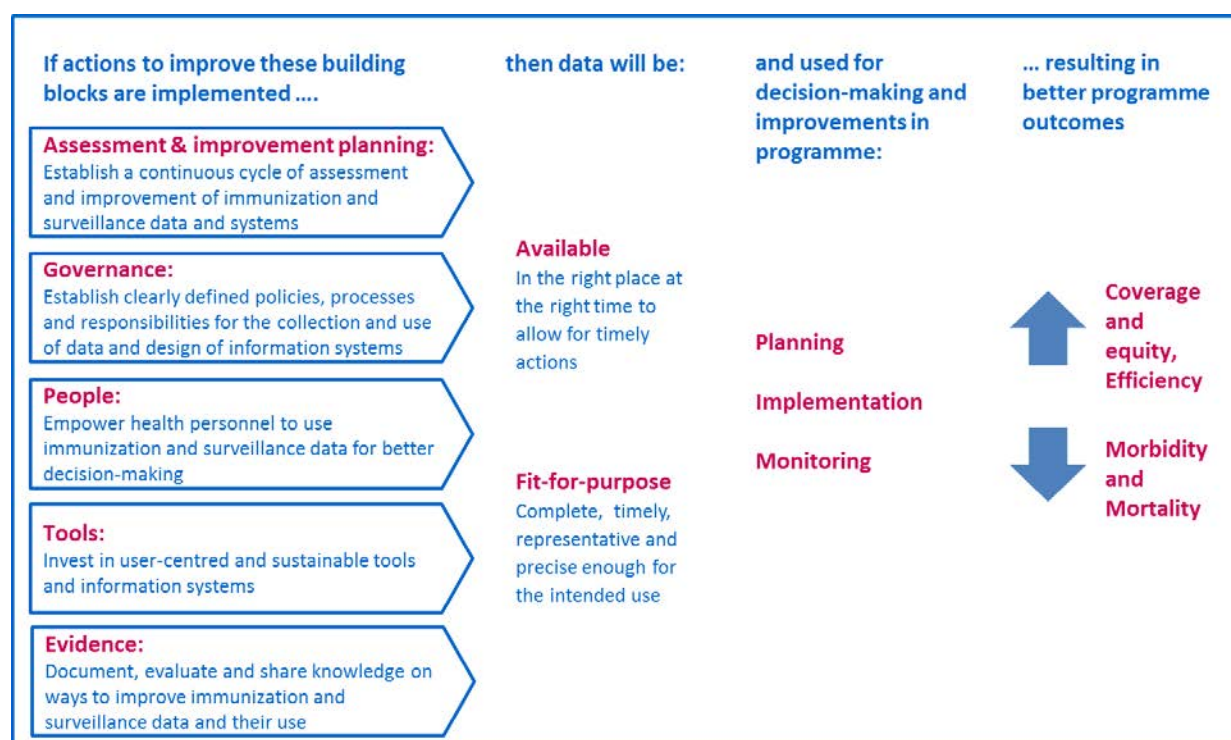
Source: Adapted from Bloland and MacNeil, In Press (as of 11 March 2019)

1.2.3. Frameworks used

WHO has a comprehensive framework for health system strengthening, which includes six “building blocks”: 1) service delivery, 2) health workforce, 3) health information systems, 4) access to essential medical products, vaccines and technologies, 5) financing, and 6) governance and leadership (19).

The structure of this report is based on a simplified theory of change of how to improve EPI data and ultimately immunization programmes and health outcomes, which comes from the *Global Framework to Strengthen Immunization and Surveillance Data for Decision-making* (8) (Figure 1.1) ([Annex 1](#)). This framework identifies five pillars required to produce immunization and surveillance data that are “fit-for-the purpose” in programme planning and decision-making. The five pillars are governance, people, tools, processes (data use and continuous improvement), and evidence.

Figure 1.1. Simplified theory of change on how health system inputs lead to improvements in immunization programmes and health outcomes (8)



1.2.4 Orientation to this report

For orientation to this report, the landscape chapter contains the results of the reviews associated with TORs 1, 2, and 3 (landscapes of data availability and reporting process; standards and guidance on immunization and surveillance monitoring; data quality and assessment approaches). The four chapters that follow present key issues and evidence relating to the four pillars: governance, people, tools, processes (data use and continuous improvement). These chapters generally draw on the results of reviews associated with TOR4a (barriers limiting data quality and use for immunization data quality; VPD surveillance, as well as data access and sharing) and TOR4b (review of what works to improve immunization data use). The Tools chapter summarizes key evidence and results from TOR5 (reviews of immunization information systems and innovative approaches; innovative approaches to polio surveillance). The Assessment and Improvement Planning Chapter includes additional results and evidence from TOR3 (triangulation landscape and data analysis). Country case studies are interspersed throughout the report (Box 1.3 and Annexes).

2. Landscape of immunization and surveillance data availability, quality, use and guidance for countries

Key messages

- A considerable amount and variety of immunization and surveillance data is available nationally, regionally and globally, but they may be inaccessible to those that need them.
- Poor quality immunization-related data still exist, especially in low- and middle-income countries, with inaccuracies in denominators especially of concern.
- The WHO/UNICEF Joint Reporting Form (JRF) on Immunization remains an important tool for global monitoring of immunization programmes, though the increasing time and resources required for countries to complete it was recognized.
- WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) remain a key data source with improved reliability and comparability across countries, relative to reported data.
- Disaggregated coverage and surveillance data (e.g., subnational, individual-level) are increasingly being collected at regional and global levels to meet immunization program monitoring needs.
- Key data that were missing were data from the private sector, data for monitoring equity, and data pertaining to high-risk groups, including migrant or mobile populations.
- Under development are a global WHO Immunization Information System (WIISE), which will include an electronic JRF (eJRF), and a global comprehensive VPD surveillance strategy that are projected to improve data collection, management, and use.
- Efforts are being made in countries and regions to improve data quality and use, including conducting data quality assessments and developing of electronic immunization registries and web-based surveillance information systems.
- A number of guidance materials addressing immunization monitoring and data quality improvement are available, though awareness and discoverability of these materials needs to improve, and user-friendly, practical guidance is still needed for a number of topics.
- Recent data quality assessment tools showed positive trends in increased country ownership and inclusion of root-cause analysis and data improvement plans.
- More work is needed to define a common lexicon and standard set of indicators to measure data quality and use, as part of comprehensive programme monitoring (see also Chapter 6).

2.1 Data availability and the reporting process

A landscape analysis was conducted to assess data availability and unmet monitoring and evaluation needs at the national, regional and global levels. This involved interviews with 22 key informants, including staff from WHO Headquarters, UNICEF, Gavi, the Bill & Melinda Gates Foundation, the U.S. Centers for Disease Control and Prevention, the International Red Cross, WHO Regional Offices, several WHO country offices, health ministries, and expert consultants. The interviews focused on what data are available and by whom, their relevance for decision-making, what's missing, views on the reporting process, and what could be improved and how. [Annex 4](#) summarizes all the answers collected through the interviews.

2.1.1 Data available at the national level

At the national level, routine coverage data are available, through national health management information systems (HMIS), and in some cases, stand-alone immunization reporting systems (such as the District Vaccination Data Management Tool [DVTMT] in the African Region), and coverage surveys (Multiple Indicator Cluster Surveys [MICS], Demographic Health Surveys [DHS], or stand-alone), and are shared with the regional and global levels. Data from private providers may not be included in routine reporting. Data for monitoring equity usually comes from subpopulation analysis of these periodic surveys, while data for routine monitoring of high-risk populations may not be available in most countries. Coverage data from supplementary immunization activities (SIAs) are available, but may not be well-archived or in a standardized format for use.

VPD surveillance data are collected by integrated systems in place nationally, such as the Integrated Disease Surveillance and Response (IDSR) or Early Warning and Response System (EWARS) or others, and also disease-specific case-based surveillance. Most countries currently have national case-based surveillance for polio (acute flaccid paralysis [AFP]), measles, rubella, and neonatal tetanus. The systematic linkage of laboratory and epidemiological data was identified as a current gap in many countries (24). Adverse Event Following Immunization (AEFI) monitoring systems exist in some form in most countries, though they may not be robust (25).

Beyond epidemiological data on VPDs and immunization coverage, vaccine and supply chain data obtained from logistics management information systems (LMIS), pricing information from the Vaccine Product, Price and Procurement (V3P) project, and cold chain assessments can help monitor the delivery and effectiveness of immunization programmes, including their costs. Other sources of data that may be relevant for monitoring of immunization programmes include reports from outbreak investigation reports, EPI reviews, VPD surveillance reviews, post-vaccine introduction evaluations, data quality assessments, or other reports related to supervision feedback. Most of the qualitative data from these reports (e.g., recommendations) is not stored in a usable format to support use and follow-up for continued improvement.

Data from other programmes (e.g., population statistics, maternal and child health programmes) may also hold relevant immunization or surveillance data, or data on denominators, socio-economic status, and geographic information systems (GIS) (26). These data sources are often used to generate key immunization programme performance indicators— both epidemiologic (e.g., vaccine coverage or disease incidence) and programmatic (e.g., performance indicators for surveillance logistics systems) – and can be triangulated to improve data quality and create a more comprehensive picture that can inform key strategic decisions. National Immunization Technical Advisory Groups (NITAGs) provide an organizational structure to support this process.

National reporting processes for administrative immunization and VPD surveillance reporting were considered to be functioning well, despite concerns about quality, timeliness and ready availability/access. In addition, guidance on data use for planning and monitoring is not always implemented (27). Due to the regular reporting processes in place, national reports on vaccine coverage and service delivery were available and found to be useful. These have enabled countries to plan efficiently for vaccine supply and logistics and monitor the cold chain. However, immunization and surveillance reporting process were found to be time- and resource-consuming, and there were concerns about the quality of the data. Reporting was not always conducted according to guidelines, and the tools available (forms, hardware and software) did not optimally support the reporting process. Other specific quality concerns highlighted by the key informants included AEFI data, and an absence of data for specific high-risk populations including migrants/ mobile populations.

2.1.2 Data availability and the reporting process at the global and regional levels

The WHO/UNICEF Joint Reporting Form (JRF) on Immunization

A key source of immunization data available internationally since 1998 is the JRF, which collects a standard set of immunization, surveillance and other programme data from countries on an annual basis and is coordinated jointly by WHO and UNICEF (Box 2.1). Since 2017, the global form has also collected subnational-level vaccine coverage data for DTP and measles-containing vaccine, with known limitations (28); some regional variations of the JRF collected subnational data before 2017. Data from the country reports are extracted, reviewed for completeness and consistency and queries are sent back to countries to clarify absent information and inconsistencies. The nationally reported immunization performance data are then made publicly available on the WHO website.³ The JRF reporting and validation process has improved over time and the data have become more comprehensive, expanding beyond coverage and surveillance (Box 2.1). In 2018, 100% of the 194 WHO member states submitted 2017 data through the JRF. Plans to switch to an online reporting system (eJRF) are ongoing and are related to the development of WHO Immunization Information System (WIIS), a global level integrated platform for management and visualization of coverage, surveillance and other data that is projected to improve data availability and usefulness (Box 2.2).

Box 2.1. Data collected from national immunization programmes through the WHO/UNICEF Joint Reporting Form (JRF)

- Reported cases of selected VPDs and general information on surveillance systems
- Updates to national immunization schedules
- Source of vaccines and supplies
- School based immunization activities
- Administrative data system derived immunization coverage
- Official government immunization coverage estimates
- Immunization system planning and management indicators
- National immunization advisory mechanism indicators
- Proportion of districts by coverage levels for DTP3 and MCV1
- Subnational (admin 2) level coverage data for DTP3 and MCV1
- Vaccine and supply stock-out information
- Vaccine safety indicators
- Home-based records
- Immunization financing data
- Supplementary immunization activities completed and planned

JRF data are used by WHO and UNICEF to produce estimates of national immunization coverage (WUENIC), which are in turn available to member states and global immunization partners (Box 2.3) (29). Data from the JRF and WUENIC serve as a critical resource for tracking implementation of the Global Vaccine Action Plan (GVAP) and Regional Vaccine Action Plans. Other uses of JRF data include monitoring countries' health situation and assessing health trends, monitoring progress towards the SDGs; and informing VPD burden estimates.

The main reason the JRF was created was to harmonize UNICEF and WHO immunization data collection for global and regional use, and not specifically for use at the country level. As such country programs may perceive the JRF as a burdensome exercise requiring significant time and resources. An assessment at the global level has shown that the JRF is meeting the needs of WHO and UNICEF, in terms of decision-making and programme monitoring (30). Regions can add questions to their regional forms, but must keep the global core. And to ensure its continual relevance, the form is reviewed and revised every two years taking into account data use, needs and feedback from the regions. For example, to further improve the relevance of these data for global immunization programme monitoring, the number of VPD cases by age group will be added to the form, starting in 2019.

³ https://www.who.int/immunization/monitoring_surveillance/en/

Box. 2.2. WHO Immunization Information SystEm (WIISE)

Although WHO has been collecting, analysing and reporting immunization programme and vaccine-preventable diseases surveillance data for decades, there has never been an effort to harmonize the processes and workflows across WHO Regional Offices and Headquarters. Different technological solutions were independently developed by each Regional Office to handle data from their respective regions. This has resulted in fragmented systems based on regional priorities that depend on specific individuals for access and support and that may use outdated technologies with limited capacity for analysis, visualization and triangulation. In recognition that this situation was neither efficient nor sustainable, all WHO offices supported the development of a new integrated platform, which gave birth to the WIISE project. The main objectives of the project are to develop a new information system for immunization data hosted at WHO that will:

- Simplify data collection and management processes for Regional Offices, Country Offices and Member States;
- Collect, harmonize, and consolidate various sources of immunization and surveillance data.
- Simplify data management through web-based tools, and automated data transfer and validation checks;
- Produce standard outputs (e.g. graphs, tables, and maps) for more consistent reporting and usability;
- Facilitate in-depth data analyses by easy access to different datasets by internal and external stakeholders; and
- Leverage existing technologies and expertise to maximize the benefits of the project's products to other WHO departments.

Key priorities for information to include in the WIISE platform are measles and rubella surveillance data, the annual JRF, subnational coverage data, data on supplementary immunization activities (SIA), and cross-cutting reference data supporting all programmes.

Box 2.3. WHO and UNICEF estimates of national immunization coverage (WUENIC)

In 1998, following a retrospective analysis of annual vaccination coverage reports from countries that revealed poor data completeness, consistency and concurrency, the SAGE recommended investing resources to improve the completeness, accuracy and precision of the vaccination coverage estimates published by WHO. To address these issues, WHO and UNICEF jointly developed methods that were approved by WHO's Quantitative Immunization and Vaccines Related Research (QUIVER) Advisory Committee, and externally reviewed again in 2009. Following criticism and concerns about a lack of replicability, consistency and transparency of the estimation methods, a WHO and UNICEF Working Group developed WUENIC, a formal system that uses computational logic to determine the data, decisions, and rules used to derive the estimates of national immunization coverage. Following concerns about the absence of a measure of uncertainty in the coverage estimates expressed during the 2009 QUIVER review, the WHO and UNICEF Working Group developed a Grade of Confidence, which was introduced and published alongside the WHO and UNICEF WUENIC estimates for the first time with the 2011 revision (31).

Other sources of global and regional data

In addition to data collected through the JRF, all regional offices collect case-based surveillance data for polio, measles, rubella and neonatal tetanus. Case-based surveillance data for rotavirus, invasive bacterial disease (IBD) are also collected from sentinel sites in selected countries. These data are shared with WHO-HQ, which publishes surveillance reports (weekly for polio, monthly for measles and rubella, quarterly for new vaccines). In 2017, WHO also produced a one-off surveillance supplement that collected information on the status of surveillance systems for a wide range of VPDs, a summary of which was published online (32). Currently, efforts are underway to develop a global strategy for comprehensive VPD surveillance to improve the efficiency and relevance of data collected, as well as use for immunization program monitoring (Box 2.4).

Box 2.4. Comprehensive vaccine preventable disease (VPD) surveillance

There are considerable challenges and weaknesses with VPD surveillance systems in many countries. These include fragmented or parallel systems, the fact that most data collected are not “fit-for-use”, weak laboratory capacity for most diseases (especially bacterial), and the risk of their losing resources as polio funding diminishes as eradication nears.

A global strategy is being developed to transform the current fragmented VPD surveillance into a more cohesive and comprehensive system. **Comprehensive VPD surveillance is defined as the country, regional and global systems required to meet the minimal recommended standards for surveillance of a set of priority VPDs, with integration of surveillance functions across other diseases where possible.**

Comprehensive surveillance will include more VPDs, based on country priorities, and a mix of nationwide case-based, aggregate, and sentinel site surveillance, based on specific surveillance objectives. But, in general, more individual-level and laboratory data will be needed. Greater emphasis will be placed on the visualization and use of surveillance data for routine program monitoring, decision-making and response.

In addition to surveillance data, Regional Offices may collect monthly subnational coverage, but the degree of completeness varies by region. For example, in the WHO African region (AFR), immunization and VPD control programmes use a standardized reporting system across countries in the region. While national-level data remains country-owned, various datasets are shared with the regional office to monitor coverage and disease trends in the Region (Table 2.1) (33). Some of these data are shared with technical and donor organizations (e.g. IHME, U.S. CDC, USAID, BMGF, World Bank, Gavi).

Table 2.1. Type and format of immunization and surveillance databases handled at WHO African Regional Office

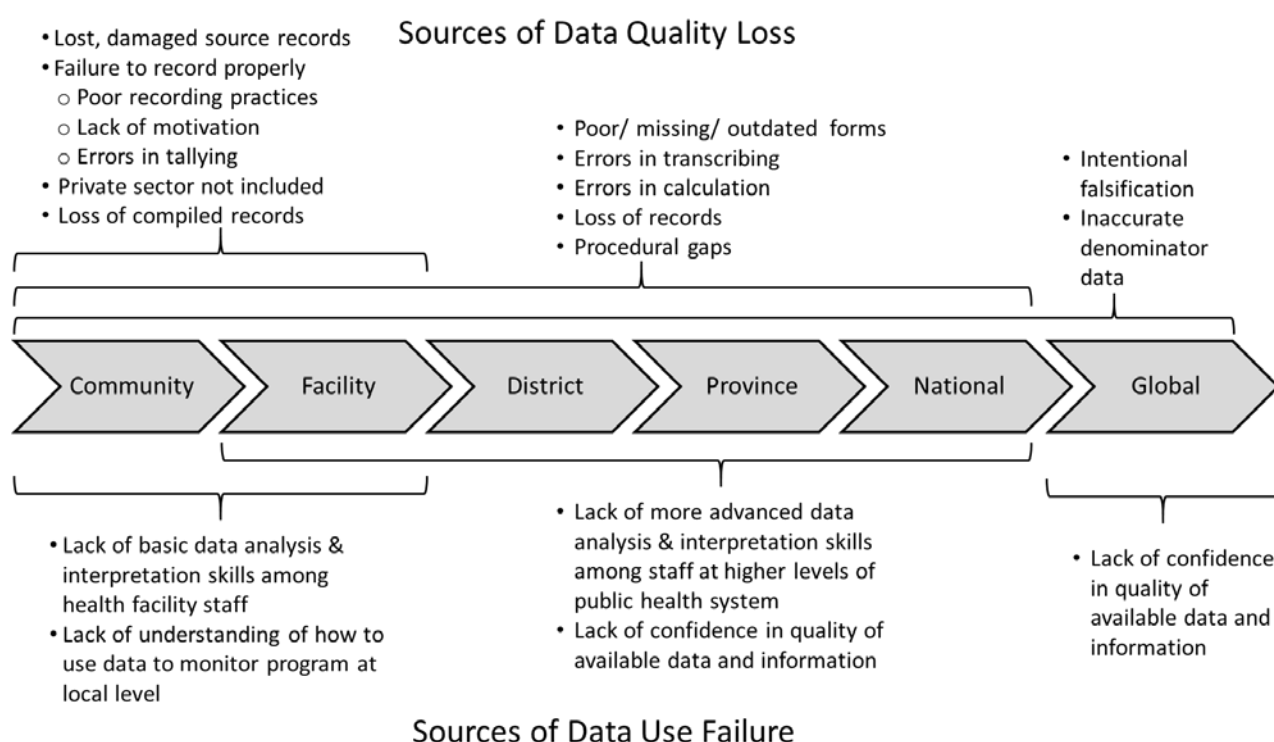
Database	Frequency of sharing with WHO	Format of database	Datasets expected per year
Population data	Annually	Excel	47
Routine immunization coverage	Monthly	MS-Access	564
Stock management tool	Weekly	Excel	564
District vaccine data management tool	Weekly	Excel	564
WHO-UNICEF Joint Reporting Form: coverage and incidence data	Annual	Excel	47
SIAs coverage data	Activity related	Excel	Ad hoc
SIAs independent monitoring data	Activity related	Excel	Ad hoc
SIAs lot quality assurance survey data	Activity related	Excel	Ad hoc
AFP/polio surveillance	Weekly	MS-Access	Ad hoc
Measles surveillance	Weekly	MS-Access	2 444
Yellow fever case-based surveillance	Monthly	MS-Access	2 444
Neonatal tetanus surveillance	Monthly	MS-Access	564
Paediatric bacterial meningitis surveillance	Monthly	MS-Access	564
Rotavirus surveillance	Monthly	MS-Access	324
Polio lab data	Weekly	MS-Access	324
Measles rubella national lab data	Monthly	MS-Access	832
Measles rubella regional referral lab data	Quarterly	MS-Access	528
Yellow fever national lab data	Monthly	MS-Access	36
Yellow fever regional reference lab data	Monthly	MS-Access	12
Integrated disease surveillance data	Weekly/monthly	MS-Access/ Excel	564

Source: Poy A et al. Immunization monitoring and vaccine-preventable diseases surveillance data management in the African Region. African Health Monitor. 2015; 19: 46-50.

2.2 State of immunization and VPD surveillance data quality

Countries and immunization partners have made a number of efforts in recent years to improve the availability, quality, and use of immunization-related data (5). However, poor quality data still exist in high, middle and low-income countries. Deficiencies in immunization and VPD surveillance data quality are often more pronounced in LMICs, where immunization data needs are greatest in order to be able to target missed populations (34-37) (*Annex 5*). Data issues affect both numerators and denominators used to calculate administrative coverage or disease incidence rates, and also affect surveys. The many possible sources of data quality loss and data use failure for administrative reporting are depicted in Figure 2.1. A summary of suggestions for improving data availability, quality and use from the key informant interviews is shown in Box 2.5, categorized by the pillars of data quality and use described in Chapter 1.

Figure 2.1. Possible sources of data quality loss and data use failure as administrative data progress from primary points of collection to global reporting (17).



Box 2.5 Suggestions from key informants on ways to improve the availability, quality, and use of immunization and surveillance data

Data processes, improvement and use

- Focus the global reporting requirements on data that is relevant to both the national level and the regional/global level
- Standardise data from countries and regions (including minimum datasets)
- Routinely analyse multiple data sources/do data triangulation, in particular between data generated by different agencies or sources
- Strengthen denominators at national/subnational levels
- Capture immunization/surveillance data from private providers/ Non-Governmental Organizations (NGOs)/ Civil Society Organizations (CSOs), not just immunization program data from public facilities
- Use other data sources that include socio-economic data to better measure equity estimation with regards to vaccinations
- Develop and implement monitoring and evaluation frameworks and dedicated activities (e.g., annual regional data meetings)
- Implement data quality improvement plans
- Strengthen JRF data validation
- Create a repository for qualitative data

Tools

- Technological options to facilitate data capture, validation, storage, linkage, and sharing (e.g. data entry platform at health facility level, laboratory/case-based surveillance linkages)
- Data visualization tools with inter-regional dashboard (e.g. WIISE)
- Data repository for data and reports from NITAGs/RITAGs/National Verification Committees (NVCs)
- Guidance for classification of AEFIs, especially when data is lacking for full causality assessment, and sharing of summarized outcomes of classified cases

People

- Capacity development of workers at all levels to collect, analyse and triangulate data
- Demonstrate the value of collecting and using data at all levels to improve staff motivation to create a data driven service delivery

Governance

- Guidance on what “fit for purpose” data means at different levels and for different users
- Greater support, coordination and alignment from partners on the ground
- Provide feedback of analysed data to stakeholders
- Share best practice in implementing data management
- Regular data quality monitoring at subnational and national level
- Improve the use of data to make decisions about the programme at all levels
- Rethink incentives, which sometimes become disincentives (35, 38), to report accurate data

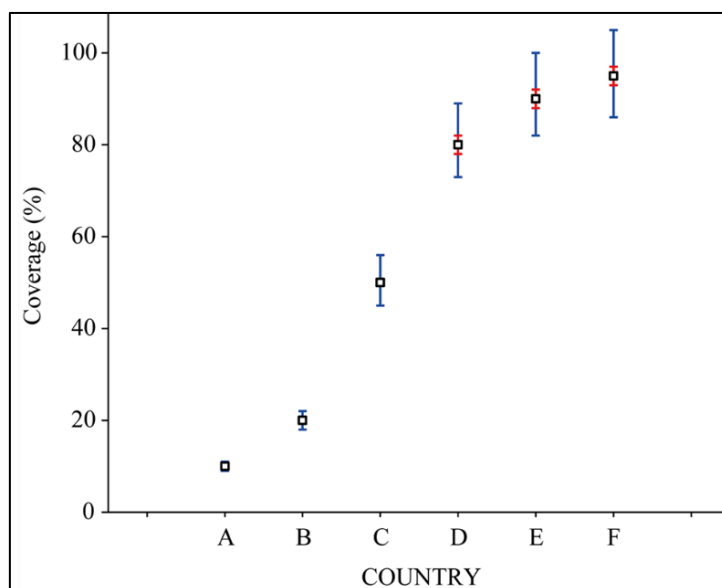
2.2.1 The quality of vaccination coverage data

Studies in low- and middle-income countries have shown that officially reported immunization coverage figures are often of poor quality, with coverage rates most commonly over-reported (34, 35, 39-44) but sometimes under-reported (34, 35, 40, 43). A recent review of global coverage raised the issue of the number of subnational areas with coverage >100% in terms of interpretability of the subnational coverage figures used for GVAP monitoring (41). The literature describes data disagreement at all levels of the health system, from facility-level to national reports (41, 45-47), due to problems with both numerators and denominators.

Inaccuracies with denominators, which are critical for microplanning and administrative coverage calculation, have especially been documented in the literature (40, 43-46). For example, one review found that while national denominator figures were updated annually, 87% of districts used the same figure over several years (45). In fact, only 14% of the countries reviewed had an agreed-upon

denominator at both the district and national level. A recent global review found 11% of all reporting events (country-years) had substantial (>10%) year-to-year differences in the number of reported live births, as well as BCG coverage rates of more than 100% (43). It is important to highlight that target population estimates at the global and regional levels involve less uncertainty than those at a country and subnational levels, as errors at the country level tend to offset each other when aggregated (48). The accuracy of target population estimates especially affects the precision of vaccination coverage rates in places with high levels of coverage. In fact, as coverage levels approach 100%, errors in target population estimates can mask differences in vaccination coverage rates, resulting in pockets of missed unvaccinated children (49) (Fig. 2.2).

Figure 2.2. The effect of 10% error in target population estimates on estimated immunization coverage rates (49)



In some cases, immunization programmes estimate the number of children in the target population (e.g., surviving infants) based on counts or estimates by local programme staff or health workers. In others, immunization programmes rely on population projections from the latest census data. Changes in fertility, mortality and/or migratory patterns over time create challenges for obtaining robust target population estimates. While complete vital registration would be the most reliable source for denominators, few countries use this, as problems with vital registration systems exist in the majority of the low- and middle-income countries (50, 51). Two-thirds of the countries with the highest mortality rates, which account for 95% of all maternal, newborn and child mortality, lack the vital registration systems necessary to accurately project denominators (52). Use of alternative data sources from other programs and/or good coordination with national bureaus of statistics to improve denominators is rare in countries (53).

Problems with numerators have also been documented in the literature. Studies using the standardized WHO Data Quality Assessment (DQA) tool found that only one-fifth to one-third of countries evaluated had verification factors that suggested consistent immunization numerator data. Meanwhile, one third had VFs in keeping with moderate over-reporting and one third had VFs consistent with considerable over-reporting (45, 46, 54). Another issue with the numerator data at the national level is the completeness of reporting of this data from all vaccination sites, including private providers which may represent a large proportion of health services provided in LICs and MICs (55).

Some countries using electronic immunization registers (EIRs) have reported improved data quality (46, 56), while other countries with EIRS continue to report quality data issues (57, 58). A case study on an EIR from Chile (done for this report) shows the relevance of including vaccination reporting from the private sector and how using numerators that consider the place residence ensured optimal data quality and ability to locate unvaccinated children (Box 2.6 and Annex 6). Efforts are also ongoing to improve data quality from EIRs through guidance and the development of built-in routines to flag potential problems (59, 60).

Box 2.6. Effect of private sector engagement and place of residence vs place of vaccination on coverage estimates in Chile

Chile began the implementation of its online national Electronic Immunization Registry (RNI in Spanish) in 2010. Its use is mandatory in all public facilities and also in private clinics as per a Ministerial mandate. A total of 2,075 facilities were using RNI in 2018, with 241 (12%) of them being private. In the Metropolitan Region of Santiago, one in four children were vaccinated in private clinics, and some districts had up to 94% of their children vaccinated by the private sector. Also, one in five children were not vaccinated in the same district where they reside. This phenomenon resulted in coverages ranging from 29% to 325% by district when the place of vaccination was used as a denominator, but when coverage was calculated based on the district of residence, the range narrowed to 79% to 140% coverage ([Annex 6](#)).

Surveys are often seen as more reliable than administrative coverage estimates, as they do not rely on inaccurate denominators. It is important to note that while being useful for national or regional monitoring, surveys do not typically provide programmatically useful information at the local level (12). Further, not all countries conduct surveys and in those who do, surveys coverage estimates may also be inaccurate as a result of selection, information or other biases. Information bias is especially an issue in determining vaccination status using caretaker's recall when vaccination cards or home-based records (HBRs) are not available (12, 61, 62). Studies looking at the validity of recall have highlighted how it varies in different settings (63-65); the impact of recall bias on survey coverage estimates has been highlighted as a research priority (13). Crucial data like date of birth may be missing, preventing estimation of the timing of children's vaccinations (66). Countries with inaccurate administrative data often tend to have challenges in obtaining accurate survey estimates, as a result of outdated sampling frames, inaccessible areas, or low availability of HBRs (12). An analysis of survey results from countries where a vaccination coverage survey was conducted within one year before or after a DHS or MICS identified several instances where the findings diverged substantially, in terms of coverage estimates and in the percentage of vaccination cards or HBRs seen, leaving decision-makers unsure what to believe or to do (D. Brown, personal communication) (13).

2.2.2 The quality of VPD surveillance data

The literature has also identified quality issues with VPD surveillance data. These include incomplete or delayed routine surveillance reporting, inconsistent use of standardized disease case definitions, a lack of laboratory confirmation, and insufficient completeness of critical information, including absence of documented evidence of vaccination history of cases — all of which can negatively impact the use of surveillance data for decision-making ([Annex 7](#))(67-69). While case-based surveillance data for polio, measles, rubella and new vaccines are routinely analyzed and used at all levels (despite documented challenges in performance monitoring indicators) (70-72), most of the aggregate incidence data collected through national surveillance systems and the JRF are seldom analyzed and of limited use ([Box 2.11](#)) (36, 73, 74). This is related in part to doubts about the completeness of the data, but also to the fact that relevant data, such as age-specific incidence and laboratory confirmation, may not be collected or reported, thus limiting the usefulness of available data for immunization program monitoring (30). Global efforts are also underway to improve surveillance quality ([Box 2.4](#)).

2.2.3 Other evidence of data quality: an example of a global analysis

The Working Group commissioned an analysis of the use of tetanus incidence data reported to the JRF to monitor DTP coverage, including doses provided beyond infancy in light of the shift towards a life-course of vaccination approach. The analysis found substantial data quality issues — both with surveillance and vaccination coverage data — that affected the ability to perform the analysis ([Box 2.7](#)). Of the indicators assessed, only WUENIC estimates of DTP3 coverage were available for all countries during 2011-2016. Otherwise, there were large variations in the number of countries reporting immunization and surveillance data across regions and income levels. These findings reflect the challenges inherent in making systematic comparisons at the global level ([Annex 5](#)) (37).

Box 2.7. Challenges with the quality of JRF data during a global tetanus triangulation analysis: looking towards monitoring the life-course of vaccination approach

The U.S. CDC conducted an analysis that triangulated data on the immunization schedule for tetanus containing vaccines (TTCV), coverage, and tetanus surveillance — both neonatal and non-neonatal tetanus (in persons aged >28 days) — data collected by WHO from 194 countries. The aim of the analysis was to evaluate the feasibility of using non-neonatal tetanus surveillance data to assess the potential of using the data to monitor the coverage of diphtheria, tetanus, and pertussis containing vaccines (DTPCVs) (Annex 5). As part of the evaluation, challenges were noted with the availability and quality of current immunization and surveillance data, including the following:

- WUENIC had good completeness and seemed more reliable compared to official reported coverage.
- Administrative coverage data differed from survey coverage, especially in LICs and LMICs (but, few surveys were in upper middle-income and high-income countries).
- Data on coverage for booster doses were not generally available (e.g., poor completeness of reporting DTP4 coverage, lack of WUENIC estimates for DPT4, no DTP5 coverage collected).
- Immunization schedule data required substantial cleaning before use.
- Collated data on the timing of TTCV booster introduction or schedule changes were unavailable.
- Variations in how countries interpreted the definition of “total tetanus” cases led to challenges in interpreting the number of non-neonatal tetanus cases.
- Non-neonatal tetanus is under-reported, based on comparing reports of total tetanus cases with neonatal cases, which is a marker of endemic disease.
- Age-specific disease data were only available for AFR and AMR and were of poor quality.
- It was difficult to make country-level epidemiologic interpretations with the existing data.

Based on this analysis, the 2019 JRF (for 2018 data) was revised to enable monitoring of the life-course approach towards tetanus vaccination, including report neonatal and non-neonatal tetanus cases separately (revised from “total tetanus”), and collecting age-specific tetanus incidence data (an example of how data use can lead to improvements in data quality). The WG also recommends that data on booster dose coverage be collected, that a plan is developed for WUENIC estimation of DTAPV booster doses, and that the usability of schedule data is improved.

2.3 Efforts to improve the collection, quality and use of immunization and surveillance data

2.3.1 Standards and guidance on immunization monitoring and surveillance

A key component of the Global Framework to Strengthen Immunization and Surveillance Data for Decision Making are establishing clearly defined standards for the design of information systems and processes for data collection and use (3, 8). Harmonized guidelines and standards are critical to improve the quality, availability and use of immunization-related data. WHO is responsible for developing standards and guidance at the global level and regional levels. Usually, regional guidance should be adapted from global guidance for greatest harmonization. However, a specific region may identify a need for guidance and develop a regional document, which is then used as an impetus and starting point for developing global guidance. In all cases, it is particularly important for country programmes to adapt global and regional guidance to their specific context at the local level, where health workers need relevant training in core competencies (75), as well as tools and procedures to implement good practices on data collecting, reporting and how to use data for making decisions (See Chapter 5: People).

The WG conducted a thorough review of existing (including new) guidance documents and standards that include immunization monitoring and surveillance, as well as an analysis of gaps in global and regional guidance, including what's missing or needs updating to meet countries' needs. A list of published core guidance and standards at the global level was compiled, based on an existing list of WHO documents, a CDC landscape analysis of EPI guidance documents conducted in 2017, and supplemented by on-line searches and information gleaned from WG members and WHO EPI staff.

Regional documents were identified from a questionnaire sent to the six WHO Regional Offices. Potential gaps in guidance materials were identified through reviews of publications and meeting reports, the key informant interviews, input from WG members, and personal communications. It should be noted that the review did not examine country guidance materials in any systematic fashion, nor did it assess the appropriateness or completeness of individual guidance documents in addressing all relevant areas. The resulting list of published EPI guidance is included in [Annex 8](#).

The review found that there is actually a lot of existing and newly developed global and regional guidance that is relevant for immunization and surveillance data. These include a number of documents published in the last several years or available on-line that together represent a major effort by WHO and a step forward towards filling in gaps and improving existing guidance materials (see Box 2.8). In addition, 11 WHO Position Papers on specific vaccines were published in the past two years that include guidance on monitoring and data, and the WHO Immunological Basis of Immunization Series is currently being revised.

Box 2.8. Key recent WHO global guidance materials with relevance to data quality and use

Published documents:

- [Vaccination Coverage Cluster Surveys Reference Manual \(2018 revision\)](#): improvements in methods for probability-based sampling, minimizing bias, improving data quality since the 2005 version, with related capacity-building tools
- [Surveillance Standards for VPDs \(2018 revision\)](#): enhanced from 2003 version to include overview of surveillance principles, minimal & enhanced standards for 22 diseases (from 11 in 2003), outbreak investigation, discussion of integration
- [Data Quality Review toolkit for health facility data \(2017\)](#): builds on previous EPI data quality assessment methodology with integrated guidance (across HIV, malaria, TB, EPI programs) for conducting a desk review and field assessment
- [Guide for conducting an EPI Review \(2018\)](#): first global guidance that includes best practices, use for program improvement, and integrating with post-introduction evaluations, VPD surveillance reviews, and data quality assessments
- [Establishing and strengthening immunization in the second year of life \(2YL\) \(2018\)](#): guidance on planning, implementing and monitoring in 2YL, integration, and catch-up vaccination
- [Working Together \(2018\)](#): resource guide on policies and strategies for integrating various health services with immunization throughout life-course
- [Protecting All Against Tetanus \(2019\)](#): Guide to sustaining maternal and neonatal tetanus elimination (MNTE) and broadening tetanus protection for all populations
- [Missed Opportunities for Vaccination \(2017\)](#): comprehensive guidance on planning and implementing a MOV assessment, as well as implementing interventions
- [Engagement of private providers in immunization service delivery \(2017\)](#): guidance for optimal engagement of nongovernmental providers in immunization delivery and surveillance
- [How to Develop a Continuous Improvement Plan \(cIP\) \(2018\)](#): guidance on how to develop a continuous immunization supply chain improvement plan & case for supply chain investments
- Disease-specific guidance on serosurveys, including [dengue \(2017\)](#), and [tetanus \(2018\)](#), measles & rubella (draft), added to existing guidance for [hepatitis B \(2011\)](#)
- [Guidelines for Accurate and Transparent Health Estimates Reporting \(GATHER\) \(2016\)](#): outline recommended documentation for releasing health data
- Capacity-building approaches and [training](#) for improving data quality and use:

- A 2-hour [e-learning](#) module (2015) describes how to monitor immunization coverage, assess data quality, and interpret and use that data for action
- [Immunization Monitoring Academy](#) (2018): comprehensive multi-month distance learning program requiring participation in lectures, discussion sessions, and projects
- [Survey Scholar](#) (2017–2019): hands-on distance learning on designing, implementing, analyzing and interpreting vaccination coverage survey using the 2018 revised guidance
- [E-learning course on Vaccine Safety Basics](#) (2013): online course on adverse events, pharmacovigilance, and communications related to AEFI and its risks
- [Effective Vaccine Management \(EVM\) system training course](#) (2012): developed by WHO and UNICEF to train immunization staff on conducting EVM assessments

WHO Working Documents:

- Global Framework to Strengthen Immunization and Surveillance Data for Decision-making (2019) (included in [Annex 1](#))
- Handbook on the use, collection, and improvement of immunization data (2019)
- Analysis and Use of Health Facility Data: Guidance for Immunization Programme Managers (2018)
- Application of Public Health Triangulation for Immunization and Surveillance Programs: Framework Document (2019) (included in [Annex 2](#))
- Harmonizing vaccination coverage measures in household surveys: A primer (2018)
- [Standard Competencies Framework for the Immunization Workforce \(2018\)](#)
- [Assessing and Improving the Accuracy of Target Population Estimates for Immunization Coverage \(2015\)](#)

The review also found a number of regional guidance materials related to immunization and surveillance data quality and use that have recently been completed or that address gaps in global guidance (Box 2.9). In addition, there are a number of global guidance documents currently in development and planned for publication in 2019–2020, which the WG urges to be finalized as soon as possible:

- Handbook on the use, collection, and improvement of immunization data
- Guidance on measles & rubella serosurveys
- EPI competency guidelines and tools for use by country programs to assess their immunization program capacity
- Guidelines on data triangulation for program planning and decision-making.

Box 2.9. Additional key guidance documents from the WHO regions

Increasing coverage and equity

- AFR: [Reaching Every District \(RED\) guide \(2017\)](#)
- EURO: [Guide to Tailoring Immunization Programmes \(TIP\) \(2013\)](#)

Pre-service and in-service capacity building

- AFR: [EPI Mid-level Managers \(MLM\) course \(2017\)](#)
- AFR: EPI Training Curricula for [Medical Schools \(2015\)](#) and [Nursing/Midwifery schools \(2015\)](#), and an EPI/IMCI interactive training tool for health workers (2016)
- EMR: currently developing Immunization in Practice training and translating MLM into Arabic

Coverage monitoring

- AMR/PAHO: [Tools for coverage monitoring \(2017\)](#)
- WPR: [Improving data quality: Guide for developing countries \(2003\)](#)

Electronic immunization registries (EIR)

- AMR/PAHO: [Electronic Immunization Registries \(EIR\) Guide \(2018\)](#) and draft “DQS-Plus” for improving data quality and use, and assessing acceptance and functionality of eIRs
- European Centers for Disease Control (ECDC): [Designing and implementing an immunization information system \(2018\)](#)

VPD Surveillance

- SEAR: [VPD Surveillance Guide \(2017\)](#)
- AFR: currently updating the Integrated Disease Surveillance and Response guidelines

Gaps in guidance materials and key emerging issues related to guidance

Despite the considerable number of relevant guidance materials available, a key finding of the review is that people working in immunization and surveillance are often unaware of what materials exist. Management of these materials on websites that are not intuitively organized or easily searchable makes the discovery of documents challenging. Communications about recently published documents through appropriate venues (e.g., EPI managers meetings, BID Learning Network, TechNet-21) may also be insufficient, resulting in low awareness. For example, most key informants noted immunization targets (denominators) as a major issue that needed to be addressed by guidance, but few had ever heard of or used the existing [2015 draft denominator guide](#), that is on the WHO website (Box 2.9). With the ability to publish electronically, which saves printing costs, guidance documents also seem to be growing in length (regularly 200+ pages) and more technically complex. All of these issues may limit their broader use or result in a duplication of efforts.

An analysis by the Working Group of gaps in critical guidance materials did find, however, that guidance was lacking or insufficient at the global or regional levels in a number of technical areas and should be developed (Box 2.10).

Box 2.10. Gaps in guidance materials in immunization monitoring, data quality and use: areas where guidance is lacking, insufficient or out-of-date

- Pre-service EPI training curricula for medical, nursing/midwifery schools (following [AFR example](#)) for not only growing immunization knowledge, but data collection and use skills
- Guidance for improving immunization targets (denominators) and how to deal with migrant populations, e.g., temporary workers, undocumented immigrants, nomads (i.e., revise and finalize global [2015 draft guide](#) to meet user needs), alongside capacity-building activities
- Capacity-building approaches for data analysis and use (see examples of global e-learning and distance learning; global MLM is out-of-date)
- Comprehensive VPD surveillance standards for some regions and most countries (adaptation of global guidance)
- Global guidance on creating electronic information system standards, including minimal data elements, interoperability with other systems, data flow and user access, validation checks:
 - Routine (aggregate) immunization data
 - Electronic immunization registries (following [PAHO example](#))
 - VPD surveillance (aggregate and case-based data)
- Improved guidance on monitoring approaches, including generic indicators that countries can adapt, for the following:
 - Equity and universal health coverage
 - Routine immunization data quality
 - Data quality in eIRs (following the example from the American Immunization Registry Association [AIRA](#))
 - VPD surveillance data quality
- Life-course and special population guidance, such as:
 - Introduction guide for Penta/Td boosters (disease burden, school-based programs, monitoring coverage, etc.)

- Guidance on school entry and adolescent vaccination, school checks, and mandatory vaccination for schools
- Immunization of pregnant women (whether to vaccinate) and surveillance recommendations (pertussis, flu, vaccines in pipeline) (see [PAHO example](#))
- Adult and elderly vaccination (influenza, pneumococcal)
- Technical guidance on how to manage, analyse and better use qualitative data for immunization program improvement (e.g., assessment recommendations, case studies)
- Recommendations from SAGE on the role of serosurveys for immunization program monitoring and use in management

These gaps include guidance on effective approaches in building capacity at each level of the health system to strengthen data quality and use. The WG did note a positive trend in including capacity-building approaches as part of guidance roll-out (e.g., coverage survey), as well as efforts to develop e-learning curricula (on coverage monitoring, vaccine safety, logistics management). This is a positive trend that should continue. In particular, the [WHO Immunization Monitoring Academy](#) is potentially a useful modality for sharing guidance on data quality and use, especially if tailored to meet needs at different levels (Box 2.8). However, guidance on mapping of minimum capacity for data collection, use and analysis at each level could be useful to support the development and use of training materials, or to identify strategies to build capacity at various stages (e.g., pre-service, service induction, on-the-job training, leveraging broader data/epidemiology training). Simple guides and practical job aids are still largely lacking on how to use available complementary data to address various questions across all levels of the health system. Overall, guidance should emphasize the analysis and use of data, instead of simply data collection and reporting.

Another area where additional technical guidance is needed is on how to introduce information, technology and communication solutions for data management, including Electronic Immunization Registries (EIRs). The PAHO [EIR guidelines \(2018\)](#) were consistently cited by key informants as an example of good guidance, which could be replicated to include solutions for aggregated data, mHealth applications, and so forth. A [Planning and Information Systems Project \(2013\)](#) toolkit for other information systems exists and may also be helpful. However, national electronic information system standards are still needed that are specific to country contexts. To guide countries in their development, it would be useful to develop global guidance on the process, key issues, and best practices for creating functional standards, and for defining the minimum data elements for immunization information systems, EIRs, and VPD surveillance information systems.

Effective guidance was also felt to be needed to address emerging and increasingly critical issues for data collection and use related to both numerator and denominator. These include coverage monitoring among mobile populations or those living in informal settlements; recording and reporting of doses administered late; the management of data monitoring of vaccines given across multiple age groups and during the life-course; how to monitor and address issues of coverage equity to achieve universal health coverage; and how to effectively manage and use qualitative data generated in assessments or routine monitoring. In summary, while there is a considerable amount of guidance documents available globally or regionally, the awareness and discoverability of these materials among those working in immunization must be increased, guidance in a number of technical areas is still needed, and the guidance developed must be very practical and user-friendly.

2.3.2 Data quality assessment approaches and indicators

Achieving equitable immunization coverage and timely detection of VPDs requires high-quality programme data. GVAP includes a target that states: “All countries [are] to have high quality immunization coverage data by 2020” (76). However, GVAP does not describe what defines “data quality” or when data become “high quality.” Prior attempts to develop a GVAP data quality indicator for assessing and monitoring progress of vaccination coverage proved unsuccessful (76). In addition, prior work has highlighted challenges with the underlying data GVAP uses for programme performance indicators (41).

Tools for assessing the quality of immunization coverage data

A number of tools to assess the quality of vaccination coverage and VPD surveillance data at the national and local level have been developed since 2000. These tools were developed to enable funding agencies to monitor progress and justify their investments, as well as to assist countries in conducting their own assessments in order to improve data quality. Below is a summary of the main data quality assessment tools developed in recent years, based on a landscape analysis commissioned by the WG. It should be noted that the impact of these assessment approaches on actually improving data quality and use was not systematically reviewed.

- [Data Quality Audit \(DQA\)](#): The DQA was developed in 2000 to enable Gavi to validate country reports of the number of children vaccinated with DTP3 — a measure used for the Alliance's performance-based grants (77). While the main focus of the tool was to validate number of children vaccinated, it also assessed the quality, efficiency, security and usefulness of the administrative data system at each reporting level to develop practical recommendations for data recording and reporting. However, the tool had several limitations: a) It was not a country-owned or country-led process and as such was not flexible or based on the priorities of country programmes; and b) the methodology is challenged by small sample sizes at the district level, which creates problems with large variation in the measured verification factors of reporting accuracy.
- [Data Quality Self-Assessment \(DQS\)](#): In response to the limitations and critiques of the DQA, WHO developed the DQS in 2005 to assist countries to self-diagnose data quality problems in order to improve their monitoring systems. It is a flexible toolbox of methods intended for use by programme staff that can be adapted to meet their needs in assessing immunization data at the national, provincial, or district levels. The DQS includes a review of data integrity, completeness and timeliness, as well as a self-designed questionnaire for reviewing system quality issues (e.g. availability of home-based records (HBRs), directly-observed recording and reporting practices at health facility level). The tool has been widely and regularly used by countries and its use is now encouraged as part of [EPI reviews](#).
- [Assessing and Improving the Accuracy of Target Population Estimates for Immunization Coverage](#): In 2015, WHO produced a working draft of a guide to facilitate national immunization programmes to assess their target population estimates for vaccination coverage. The assessment includes assessing internal (i.e., trends over time, comparison of target populations across vaccines) and external consistency (i.e., comparison with alternative sources, examining population growth rates and implied mortality rates). As mentioned above, awareness of this tool was noted to be low among key informants, and the extent of use of this tool is unclear. The WG has recommended the guidance to be finalized.
- [Tools for Monitoring the Coverage of Integrated Public Health Interventions](#): In 2017, the Pan American Health Organization (PAHO) published this guide provide health staff at the local, district/municipality and national levels practical methods and tools to facilitate the management, analysis and coverage monitoring of vaccination and deworming interventions. Building on the DQS and other tools described above, the PAHO guide encourages in-depth evaluations of data quality every three to five years, complemented by abbreviated annual assessments and data congruence exercises based on supervisory visits. The guide encourages a focus on data accuracy, timeliness and completeness, as well as an overall evaluation of the recording and reporting system.
- [Data Quality Review \(DQR\)](#): This toolkit, developed by WHO, Gavi, the Global Fund and USAID and published in 2018, uses a unified approach to data quality across many disease control programs (including TB, malaria, HIV and EPI) to assess data quality at the health facility level. It builds upon a health facility [Data Quality Report Card \(DQRC\)](#) tool developed by WHO in 2015, as well as other data quality assessment tools (e.g., DQA and DQS), and takes into account best practices and lessons learned from many countries. The DQR framework includes: 1) routine and periodic reviews of data quality built into a set of checks of the health information system as part of a continuous feedback cycle; 2) annual independent assessments to identify reporting system gaps as well as the credibility of health facility reported data during the prior year; and 3) periodic in-depth reviews of data quality for specific programmes. The toolkit includes a desk review module that assesses: 1) data completeness, 2) timeliness, and 3) internal and external consistency. A module to validate data integrity in the field and assess the system is also included. Related

guidance on routine Analysis and Use of Health Facility Data has been developed along with a module for the District Health Information System 2 (DHIS2) that includes data quality (11).

- Handbook on the use, collection, and improvement of immunization data: WHO has also recently developed a working draft of this handbook to provide practical assistance to country-level decision-makers who want to: a) decide what data are needed for programme improvements and decision-making; b) develop tools and systems to collect and analyze immunization data; and c) assess the quality of data produced by their immunization recording and reporting system and implement improvement plans to address gaps within the system. Building on the DQR, the Handbook proposes a review of the design and organization of the information system, a desk review of data produced by the information system, a field review to verify reported data from source documents at the health facility and district level, and to perform a root-cause analysis to tailor recommendations and feed into a data improvement plan.

Recent data quality assessment tools showed positive trends in increased country ownership (DQS) and inclusion of root-cause analysis and data improvement plans (Data Handbook). However, it remains unclear as to how well these tools fit the data quality needs of country programmes and at what levels (8). In many situations, data quality assessment measures for data collection, analysis and use appear to remain a “tick-box” exercise to satisfy those at the international level demanding attention to data quality. However, periodic data quality assessments can be important to ensure that the methods, tools and indicators used, as well as accompanying visualization dashboards, fit the needs of national immunization programmes and are institutionalized and sustainable. Outcomes of assessments should feed into planning and improvement cycles. Summaries of DQA results suggest improvements in some aspects of data quality in some countries (45, 46), but whether these improvements persisted over time is unknown.

Approaches for assessing the quality of VPD surveillance data

While not receiving as much attention as data quality for vaccination coverage monitoring, standardized approaches to evaluating and monitoring VPD surveillance systems have existed since the 1980s (14, 21, 23, 78, 79). All VPD surveillance evaluation tools have been regional and disease specific (e.g., AFP, measles), until the publication in 2017 of the first global guidance on conducting EPI and integrated VPD surveillance reviews (78). Methodologies that have been used to assess surveillance data quality include capture-recapture (80, 81), reviewing facility registers for “missed cases,” and comparing aggregate reporting from health facilities with case-based reporting systems (14, 82). Box 2.11 describes a recent example of validating the quality of reported surveillance data in Uganda.

Similarly, disease surveillance performance indicators have been used routinely to monitor polio incidence since the 1980s and measles since the 1990s. Indicators specific to each VPD were included in the 2018 revision of the *WHO Surveillance Standards for VPDs*, but generally include completeness and timeliness of reporting, sensitivity (a surveillance-specific proxy measure for accuracy), representativeness (geographic completeness) of case detection, and adequacy of case investigation and laboratory confirmation to inform decision-making (14). These indicators have served as the basis for a strong monitoring and accountability framework for the global elimination and eradication programs (70, 83, 84).

Box 2.11. High tetanus burden or surveillance reporting error?

Globally, reporting of non-neonatal tetanus (non-NT) to the through [the Joint Reporting Form \(JRF\)](#) has generally been weak (74). In 2011, Uganda established a District Health Information System version 2 (DHIS2) platform that includes weekly reports of neonatal tetanus (NT) and other notifiable diseases sent by short message service (SMS) and monthly reports of both NT and non-NT (aged >28 days). In Uganda, infants and reproductive-age women are given tetanus toxoid-containing vaccines (TTCV), but the schedule does not include the three WHO-recommended TTCV booster doses (85). In 2013–2015, a small cluster of non-neonatal tetanus cases, associated with male circumcision for HIV prevention, helped highlight that Uganda had one of the world’s highest reported incidences rates of non-NT (74), which has a case-fatality rate approaching 100% without medical intervention.

To evaluate whether reported data reflected Uganda's true tetanus disease burden, the Ministry of Health in 2017, in collaboration with the Field Epidemiology Training Program, U.S. CDC and WHO, conducted a medical records review of 26 facilities across the country's four regions. The investigation confirmed that the non-NT burden was high, but likely over-reported. The vast majority of cases were identified from inpatient registers of referral hospitals; 81% were among males and the reported CFR was 54%. Data entry errors of conditions adjacent to "tetanus" on the reporting form were observed in multiple cases. In addition, more than 4,000 tetanus *vaccine doses* were recorded as tetanus *cases* at a single health center in Kampala (an error that was corrected in the DHIS2 database) (86). The results of this investigation were used in developing the first global standards for non-neonatal tetanus surveillance (14).

Indicators of immunization and surveillance data quality

A systematic review of data quality assessment methods for public health information systems found that completeness, timeliness and accuracy were the most commonly used attributes of data quality, among a total of 49 attributes (87). Another review specific to immunization data quality noted that a wide variety of data quality attributes and indicators had been used and attempted to systematize a limited defined set of attributes that were operationally relevant for monitoring (17) (Box 2.2). Similarly, the review completed for the WG identified many versions of data quality measures for immunization coverage, denominators, and surveillance related to the same attributes, but was not exhaustive (Annex 9).

Though many measures exist, it could also be said that the same analysis approaches and indicators to assess immunization and surveillance data quality have more or less been in use since the beginning of this discussion with the SAGE in 1998 (see 1.1 Background). Moreover, use of a handful of key indicators has generally coalesced as various guidance has evolved, and publications have been informed by the guidance. Efforts by the GVAP WG to develop data quality indicators for immunization coverage presented to the SAGE in October 2015 largely focused on a composite indicator that included the following: (i) completeness of reporting, (ii) internal consistency of the administrative coverage numerator, (iii) internal consistency of the administrative coverage denominator, and (iv) external consistency of administrative coverage with other data sources. The composite indicator was rejected because of issues of interpretability for monitoring. In the absence of global indicators, Gavi established their own panel of indicators for monitoring data quality in Gavi-supported countries (Box 2.12).

Box 2.12. Gavi, the Vaccine Alliance efforts to improve data quality and use

Beginning in 2014, funding proposals submitted to Gavi required countries to address data quality in four ways:

1. conduct an annual desk review;
2. conduct periodic (i.e., at least once every five years) in-depth system performance assessment that includes a desk and field review;
3. conduct a national vaccination coverage survey at least once every five years; and
4. develop a data improvement plan.

In 2016, the Gavi Secretariat launched a new strategy for 2016–2020 with ambitious goals and targets. To monitor progress against these goals, Gavi relies on a set of performance indicators to track the number and percentage of Gavi-eligible countries that:

- have conducted a nationally representative household survey within the prior five years;
- have less than a 10%-point difference between reported national administrative vaccination coverage for DTP3 and the estimated vaccination coverage from the most recent nationally representative household survey;
- have available subnational vaccination coverage data;
- report national administrative DTP3 coverage of >100%;
- have ≥10% of their districts reporting administrative DTP3 coverage of >100%;
- have <10% discrepancy between country-reported target population estimates and those from the UN Population Division; and

- demonstrate the use of data to guide the targeting and tailoring of their activities.

Gavi's efforts to emphasize data quality and data use as critical components of national immunization programme monitoring and evaluation is promising. Further work is needed to evaluate the quality of country efforts and the actual impact of the new focus on data quality in Gavi funding proposals.

While the focus has been on measuring data quality, measures of data *use* are generally lacking. This is despite the strong global interest in creating a "culture of data use" centered around continuous improvement. Gavi has included a data use measure among their monitoring indicators (Box 2.12). The use of VPD surveillance data is often identified through follow-up case investigation and public health response activities (14). NITAGs also use this data (Box 3.2). There is some evidence from the literature that the data quality improves as data use increases (88). Increased immunization program performance has also been noted to coincide with increased data quality and use (5, 83, 84, 89). While these relationships have been demonstrated in the field of healthcare quality improvement, further work to examine the relationship between data quality, data use, and immunization program improvement would be useful. But, developing a common lexicon of definitions, attributes and indicators is needed first.

The WG proposes that a panel of indicators (with 1–2 "key indicators") relating to key data quality and use attributes, similar to what exists for surveillance performance monitoring, be developed for use in routine monitoring of immunization data quality alongside coverage and equity monitoring. The WG's perspective is that composite indicators are of limited value because of they can obscure issues with the individual components of the composite indicator. The indicators identified in [Annex 9](#) can be used as a starting point to creating such a panel, recognizing that the indicators identified do not cover all attributes of data quality (e.g., relevancy,⁴ which is rarely, if ever, evaluated using measures).

2.3.3 Recent examples of regional and national efforts to improve data quality

Improvements in the area of data quality and use have recently been highlighted by the SAGE, the GVAP SAGE Working Group, Gavi and the WHO regions. In the 2016 GVAP progress report, the collection of district-level coverage data for the WHO-UNICEF JRF was highlighted, as were two countries (Mexico and Uganda) that took decisive steps to improve data quality (5). Box 2.13 highlights different initiatives to improve data quality and use across the regions. Boxes 2.14 and 2.15 highlight efforts to improve vaccination coverage in China and India, respectively. Other country case studies are included in the Annexes.

Box 2.13. Recent WHO Regional efforts to improve immunization data quality and use

African: Support of immunization monitoring within District Health Information System 2 (DHIS2), a tool widely used in the Region, including piloting of a Data Quality module

Americas: Work on Electronic Immunization Registries (EIR), particularly the [Regional guide](#) and the [Data Quality Self-assessment \(DQS\)-Plus](#) assessment tool including EIRs

Eastern Mediterranean: Quarterly feedback to countries with an analysis of subnational level immunization data, which countries have appreciated

European: Prioritization of immunization data use for action exemplified through formation of a new "Immunization and Surveillance Data Team" in the Regional Office

South-east Asian: Push to develop comprehensive [VPD surveillance standards](#) in 2017, ahead of the global guidance

Western Pacific: Support of web-based information systems for surveillance that allow direct integration of epidemiological and laboratory data (e.g., measles and rubella)

⁴ Degree to which the data collected and reported reflect what is most important to support decision-making and not in excess of what is needed so as to consume scarce resources.

Box 2.14. Efforts to improve vaccination data quality in China

In China, the country program recognized that despite high coverage, poor data quality was preventing identification of measles immunity gaps, resulting in barriers to achieving measles elimination. After soliciting and undergoing a consultative assessment process with support from WHO and the US CDC in 2017, China is starting to implement the recommendations, including improving coverage monitoring methods, including disaggregating by residential status, triangulating surveillance data to identify immunity gaps, assessing the utility of different target population ascertainment methods, and planning to conduct coverage surveys (Annex 10).

Box 2.15. Improving state and national official coverage estimates in India

In 2014, the Government of India and its partners conducted a data review process similar to that used by WHO and UNICEF at the global level (see Box 2.3). Vaccination coverage data from 1) administrative reports, 2) coverage surveys and 3) rapid monitoring were used to estimate state coverage (39). In more than half of estimates, the official coverage was based on a survey estimated coverage value or an interpolation from a survey estimated coverage value. Only about 10% of estimates were based solely on administrative coverage. While estimates of coverage are subject to limitations of the underlying data, the resultant state and national level official vaccination coverage estimates produced through the process were felt to be improved over previous official coverage estimates based only on administrative coverage. Reports suggest that the Government of India has repeated the data review and estimate production exercise at least once since the original exercise (Annex 11). Similar triangulation exercises were done, with WHO and UNICEF support, in Indonesia (2017), Ethiopia (2017) and Pakistan (2018).

Box 2.16. Immunization data quality improvement activities in Nigeria

The Nigeria EPI program faces several challenges, including insufficient health workforce, insufficient cold chain capacity, weak supply chain, issues with demand for immunization (lack of awareness, distrust, and social-culture norms), and poor routine immunization (RI) data quality. For example, administrative coverage rates calculated using denominators based on census projections routinely exceed 100%. Historically, large discrepancies have existed in the coverage estimates from DHS or MICS and EPI surveys. The Nigeria EPI program has recently undertaken many efforts to improve data quality, including:

- Pilots to improve denominators through triangulating different potential data sources: a) satellite imagery/geographic information system information, b) house-to-house enumeration of children younger than 15 years, and c) micro-census enumerations.
- The government collaborated with MICS on a national immunization coverage survey (MICS/NICS) in 2016 and has preferentially used these results compared to questionable administrative coverage data.
- The web-based software District Health Information System, version 2 (DHIS2) was adopted in 2013 as the Health Management Information System (NHIMS). An RI Module was launched in 2014, and is currently present in all 36 states of Nigeria with more than 67,000 health care professionals, local government area (LGA) officers and state officials trained, and 774 laptops provided. This Module serves as the only platform for reporting RI data in the country from December 2018.
- A DHIS2 RI dashboard was developed to support improved accountability and use of data for action down to the health facility levels. The dashboard includes indicators for: data reporting, coverage and drop-out rates, RI vaccination sessions, supportive supervision visits, vaccine management and logistics, cold chain functionality, and RI funding disbursed to HFs.
- Workforce capacity support for data improvement occurs through the on-the-job mentoring and supportive supervision of a network of 266 Nigeria Stop Transmission of Polio (NSTOP) officers assigned to high-risk states and LGAs (Annex 12).

3. Governance: Leadership, Policies, and Standards to Maximize the Data Quality and Use

Key messages

- The generation and use of data, including immunization and VPD surveillance data, needs to be an integral part of a country-owned health system, rather than a separate, often donor-financed project (especially in LICs). Strong leadership and political will on the part of national governments are critical to developing efficient and effective information systems.
- Generating data that is of high-quality requires developing and implementing national policies and standards that govern all stages of data generation and use (from selection of variables to methods of data collection, analysis, reporting, storage/archiving and sharing).
- Often the costs and amount of personnel time required for data collection, management and reporting activities are overlooked or under-estimated. Adequate resourcing of data-related activities is critical for obtaining quality data that are relevant for use.
- Articulating clear roles, responsibilities, deliverable at all levels, along with frameworks for monitoring serves as the basis for monitoring and accountability towards programme improvement.
- Good coordination and collaboration across areas and organizations is necessary to avoid the common problems of fragmented information systems (e.g., disease-specific) and inefficiencies related to lack of data sharing or non-interoperable systems.
- Governments need to have plans, policies (including legal frameworks) and mechanisms in place for the sharing of immunization and VPD data — both within countries and across borders — to enable decision-making and effective public health responses.

3.1 The importance of governance in maximizing data quality and use

Developing strong information systems for immunization and VPD surveillance data involves a wide range of activities and functions by government decision-makers, program managers and other key stakeholders. Policies, processes, and organizational structures must be put in place to provide EPI managers and frontline workers with the authority and skills necessary to collect high quality data and make use of data for action (75, 90). Standards and operating procedures for data and information systems must be developed; sufficient resources allocated for data collection and analysis, as well as for data quality improvements; and transparent and effective accountability mechanisms established for the collection, use and distribution of data (91-93). Good governance related to immunization and surveillance data also requires that governments, international organizations and partners share a common vision, set of strategies, and framework for monitoring and evaluation, as well as collaborate and coordinate on activities to improve data and use (94). Regulations and agreements governing the sharing of data that also take privacy and security concerns into account are also critical.

Different sources of information were reviewed to develop this chapter, including literature reviews; frameworks, approaches and tools on governance and; and global, regional and country experiences and lessons learned gleaned from expert interviews and the published and grey literature. Below is a summary of the findings for different critical elements that are required for good governance of immunization and surveillance data.

3.2 Leadership, ownership, political will

Strengthening immunization data quality and use is a long-term process requiring evidence-based decisions that must be owned by countries down to frontline where data is collected. To be successful, immunization monitoring and VPD surveillance systems must have political support; clearly defined objectives and scope; infrastructure; sustained and human, technological and financial resources; and a transparent and closely monitored plan, with timelines and responsibilities (60, 95). The process must be resilient to changes of administration, so that new authorities remain committed to the data systems and plans for improvement in place. Systematic progress reports of data improvements should be provided to track progress against the plan of activities and budget and to make adjustments, as needed.

An information system for immunization must meet the needs of decision-makers, while at the same time, be useful and accepted by health workers at all levels, and particularly at the local level, it should facilitate their work, not slow them down. The systems should also allow for effective feedback mechanisms, so that health workers at the lowest level feel empowered to use the data to improve programme performance and to contribute to strengthening the system at their level (8).

Effective leadership and organizational culture have been cited as factors influencing the successful implementation of functional health information systems (96-103). Lorenzi et al., (98) argue that people and organizational factors have been overlooked in the implementation of health information systems, and maintain that these factors determine the success or failure of these systems, especially a sense of ownership and the qualities of the leadership. They highlight three domains that should be further researched in terms of their impact on information systems: *motivation, culture and leadership*.

The lack of political commitment to improve the use and quality of data has been reported as a reason for the failure of immunization information systems in many settings, as a result of a lack of policies, regulations and prioritization, such as a dedicated budget for surveillance or allocation of funds for implementation (104) (*Annex 7*) (69). Mexico's experience with its PROVAC electronic immunization registry is an example of the challenges of governance and sustainability of the immunization information systems, as well as the demonstrated political will of the government in making necessary improvements that resulted in reductions in reported coverage rates (Box 3.1) (105).

Box 3.1 Lessons learned from the immunization information system in Mexico (PROVAC)

Mexico's PROVAC was one of the world's first Electronic Immunization Registries (EIR), used between 1991 and 2013. PROVAC allowed recording of the immunization status for children and pregnant women and the calculation of coverage rates. Use of an open-source and open-access program allowed the generation of multiple versions of the same program, which led to the system becoming fragmented and obsolete over time (105). This was likely also related to the original PROVAC not being flexible enough to adapt to the rapidly changing immunization schedule, insufficient resources devoted to the maintenance of the system, and inadequate monitoring of the data being produced. Reported coverage levels were high, but numerator data could not be confirmed, and denominators used for immunization monitoring had not been validated against data from the National Statistics Office.

In 2013–2014, Mexico acknowledged the poor quality of its vaccination data, stopped using PROVAC, and developed a plan to create an improved EIR. This involved modernizing the information system, revising local and regional population estimates, and returning to use of the administrative method to calculate coverage. These efforts to improve the accuracy of coverage data resulted in a decline in reported vaccination coverage levels (e.g., from 99% to 83% for DPT3) and were consequently recognized globally as an example of transparency and accountability.

Currently, Mexico has made significant progress with its new EIR and in implementing "[la cartilla electrónica de vacunación](#)", a vaccination home-based record. The record includes a chip that saves the user's vaccination history electronically, along with the traditionally hand-written data. The transition has been difficult due to challenges in coordinating public and private immunization service providers and multiple health insurance mechanisms, but the country is committed to moving towards an improved EIR.

3.3 Coordination and collaboration

In today's public health system, immunization data are produced and used by many different institutions, including ministries of health, national statistics offices, the private sector, NGOs, CSOs, donors and stakeholders. Thus, in many places, health information systems have evolved in a haphazard and fragmented way as a result of administrative, economic, legal or donor pressures. Coordination between different health facilities and across health programmes are necessary for there to be complete, accurate and timely information to support decision-making. For example, the lack of coordination, data harmonization and communication between different units involved in VPD surveillance can result in a lack of agreement between epidemiologic and laboratory databases or between aggregate and case-based surveillance databases, thus negatively impacting data quality (106). Lack of engagement of private providers to report immunization and surveillance data can result in data that is incomplete and not representative of the country ([Annex 7](#)); this has already been highlighted by SAGE (69, 107).

To strengthen health systems, including immunization and surveillance information systems, partners and related initiatives must coordinate their technical assistance with the government and each other. This is especially true in low and middle-income countries with weaker health systems, where multiple partners provide technical, operational and financial support for health systems strengthening (108). The [Health Data Collaborative](#) (HDC) is an example of collaboration among multiple global health partners — international agencies, governments, philanthropies, donors and academics — working together to empower countries to strengthen the availability, quality and use of health data for local decision-making. The HDC is not a fund, but rather a partnership that aligns countries, donors and other partners to make investments in the most efficient and effective way (109).

It is also critical that national organizations be identified to support the immunization program, such as universities and schools of public health, professional associations and group of experts. Experience with national immunization technical advisory groups (NITAG) demonstrates how the participation of group of national experts from a range of disciplines and organizations can improve the process of synthesizing evidence and making decisions (Box 3.2).

Box 3.2. Coordinating bodies for data use and decision-making on the national and regional levels

[National Immunization Technical Advisory Groups \(NITAGs\)](#) are multidisciplinary groups of national experts responsible for providing independent, evidence-informed advice to decision-makers and programme managers on policy issues related to immunization and vaccines. The Global Vaccine Action Plan calls for all country to establish or have access to a NITAG by 2020. Regional Immunization Technical Advisory Groups also provide advice on regional policies and strategies, ranging from vaccine research and development, to immunization service delivery and disease surveillance, and linkages with other health interventions (110).

The Global Certification Commission (GCC), Regional Certification Commissions (RCCs), and National Certification Committees (NCCs) provide a framework to assist the Global Polio Eradication Initiative (GPEI) in independently certifying and maintaining polio eradication in a standardized, ongoing, and credible manner. Members meet regularly to comprehensively review population immunity, surveillance, laboratory, and other data to assess polio status in the country (NCC), region (RCC), or globally (GCC) (111).

Similarly, for measles and rubella, National Verification Committees (NVCs) at the country level gather, analyze, and validate national data, and submit the necessary documentation to the Regional Verification Commission (RVC). RVCs are comprised of independent experts tasked with reviewing annual progress toward measles and rubella elimination for each country or area in the region (111).

Malawi's experience with the Malawi Health Data Collaborative (MHDC) demonstrates how a collaborative approach between development partners and the government can successfully align country needs and partner support. The Collaborative was launched in 2015 to improve real-time data and align reporting requirements, including harmonizing health indicators. When this experience started, health facilities were reporting on hundreds of different indicators and using 16 related electronic systems — only two of which routinely exchanged information — resulting in a fragmented information system. The reporting rate for most programmes was below 80% and the timeliness of

reporting was below 65%. A country plan was developed to align government and partner investments in health information systems, using the District Health Information System (DHIS 2) as the common reporting platform. However, despite the successes of the MHDC approach, fragmentation of the system still exists, often caused by development partners introducing systems that are duplicative or are siloed by programmatic area or geographic location. High-level leadership within the Ministry will be critical to ensure harmonization and streamlining of health data and reporting systems from all partners (112) (*See also Tools Chapter*).

3.4 The role of data in ensuring accountability of immunization programmes

Good governance requires evidence-based policies that inform decision-making on issues related to public health by upholding the key governance principles of fairness, accountability, transparency and participation (113). As funding for global health has grown during the past years, it has become increasingly clear that data quality and use is key to monitor progress and allocate the resources needed to achieve the expected results (114).

The use of results-based financing mechanisms by major global donors has created further demand for timely and reliable data for decision-making (56). This is particularly relevant in the low-income countries facing the biggest challenges with data quality, particularly coverage data. In the era of global initiatives and funding opportunities that are target- and performance-based, there are concerns about the possibilities for perverse effects encouraging over-reporting, for instance, of vaccination coverage data. Furthermore, SAGE, in 2011, noting the issues related to the accuracy of coverage figures, cautioned against their use for performance-based financing (4). This approach can create a strong argument for not focusing entirely on achieving absolute targets as funding criteria but also on improvement, in terms of both programme performance and the quality of the data.

In order to hold immunization and disease surveillance programmes accountable, the roles and responsibilities of health workers at all levels of the system concerning the collection, analysis, review and use of immunization and surveillance data should be clearly defined in their terms of reference. The WG has developed a basic framework defining roles and responsibilities for data quality and use from the local (facility) level all the way to the national, regional and global level (Figure 4.1 in *Workforce chapter*). Articulating clear expectations for job duties and deliverables can serve as a basis for monitoring and accountability. The introduction of an accountability framework in the polio eradication program in Nigeria and Ethiopia resulted in improved staff performance and overall program indicators for AFP surveillance (83, 84). Lessons learned from these experiences have the potential to benefit other disease programs and potentially immunization monitoring in general.

3.5 Resource allocation for generating and improving immunization and surveillance data

It is critical that accurate estimates be made of the resources needed for implementing activities related to immunization and VPD surveillance data and funding any gaps identified in order to ensure sufficient financing for these activities. Adequate resources are needed to cover the costs of personnel dealing with data collection, analysis and reporting at all levels; electronic information systems (e.g., computers, servers) and their maintenance; data review meetings; and communications. High-quality VPD surveillance systems require sufficient investments in personnel, laboratories (including equipment, reagents, test kits and other supplies), and logistics and communications for field investigations, as well as sample transport (115). A lack of funds for these critical resources can result in data that is of poor quality and limited use (104), as found in a systematic review of the implementation of the Integrated Disease Surveillance and Response (IDSR) (67). The comprehensive multi-year plans (cMYP) that countries prepare for their immunization programmes can be used to advocate for funding these critical operational costs (116).

The costs of personnel involved in data activities — in terms of the number of staff needed to adequately manage information systems and the amount of time health workers spend on data collection and reporting — can especially be overlooked or under-estimated, particularly as information systems are expanded and improved. A five-country study by WHO showed that health workers in LMIC setting spend a third of their time on data recording and monthly reporting processes at the primary care level (A. Siyam, WHO, personal communication). As countries expand and upgrade their information systems, e.g., as a result of new vaccine introduction, the impact of these changes on the number of

staff required and their workload needs to be considered in human resource planning. England has recognized this problem and now requires that the additional work-burden on staff and related costs be assessed before any changes in immunization data collection requirements be implemented (Box 3.3).

Box 3.3. Assessing the data-related burden on the workforce in England

In England, *NHS Digital* is the government organization that, among other responsibilities, provides the National Health System (NHS) with information, data and IT systems. Part of its mandate is to offer data standards assurance services (DSAS) that ensure that any new data collection or changes to existing data collection comply with data standards and have a legal basis, and that the benefits of the changes outweigh any additional burden on the system. To ensure that is the case, when changes to immunization data requirements occur – with recent examples including the introduction of new vaccines and the move to collect facility-level rather than district-level data – the immunization team at the national level must re-assess the implications of these changes on the health workforce. This assessment includes estimating the staff time required at both at the local level where data collection and reporting occurs, and at the central level, where data management, analysis and dissemination takes place, as well as associated costs. The DSAS then examines the request and the resulting analysis and determines whether the additional burden on staff resulting from the new requirements is acceptable in relation to their benefits.

3.6 Establishing standards for data collection, analysis, management, use and storage/archiving

Functional and efficient data systems that are useful for programme monitoring and decision-making require the development of standards for all aspects of data management, including standards (e.g., what variables to include and how to name them), and detailed procedures for collecting, processing, preserving, using/reusing, sharing, and disposing of data (117). Such management strategies and standards must address not only immunization and VPD data collected in the public sector but in all sectors, i.e., the private sector, NGOs, etc. Standards must not only exist, but also must be used (e.g., through sufficient training and incentives for health workers).

These standards are especially critical when immunization information systems are being integrated into, or need to interoperate with, broader health management information system, which GVAP recognizes as important to increase the efficiency and effectiveness of data systems (e.g., to avoid errors by having to enter the same data in different systems and reducing the burden on health workers). This integration can be accomplished by developing an integrated electronic health management information system (HMIS) that includes the required elements for monitoring immunization data, or alternatively, through electronic data exchange protocols between different systems following interoperability standards. There are several documents available, such as the WHO Health Metrics Network Framework, that outline global standards for health statistics and indicate how they can be integrated into country health information systems (118). Standards for electronic information system allow for the accurate and consistent exchange of data across various health programmes and departments and different geographical areas. Failure to adopt electronic information standards could result in collecting data that is not fit-for-purpose or challenges to share data across different information systems and/or different levels. An experience with electronic system standardization at the regional level is described in Box 3.4 (*See also Tools Chapter 5*).

Box 3.4. The European Surveillance System (TESSy)

The European Centre for Disease Prevention and Control (ECDC) collects, analyses and disseminates surveillance data for 52 diseases from 31 countries. In 1998, the European Commission formalized disease surveillance networks previously funded as pilot projects. As a result, these informal networks grew and were standardized, and specific reporting meta-datasets were adopted and eventually incorporated into a single system — [The European Surveillance System \(TESSy\)](#). Access to TESSy data are restricted by EU data protection laws. However, member states have interpreted EU legislation on processing personal data in different ways, resulting in countries transferring different types of data to ECDC. This has made the standardization of surveillance data collection difficult. The solution has been to allow ‘mandatory’ and ‘voluntary’ variables to be reported, as well as the reporting of aggregate data in some instances.

Since the system was built gradually and upon existing networks, flexibility when harmonizing different pieces of national legislation has been essential, even at the expense of the ability to standardize. Even though it was not possible to involve all countries at the onset, the EU legal framework is capable of change as new needs and technologies arise, and agreements can be updated to reflect such developments (119).

Numerous assessments in many countries, however, have reported a lack of standards, guidelines and other tools for immunization and VPD surveillance data systems. Murray et al. reported that data collection tools for immunization coverage were not standardized, limiting comparisons within and across countries, and making assessments of trends in coverage challenging (38). Other studies report a lack of VPD surveillance standards, including for case definitions, methods for case detection, active case searches, case investigation, and response ([Annex 5 and 7](#)) (37, 69). As described in Chapter 2 (Section 2.3.1), WHO has made a major effort in the past few years to fill in existing gaps in needed guidance materials by publishing a series of global guidance and standards, as well as regional tools, such as the Integrated Disease Surveillance and Response (IDSR) guidelines for Africa.

Other types of standards are related to VPD surveillance, they need to be assessed and must be modified as the epidemiologic situation and disease control goals and targets change. A salient example is how polio surveillance standards had to be adapted once regions were certified as having been polio-free. This is because post-certification surveillance requires very sensitive surveillance systems to detect the presence of poliovirus of any kind, such as wild poliovirus, Sabin, or vaccine-derived (VDPV); on the latter, further differentiation is needed as to identify whether the VDPV is circulating or Immunodeficiency-related or ambiguous ([Annex 13](#)) (120).

Archiving historical immunization data and ensuring these data are incorporated into new information systems is essential to monitor epidemiological trends of VPDs, since current population immunity is largely the result of vaccine coverage in birth cohorts vaccinated in the past. Nevertheless, data archiving is often an overlooked aspect of data management in electronic immunization registries (EIRs), even in high-income countries (121). In the United Kingdom (UK), for instance, immunization registers discard records once an individual reaches the age of 18. Some countries have recognized this as an important problem; Australia, for example, has recently moved to life-long immunization records (122).

Data security is also becoming an emerging issue, as EIRs which contain individual patient records, are increasingly introduced. Planning for data security requires a professional ethics officer who is responsible for protecting identifiable data, which are often collected without individual consent. Preserving confidentiality of individual-level data is critical because societies can sometimes respond to persons with infectious diseases in stigmatizing and discriminatory ways (123). Similar principles need to be followed when private sector data is shared within the country.

3.7 Data sharing policies and agreements

Sharing routine public health surveillance data enables regional collaboration, capacity strengthening, insight into public health system performance and ultimately better control of infectious diseases (124). This is true between levels of the health system within individual countries, between countries at the regional level, as well as at the global level. Nonetheless, despite examples of success, sharing public health surveillance data beyond national borders is still not the norm.

A systematic review by van Panhuis et al (2014) identified five types of barriers to local, national and international health information systems sharing surveillance data:

- **Technical barriers**, including a lack of or inadequate data collection and preservation, restrictive data formats, lack of meta-analysis and standards, and language barriers (106, 125);
- **Motivational barriers**, including institutional or personal factors that limit data sharing, such as the presence or lack of incentives, lack of trust between data providers and users, and a lack of resources and time needed to share data;
- **Economic barriers**, which include the potential negative economic effects of reporting disease outbreaks.
- **Political barriers**, such as a concern for potential negative consequences of high reported disease incidence or outbreaks, bureaucratic hurdles, a lack of political will to promote a culture of data sharing, and a lack of trust (104, 126); and
- **Legal and ethical barriers**, including various legal instruments that restrict data sharing, such as data ownership and copyright laws, often resulting from mandates to protect individual and community privacy (125, 127).

An expert consultation tasked with finding solutions to overcome these barriers to sharing public health surveillance data defined seven key principle to achieve this: 1) building trust, 2) articulating the value of sharing data, 3) planning for data sharing, 4) achieving quality data, 5) understanding the legal context, 6) creating data-sharing agreements, and 7) monitoring and evaluation. To be successful, data sharing agreements do not always need to be formalized. In fact, evidence suggests that such agreements are unnecessary if informal arrangements can accomplish the goal of sharing as long as the rights, interests, needs and expectations of stakeholders are taken into account (123).

The legal implications of sharing routine surveillance and immunization data vary based on geographic level, the type of institutions involved (e.g., private vs public), the type of data, the level of public health threat, and other contextual factors. Legal restrictions with sharing data across borders mainly relate to disaggregated data containing confidential or personal information. Aggregated VPD surveillance or vaccine coverage data shared with WHO through the JRF, for example, are not subject to complex legal regulations. Legal instruments exist where there are urgent public health imperatives to sharing information, both at the regional level (128) and globally through the International Health Regulations (129). Legal barriers to data sharing are uncommon, but may be cited when the obstacles are more political or motivational in nature (119). Data-sharing agreements can help resolve differences or ambiguities in law and are most successful when the context is defined as precisely as possible, supported by local knowledge, and when relevant laws and regulations are taken into account. In some instances, an agreement that is not legally binding may be more suitable than using legal means.

3.8 Conclusions

A number of policies, processes, standards and mechanisms need to be established to improve the access to quality and useful of immunization and surveillance data. The quality and use of these data will only improve if countries and all immunization stakeholders agree to a common vision and set of strategies, and collaborate more closely on activities to improve immunization-related data. Partners should collaborate on the assessment, planning and implementation of plans to strengthen data quality and use, and align their support, investments and activities to national plans and strategies to avoid parallel or fragmented information systems and data collection efforts. Communication and information sharing between different health facilities and across different programs and partners are crucial for the availability of complete, accurate and timely information to support decision-making. Achieving these goals requires the development and implementation of data standards and clear processes – for all steps involved in data generation, from data collection to analysis, reporting and use. At a national level, policymakers must address the fragmentation of health information systems, and encourage data sharing between the public and private sector, NGOs and anyone providing vaccines, or who potentially can identify a VPD case. Legislation, policies, and accreditation/certification protocols should guarantee data security in order to prevent loss of data and protect confidentiality protection, but data sharing agreements are also needed to support effective public health decisions and responses.

4. People: Building Workforce Capacity in the Generation and Use of Immunization Data

Key messages

- Health workers often lack the necessary skills, competencies, and time, to perform immunization data-related tasks adequately.
- Addressing the issues around inadequate skills in quality data collection and use requires a systematic approach and a dedicated effort by governments to provide continuous and effective competency-based training.
- Continuous training involves the inclusion of data-related competencies in pre-service training for health professionals, as well as on-going in-service training, supportive supervision and feedback to health workers — all placing a focus on data quality and use.
- There is evidence that current pre-service training does not adequately prepare health workers with the necessary skills and competencies to collect, analyse and use data, in part due to the lack of skills in this area among most instructors at professional training institutes.
- Studies show that, despite the necessity of in-service training in data-related skills, most in-service training has not made substantial differences in improving the skills and practices of health workers in the generation, management and use of data.
- Systematic reviews show that multi-faceted approaches to capacity building, e.g., mentorship, feedback, group-problem solving, are more effective than single strategies
- Supervisors should make review, assessment and feedback regarding data a critical part of their supervisory visits and be capable and trained to do so.
- Good leadership and an adequate culture of data demand and use are also vital for people to engage in improving data quality and use.

4.1 The importance of the health workforce in ensuring data quality and use

Equipping health workers at the local level with the necessary data skills is especially critical, since there is no data quality without high quality data at the local level. Capacity-building of health workers in data collection, management, and analysis has been shown to be key to improving the quality and use of immunization and VPD data. The scoping review of the barriers limiting the quality of immunization data in low- and middle-income countries highlighted the lack of capacity-building of health workers in data management and use as a key factor limiting data quality ([Annex 14](#)). Further, issues with workforce capacity were identified more frequently than all other issues, in just over 80% of the references included in the review of barriers limiting VPD surveillance data quality ([Annex 7](#)) (69). Therefore, in order to sustain investments in improving data quality in most LMICs, it is essential to increase health workers' competencies and motivation in collecting, analysing, reporting and using data.

Besides the lack of data-related competencies, another key issue affecting data quality and timeliness is that front-line healthcare workers who are responsible for completing data registers and immunization monitoring charts and for compiling monthly statistics and other data-related tasks have multiple responsibilities – with clinical care being the priority. This can result in their not completing routine data collection until many days after an event (e.g., an immunization session), if at all (130-132) and in otherwise limiting the time available for and allocated to data collection, analysis and reporting, impacting data quality (133, 134).

The focus on technology – rather than on the people who drive information systems – has often led to the development and implementation of complex health management information systems, or new electronic tools. However, these still require human resources and capability. Persistent challenges identified with these systems include inadequate human resources, insufficient capacity of Health Information System (HIS) staff at all levels, high staff attrition rates, inadequate training,

unstandardized job descriptions, limited HIS development planning and the lack of an established health information career path and accredited training programmes (135).

Interventions to address skill shortages, such as in-service mentoring and training tailored to meet the needs of information personnel, and adequate supervision for data-related tasks, are needed. If adequate resources are not channelled into developing a cadre of qualified and skilled health information personnel, these skill shortages will continue, and issues around poor data quality will continue to be a recurring problem. Continuous capacity-building in immunization data-related tasks, such as data collection, analysis, interpretation, synthesis and use, and efforts to improve data quality should be strengthened at all levels of the health system, ideally with the guidance of frameworks, such as the minimum health information competencies framework (136).

Below we highlight key elements required in the preparation and utilization of health workers in order to generate and use high-quality immunization and VPD surveillance data.

4.2 Defining and assessing competencies in data collection, analysis and use

Issues around the competencies of health workers related to immunization data management tasks have been widely documented. Competency can be defined as a combination of knowledge, skills and abilities needed to perform a specific task in a given context (137). Competencies can be gained through experience, pre- and in-service training, and the assistance of mentors and preceptors (138). WHO, building upon the work of the *Standard Immunization Competencies* project, has developed an immunization competency framework that defines the roles and responsibilities of health workers at all levels related to data quality and use (75, 139). This framework can be used to assist immunization programmes to develop or revise policies related to their workforce, including hiring, staff development, and human-resource planning. In April 2017, SAGE emphasized the “importance of looking at functions and competencies from a health-system perspective so that all the immunization functions are adequately addressed...” and 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 (140).”

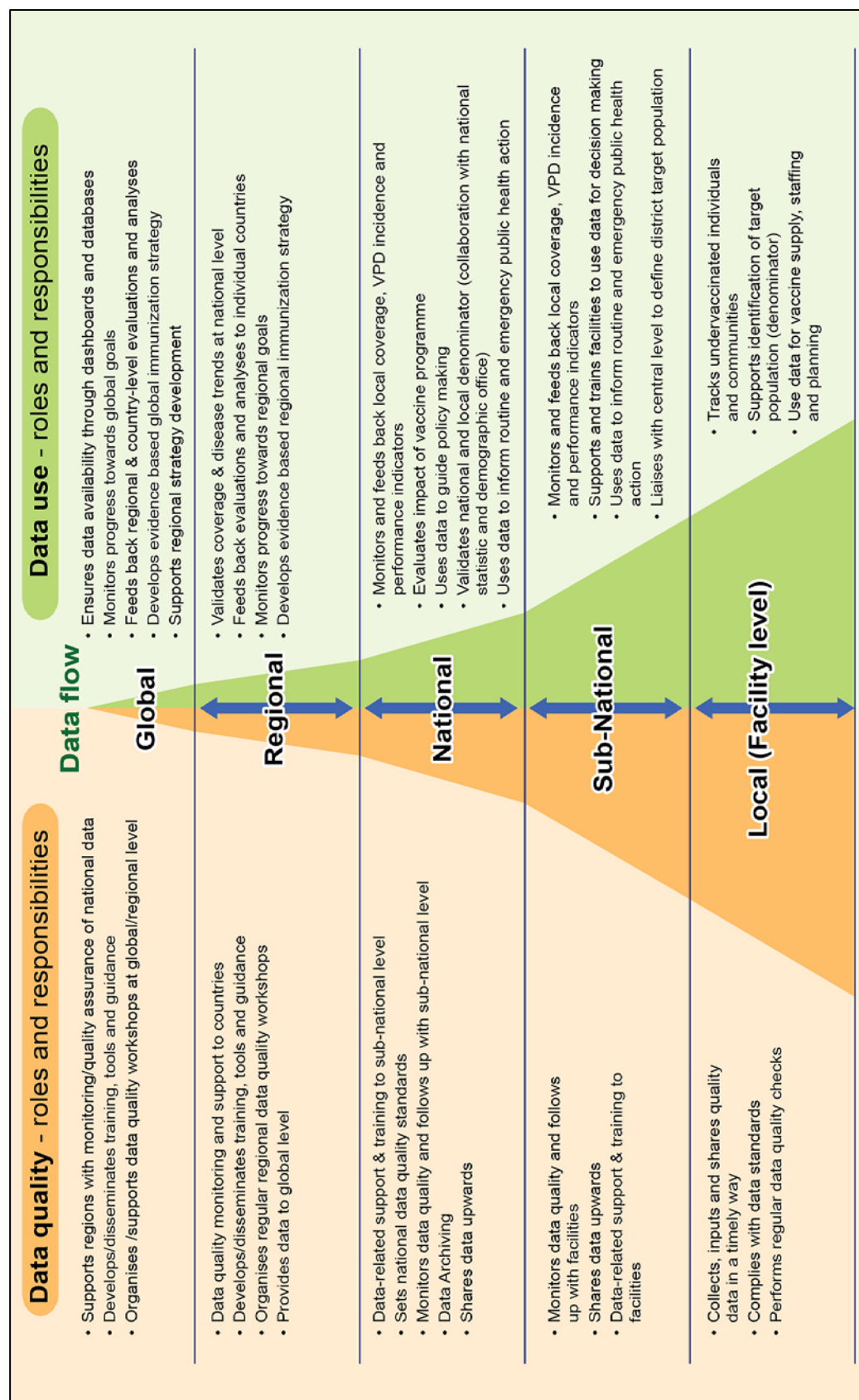
The WG further attempted to define data quality and use roles and responsibilities for the different levels (Fig. 4.1). Interventions to address issues around data quality and insufficient skills sets, including plans to hire new staff, should be focused on elements of these competency frameworks.

4.3 Pre-service training in data generation and use

Findings from the scoping review of pre- and in-service immunization data training show that both are essential for the development of health worker skills in collecting, managing, analysing and using immunization data at all levels of the health system ([Annex 15](#)) (141). However, the evidence also shows that current pre-service training often does not adequately prepare health workers, especially clinicians, with these necessary skills and competencies. More importantly, training institutions are not adequately equipped to provide health personnel with data-related skills, as most tutors and clinical instructors at these institutes often lack sufficient skills and knowledge in this area themselves. Continuous learning and development programmes are often missing to increase educators' knowledge and improve current skills (142-144).

Inadequate capacity due to a lack of relevant training in data collection processes has been widely documented (135, 145-147). Deficiencies in numeracy skills among health workers involved with data collection at both the facility and district levels has particularly been highlighted (148-150), and is attributed partly to the lack of numeracy skills among nurses when they are in training (151-153). Studies conducted in Australia and the UK found that nurses lacked the necessary numeracy skills to solve basic mathematical problems needed to perform daily clinical functions, such as drug administration and compiling statistics from patient records, let alone the skills required to adequately manage, interpret and use EPI data. The Australian study found that mathematics is not a prerequisite for entry into the nursing degree programme, nor are nursing students trained in numeracy during their nursing training (152). These nurses required additional in-service training to be able to effectively carryout EPI data management tasks.

Figure 4.1. Framework of immunization data roles and responsibilities developed by the SAGE Data WG



There are a number of recommended curricula available world-wide for pre-service training of health professionals that include modules on the collection, analysis, management, and use of immunization data (154). These include the “EPI Prototype Curriculum for doctors and nursing/midwifery schools” in the WHO African Region (155, 156) and the Mid-Level Management Course for EPI managers (157), which has been recommended for use both for pre-service training and for certifying professionals for practice (158).

4.4 In-service training

In-service training is a regular process to refresh and update skills, competence and knowledge in key areas. Given that pre-service training often does not adequately prepare health professionals to collect, analyse and use data, in-service training is critical to equip them with these skills and competencies.

As part of an effort to improve data demand and use, a “logic model for strengthening the use of health data in decision making” has been proposed (159). Among the eight interventions suggested is the ability to build the capacity of both data producers and users in core competencies around the use of data, such as the ability to analyse, interpret and synthesise data, and skills to disseminate information. However, one of the reasons cited in the literature for poor data quality is the issue of staff attrition (135, 160, 161); shortages in health information staff has been identified as a major problem affecting data quality and use (162). Cristofari et al also observed the double-edged effects that in-service and on-the-job training have on the health information system. On the one hand, training ensures the capacity of frontline staff to effectively perform their tasks while, on the other hand, it increases their market value and the opportunity to opt for better paying positions, thereby causing staff attrition. These challenges could be addressed if staff are well motivated, have a defined career advancement path and are given sufficient incentives to stay on the job (162).

Most in-service training of healthcare workers on health information-related tasks has not made substantial differences in skills acquisition and practices (135, 163). It is unclear why, in spite of the resources invested in training, health workers still lack the skills to effectively perform data-related tasks. This raises the question of why additional in-service training seems unable to upgrade the competencies of health personnel. Addressing the issues around inadequate skills therefore requires a systematic approach and a dedicated effort by governments. Rohde et al. (163) advocate for a structured approach to training, which takes into account “adjustments in nursing and medical curricula at the undergraduate level,” to include core competencies for data collection and use. In addition, they advocate for a postgraduate qualification in health information systems that would include the latest information on trends in health information systems.

Factors that can improve the effectiveness of the training include the use of adult-learning techniques, such as more interactive and participatory than traditional didactic teaching, the content and structure of the training, and the environment in which it is given. As noted in Chapter 2, the WHO Immunization Monitoring Academy, a new distance learning approach to providing opportunities for public health professionals globally, might serve as a helpful model for how online learning coupled with group discussion sessions could be used to upgrade the quality of the in service training, minimize the need for taking front line staff away from their posts and galvanize their interest in learning. Issues around language of the modules and the online discussion groups are resolvable with proper planning and resources.

4.5 Supportive Supervision

An important and, in practice often neglected, aspect of workforce development in the area of the EPI data management is supportive supervision which is an approach to supervision promoting mentorship, joint problem-solving and communication between supervisors and supervisees. Supportive supervision is a vital determinant of health information system performance, given that it not only provides a platform for in-service training, but also provides key opportunities to identify bottlenecks in implementing interventions designed to improve data quality and use, such

as through data quality self-assessments (DQSs) and the development of data improvement plans (DIPs) (see *Chapter 6 on Assessment and Improvement Planning*).

Despite its importance, supervision of front-line workers at the health facility level is often inadequate, since the logistic and financial support for supervisory visits are not readily available in many settings, and even where structures exist only a handful of facilities receive good-quality supervision (145, 146). The frequency and quality of supervision can substantially affect data quality. Ferguson et al. give an example of where weaknesses in training and supervision given to clinic staff involved in implementing a maternal and child health programme at the facility level led to data inaccuracies and substantial overestimation of the programme's coverage (146). Rowe et al. (2010) identified several issues related to the incompetency of the supervisors, including inadequate managerial skills, lack of leadership and poor coordination (164). Other issues raised included an ineffective management team, a lack of motivation and an increasing supervisory workload.

When staff have adequate supervision and receive regular feedback regarding their outputs, chances are they will pay more attention to their job. Therefore, supervisors should be capable, motivated and given the necessary support to adequately carry out their supervisory activities. These activities should be structured around providing hands-on support to health workers for specific deliverables or outcomes, especially when it comes to checking for data quality, rather than just randomly checking a few folders that may not reflect the true nature of what is happening at the facility (Box 4.1).

Box 4.1 The impact of instructive monitoring fields visits on immunization data quality and use in the Kingdom of Bahrain

Bahrain's immunization programme has achieved >95% coverage for all vaccines in the childhood schedule for the past 20 years, according to WUENIC data. To help sustain this high performance, the Ministry of Health began conducting "instructive monitoring field visits" in 1996. These visits, which are conducted randomly in all health facilities — both public and private — were first focused on evaluating cold chain and vaccine management practices, but expanded to other aspects involved in immunization in 2009 (165). These include the recording and registration of vaccinations administered, coverage data (including numerators, denominators, targets), VPD reporting, data quality and accuracy, the use of data for decision-making, vaccine stock outs, adverse events following immunization, defaulters tracing, and vaccine wastage.

Feedback to health staff is given instantly, including positive reinforcement for their achievements and progress. Health workers are also given the opportunity to express their needs and to make suggestions for improvements, which are reported up the chain to the national EPI program and to the NITAG.

These visits have reportedly improved vaccine management, reduced avoidable programmatic errors related to adverse events, and according to data quality self-assessments (DQS), improved the quality and accuracy of data. In addition, they have increased ownership, accountability, and empowerment on the part of health workers in using data for planning and decision-making. This has been achieved in the context of strong political commitments, overall health system strengthening and integration with other services for life course vaccination (165, 166).

4.6 Feedback

EPI data are often forwarded by front-line health workers to higher levels in the system without adequate or timely feedback from senior management to enable staff to identify areas requiring improvement. Timely feedback is a crucial part of the supervisory process, and is important for enhancing data quality, especially when audits using standardized feedback tools are conducted (135, 167, 168) (Box 4.1).

However, feedback is often not provided to staff at the facility level. Studies by English et al. and Muschel have attributed poor data quality and insufficient skills in analysing, interpreting and using data to a lack of feedback mechanisms between the different levels of the health system (135, 168). Mphatswe et al. also showed that a feedback training intervention could be used to improve the quality of routinely collected data in South Africa (169).

4.7 Implementing effective, multi-faceted interventions

The realist review of what works to improve immunization data use found that no single intervention is sufficient to improve data use (87). The most common and effective interventions found in the literature are those that use more than one strategy. Rowe et al, 2018 (170) report that training combined with supervision or group problem-solving proved more effective in improving health worker competence and performance than single strategies. These adult learning principles have been shown in a wide range of other health care areas to improve training outcomes. The development of national guidelines and curricula on the use of health data, and the recruitment of dedicated and skilled data managers at all levels of the health systems were identified by the Immunization data: Evidence for Action (IDEA) review as effective measures to strengthen the data-use culture in the health system. They found evidence to show that without human resource capacity, interventions such as implementing a computerized health information system is likely to be unsuccessful in improving data quality and use (88). JSI has a 5-component framework called BRICKS (Building Routine Immunization Capacity, Knowledge and Skills) for capacity-building on what's already in place (Box 4.2) (171).

In another systematic review by Vasan et al. a combination of in-service training, mentoring, and supportive supervision were identified as important interventions in improving the capabilities of health workers (172). This has been a consistent focus of different capacity-building interventions supported by the U.S. CDC for increasing health worker skills in the processing and use of data, including the Stop Transmission of Polio (STOP) teams, Immunization and Surveillance Data Specialists (ISDS), Data Improvement Teams (DIT), and Strengthening Technical Assistance for Routine Immunization Training (START) (Box 4.3). Mentorship and supportive supervision were common denominators in all of these interventions (173).

4.2 BRICKS (Building Routine Immunization Capacity, Knowledge and Skills)

BRICKS is a framework from JSI based on the capacity building systems, tools, guidelines and policies that already exist in countries. Its five components are considered together as a package: 1) EPI core competencies, 2) situation assessment, 3) supportive supervision, 4) review meetings and 5) applied training. This framework is not “one size fits all” and some of the components may have more emphasis than others, depending on the analysis and situation of each one of the countries. The goal is “not to develop new tools” or “change” systems, but rather “to strengthen what is in place in a way that incorporates modern principles of performance and quality improvement and is ideally affordable and able to be sustained by the country” (171).

Box 4.3 The use of Data Improvement Teams in Uganda

The Uganda National Expanded Programme on Immunization (UNEPI) has worked alongside its partners to implement a variety of data quality assessment and improvement activities across the country. A strategy using Data Improvement Teams (DITs) began in 2014 with the aim of improving the management, collection, analysis and use of administrative vaccination data, and ultimately data quality and service delivery in health facilities and districts (121). DIT teams are each composed of a district-level biostatistician, a surveillance officer and/or EPI focal point, as well as university students. Teams are trained to implement rapid assessments of immunization data quality and use at health facilities and districts, and to provide on-the-job training and mentorship to district and health facility staff on recording, reporting, analyzing and using administrative vaccination data.

In Round 1 of the DIT strategy (2014-2016), the teams reached all districts and 89% of all health facilities in the country at least once. During this round, the teams learned that many health facilities did not know the target population for routine infant immunization in their catchment areas, and there was wide variation in the display of vaccination data in health facilities and in the appropriate use of data recording tools. Following Round 1 and the training activities that it entailed, some improvement in collection and management practices for administrative vaccination data was seen, as well as in the timeliness and completeness of data at the district level (121). The total cost of Round 1 was US\$575,275 over the three-year period, which is 0.5%-1.6% of the estimated operational cost of implementing UNEPI over the same period (K. Ward, manuscript submitted).

Round 2 of the DIT strategy (2017-2019) aims to revisit health facilities to assess progress on recommendations made during the first-round visits and provide further on-the-job training and mentorship.

4.8 Conclusion

This chapter has highlighted the importance of identifying the competencies needed and increasing the skills and knowledge of health workers — especially at the local level — in generating and using data to improve immunization programmes. Too often, development of new electronic tools is the default solution for what may really be a workforce capacity issue. Using a multi-intervention approach seems to be the most useful strategy to improve the quality of reporting, analysis and use of EPI data at the health facility and district level. Several interventions have been outlined and can be instituted, such as including data management and use in the pre-service training of health professionals (e.g., nurses); and reinforcing and refreshing data-related skills on a periodic basis through a combination of effective in-service training using adult learning techniques, supportive supervision, and regular feedback to health workers. All of these actions require strong leadership and a culture of data demand and use.

5. Tools: Information Systems and the Risks and Benefits of Novel Approaches

Key messages

- There is a proliferation of immunization and VPD surveillance information and communication technology tools. However, most never go beyond pilot phase.
- There is evidence that some of these tools improve data quality and use, including their accuracy, completeness and timeliness (e.g., real-time data). However, rigorous evaluation around their effectiveness and cost-effectiveness is often lacking.
- Innovative approaches are not magic bullets. Success depends on their addressing a well-defined problem and in having the infrastructure (e.g., connectivity), governance structure, sustainable financing, health worker training and other critical elements in place to be ready to implement the new technology.
- Immunization and surveillance information systems and tools that are integrated or aligned with broader health information systems (e.g., the national HMIS), while responding to individual user requirements, are more likely to achieve the support of political leaders and be more sustainable than stand-alone or fragmented systems.
- Innovations are more likely to improve data use if combined with other interventions (e.g., a dashboard, health worker training and a feedback mechanism on data generated).
- More guidance on when and how to scale up innovations is needed.

Data quality issues are largely caused by data recording errors at the facility level. Therefore, tools that are intuitive and user-friendly can potentially improve data quality and efficiency. Advances in information and communication technology (ICT) have led to a multitude of tools developed to address deficiencies in data quality, availability and use. Use of these tools are collectively referred to as “e-Health,” defined as “the cost-effective and safe use of information and communication technologies in support of health and health-related areas” (174).

While some of tools, including health management information systems, such as DHIS2, have been rapidly scaled up and are now in use in many countries globally, many of the e-Health tools do not go beyond the pilot stage, wasting financial and human resources. The reasons include over-enthusiasm for adopting technological innovations without defining what problem they seek to address, a lack of rigorous evaluation of the tools, as well as insufficient consideration of critical factors that are pre-requisites for the successful implementation of new technologies. These include the governance structures and procedures needed to support the new technology, the human resource needs to operate and use it, its integration with existing systems, infrastructure requirements (e.g., hardware and connectivity) and its financial sustainability.

This chapter describes the types of e-Health approaches that have the potential to improve the quality and use of immunization and VPD surveillance data, as well as the factors that contribute to their success and their potential limitations. A table summarizing these technologies, including their main features, advantages and limitations, can be found in [Annex 16](#). This chapter is based on the following sources of information:

- Two evidence reviews of: 1) novel approaches to measuring vaccine coverage ([Annex 17](#)) and 2) novel approaches to polio surveillance ([Annex 13](#));
- The grey literature, which was identified by WG members and interviews with experts, since many innovative approaches may not yet have been formally described in the literature; and

- The PATH/PAHO [IDEA report](#) (87) which reviews which ICT approaches have evidence for increased use of data and increased data quality, as well as their limitations (Precis as an Annex in Yellow Book).

5.1 Electronic Information Systems

Health information systems (HIS) have four key functions: 1) data generation, 2) compilation, 3) analysis and synthesis, and 4) communication and use. Their purpose is to convert data into information for health-related decision-making (175). The use of HIS for immunization and surveillance is arguably the technological innovation that has been adopted the most by national health programmes for routine use.

Vaccine and VPD surveillance data can be collected as part of a stand-alone system, such as an immunization information system (IIS) or an Electronic Immunization Registry (EIR), or as part of an integrated health information system, such as the DHIS2 platform – an open-source software that many African countries are using as their health management information system (see Box 5.1). While the terms IIS and EIRs are often used interchangeably, EIRs are narrower in scope and can be defined as a collection of individual-level electronic immunization records compiled in a database, which can be part of an IIS (176). Increasingly integrated health information systems are being used to contain coverage and VPD surveillance data versus setting up a stand-alone EIRs or IISs. However, the experience with this has been mixed.

An integrated approach recognizes the similarities in data requirements across health programmes, is theoretically more resource efficient, and facilitates the linking of data across programmes and across health facilities, thus enabling monitoring along the continuum of care. DHIS2 can also improve data use (e.g., at the district level), especially when used in conjunction with tools and activities that support the use of data, such as dashboards, feedback, and regular supervision (88). However, the implementation of HIS alone may not lead to improved data use at the local level (88). One key factor is that immunization modules within these systems are often not developed specifically to meet the needs of immunization programmes. As a result, such modules are often used infrequently by health facility staff or used in parallel with existing paper-based systems, thus increasing the burden of data collection on facility staff (177).

In contrast, IIS are developed specifically for immunization programmes and may therefore be more fit-for-purpose than integrated HIS systems. However, there are two main issues that have arisen with their use. The first is the risk of developing non-interoperable parallel information systems, which are not sustainable in the long-run. To effectively link and sustain IIS with other information systems requires protocols on how data are shared and protected (177) and the establishment of information standards, including minimum information datasets and interoperability frameworks, as discussed in Chapter 3. Global standards for immunization information systems have not yet been developed (177), although there have been regional attempts to develop a set of standards (176).

The second, an issue with IIS, and particularly with EIRs, is the challenge in linking these registries with data from different sources to create accurate estimates of vaccination coverage. These sources include civil registration systems to estimate the entire target population (denominators) and not just those using healthcare services, which would strengthen health inequalities (58). They also include a range of providers of vaccination services beyond the typical public health facilities — such as private facilities, pharmacies, and schools — to ensure that all vaccinations provided are included in the numerator. This issue has not been resolved even in high-income settings.

Regardless of the approach used, both integrated and immunization-specific information systems have the potential to improve data completeness, timeliness, integrity and efficiency, especially when implemented at the subnational level.

Electronic immunization registries (IERs) facilitate coverage monitoring in terms of particularity, timeliness and accuracy. In 2016, WHO's Immunization and vaccines related implementation

research advisory committee (IVIR-AC) reviewed the status of EIRs, and recommended “that research and implementation of IERs should be prioritized and that WHO should find ways of making financial and human resources available [to work on this topic]” (178). Examples of EIR adoption have highlighted sustainable funding, health worker support and capacity building, and clear governance structures as major contributors to the successful implementation of these systems (105). The PAHO guide to EIR implementation expands upon these “readiness” factors, which are relevant to all regions (60).

Though few studies exist, there is evidence of moderate certainty that EIRs can improve data use at the district level when used consistently, and more mixed evidence that they improve data use at the health-facility level (88). The effectiveness of EIRs in improving data use is highly dependent on their function and design, as well as the completeness and accuracy of the data they contain (88). Thus, the quality of the data is still a function of the collection and recording of the data at the facility level, and therefore switching from paper records to an EIR, IIS or HIS in itself does not guarantee better data quality or use.

Box 5.1. The use of District Health Information System version 2 (DHIS2) in the African Region

DHIS2 is an open-source software platform for health information systems, which as of early 2019, is in use at various levels in 67 countries, including most countries in the WHO African Region (179). There has been robust support for reporting of HIV/AIDS, malaria, and TB program data through the platform. However, immunization programmes have been late adopters of the platform, and until recently, only a subset of DHIS2-using countries used the platform for immunization program data and an even smaller number for VPD surveillance data. Many countries appreciate the approach that DHIS2 takes, including the fact that it is open-source, is able to support integration across programs, and is being maintained by a cadre of skilled, local technicians trained by the Health Information Systems Program (HISP) in South Africa. Some countries have demonstrated strong leadership in deciding that DHIS2 will be the only HIS platform to be used in the country.

According to a recent assessment reported by the WHO African Regional Office (AFRO), 14 countries had EPI data integrated into DHIS2 and were using the data, while an additional 13 countries have also integrated EPI data into the system but were not using these data. Generally, this was a result of insufficient involvement of EPI staff in defining the minimal indicators and functionality required for immunization program monitoring and/or lack of trust in the data. A few countries have struggled with challenges caused by the switch to the new system, resulting in a lack of or incomplete reporting. These challenges include an increased burden by having to enter data into two systems during the transition period, and technical issues in implementing DHIS2 while not maintaining the old system in parallel during the transition.

Recently, AFRO, in collaboration with WHO headquarters, provided support for the development and roll-out of an immunization monitoring module within DHIS2, which includes dashboards to display analyses of indicators and assess data quality. The Regional Office is currently developing an updated DHIS2 platform for comprehensive VPD surveillance that will allow reporting of both case-based and aggregated surveillance data, as part of the Regional investment strategy in VPD surveillance.

Box 5.2 Lessons learned in incorporating immunization data in the SmartCare electronic health record in Zambia

SmartCare, an integrated electronic health record (EHR) system primarily used for antenatal care and HIV treatment, is now in use in one-third of all health facilities in Zambia. In 2011, a SmartCare module was launched that includes digital vaccination records. The system runs on desktop computers and mobile apps are also now available.

A 2016 evaluation revealed that out of 103 facilities included in the review, only two were using the SmartCare vaccination module. Reasons identified for the low use of the module included the lack of a continuous supply of electricity, low acceptability among health staff (half the facilities had previously used pilot EHRs that were discontinued, sometimes causing loss of client data), poor system design, and incomplete data for reporting, leading to parallel collection of paper and electronic data and thus increased workloads). Other lessons learned included:

- Vaccination information systems must be suitable for the infrastructure and clinic workflow;
- Negative experiences with discontinued EHRs can cause frontline staff to be skeptical of electronic data systems;
- Health records should not be fully transitioned to an electronic system without a clear plan for data migration, data back-up, and their long-term sustainability;
- The perspectives of frontline staff and a thorough understanding of vaccine-specific needs are crucial to the successful system design, implementation and evaluation of vaccination information systems; and
- Staff motivation to use a vaccination information system will be improved if they use the data they generate and perceive that the system eases their administrative burden and improves client care.

Source: A. King and K. Clarke, personal communication

Box 5.3 Development of web-based tools to report linked epidemiologic and laboratory surveillance data in the Western Pacific Region (WPR)

The Measles and Rubella Surveillance Reporting System (MRSRS) is a web-based system developed by the WHO Regional Office for WPR in response to requests from Member States to integrate measles and rubella epidemiological and laboratory surveillance data on a single platform.

Each time a case investigation record is completed for a suspected case for which specimens have been collected, the reference laboratory receives an automated email notification. The laboratory then records data about the specimens received and test results in the system. Once this occurs, the national surveillance focal points receive a notification, enabling them to complete the final case classification. The system has a set of required core variables; additional non-core variables; built-in validation checks; and standard reports for the distribution of cases by final classification, time, place and person, as well as for surveillance performance indicators.

MRSRS was first adopted nation-wide in Cambodia in 2013 and later expanded to Lao PDR and Mongolia. In addition, Vietnam is piloting a version that enables data entry at the subnational level, as well as data verification and validation at the national level. The system has been customized to meet countries' specific needs, including the possibility for a laboratory to initiate a case record when specimens are received before epidemiological data are entered in the system.

Based on the success of the MRSRS, similar systems have been developed for the surveillance of rotavirus (the RVSRS) and AFP/polio (the PASRS), which are currently being used in several countries. A system for invasive bacterial disease surveillance (IBVPDSS) has also been piloted in one country.

Box 5.4. Integration of VPD surveillance into broader communicable disease surveillance system in Vietnam

The Vietnamese Ministry of Health established a web-based electronic system (“Circular 54”) in July 2016 to serve as a single platform for case-based reporting of 42 communicable diseases, including all VPDs, in order to reduce parallel reporting for single diseases. The system, which has been implemented nationwide at all health facilities, is part of a broader process of digitalizing health sector data. It relies on dedicated focal points at each health facility, thus enabling the timely entry of data on newly identified cases. District and provincial level staff can access the system daily to check for new cases and initiate case investigations, as needed. National scale-up of the system has been undertaken through training of all users, with a focus on data entry, access to data and automatically generated alerts, and the use of dashboards, which are being developed to facilitate the description of cases by time, place and person and more easily identify disease outbreaks.

Some processes are still in transition and some weaknesses were observed during a VPD surveillance review conducted in November 2017. First, some processes, roles and responsibilities were not clearly defined especially regarding who should complete detailed case investigation forms, collect specimens for case confirmation, and classify cases (e.g., from suspected to confirmed) upon receipt of lab results. In addition, doctors and surveillance staff were not trained on new case definitions, the purpose of reporting suspected cases for some VPDs, nor in data analysis – resulting in missed cases. Other limitations of the system at present include the limited participation of the private sector and other government sectors providing health services (e.g., the military, education) and the fact that the system includes only core data elements, thus requiring district and provincial staff to still maintain an Excel line-list to record detailed information for AFP and measles cases.

The Circular 54 system offers a sustainable platform for the successful integration of VPDs, the expansion of case-based reporting to all VPDs, a reduced workload due to less parallel reporting, and improved timeliness of reporting. However, VPD surveillance would benefit from the development of clear implementation guidelines and SOPs, additional training on case definitions and case investigation, and the participation of private and non-health government sectors in the system (Annex 18).

5.2 Digitizing paper-based data

Interventions that used innovative technologies, such as scanning or image capture, to digitize paper-based immunization or surveillance data are designed to address the challenges associated with manual data entry at the point of service or at higher levels (e.g., district). As shown in Box 5.5, these technologies can potentially improve data integrity, accuracy, timeliness and especially, completeness (180, 181). In some instances, they can also eliminate the need to transport paper records.

Box 5.5. Using Smart Paper Technology to digitize immunization data in low-resource settings

The Swedish-based Shifo Foundation has developed [Smart Paper](#) — a hybrid paper-digital technology designed with in the aim of strengthening data quality and use in under-served areas. Smart Paper was developed based on [lessons learned](#) from experiences with the failed mHealth pilots in several developing country settings and could not be scaled up, due to infrastructure limitations, lack of sustainability with existing government budgets (i.e., high maintenance costs), and weak technical support available.

Smart Paper enables health workers to register children and other patients using a unique ID and capture their health data on Smart Paper Forms (regular A4 paper), which replace registers, tally sheets, and monthly reporting forms. Each month the Smart Paper Forms are scanned to generate electronic individual immunization registry entries, HMIS reports and LMIS reports. The technology integrates these data with those in other systems, such as DHIS2 and the District Vaccination Data Management Tool (DVDMT). The system also automatically provides real-time indicators and dashboards for action at the facility, district and national levels, sends reminder SMS messages to individuals, and generates stock request reports. All health workers receive their own performance feedback via SMS.

The Smart Paper technology has been piloted in Afghanistan, Uganda and The Gambia, and external evaluations in each country have shown that it generates high-quality data (based on the WHO data quality review toolkit), is cost-effective, and reduces the time spent by frontline health workers on paperwork by 60%-73% per fully immunized child. Scale up is ongoing/planned in Afghanistan, The Gambia and Uganda.

5.3 Decision support tools (dashboards)

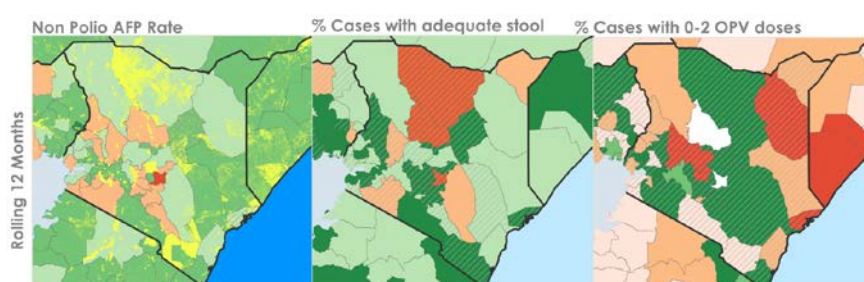
Decision support tools, such as dashboards, are being used at the country, regional and global levels to synthesize and present immunization and VPD surveillance data in a visual format (through maps, charts and tables) for programme managers and decision-makers. By bringing together data on immunization activities, surveillance data, laboratory data, location data and administration data under a single platform, dashboards can improve the efficiency of immunization and surveillance monitoring, as well as its precision (e.g., through data triangulation). At the national and subnational levels, there is evidence of moderate certainty that data dashboards (either stand-alone or integrated into HIS) can also improve the use of data by helping users synthesize disparate pieces of data and translate them into information that is useful for decision making (88).

Examples of such tools currently in use globally are the Polio Information System (POLIS) (Box 5.6) and the WHO Immunization Information System (WIISE) that is currently in development (Box 2.2 in Chapter 2). At the WHO regional level, dashboards have been used to monitor data quality, as well as immunization programme performance, and, more recently, the performance of logistics systems, such as cold chain and vaccine stock availability (89). Factors that contributed to the successful use of an immunization dashboard in several African countries included the standardization of data requirements across countries, and capacity-building workshops that were focused on the use of the dashboard (89).

Box 5.6. Polio Information system (POLIS)

POLIS is a tool for managing and presenting data on polio immunization and surveillance activities that is managed by WHO and has been fully functional since 2014. The system brings together data on immunization activities (routine and campaign), surveillance data (case-based and environmental), laboratory data (from the Global Polio Laboratory Network), geolocation data (GIS) and administrative data. These data — which come in various formats from multiple sources and data systems within each country — are collated and quality checked at the regional level before being sent to WHO in Geneva, where they are consolidated and harmonized in POLIS. The platform includes a dashboard that displays the data in maps and charts that can be used at the country and subnational level to monitor progress against indicators. Global polio bulletins are also automatically generated from POLIS data. The group developing the WIISE system has been collaborating with the POLIS team to learn from their experience and to create synergies where possible.

Example of a risk assessment for vaccine-derived polio virus transmission on the POLIS dashboard:



5.4 Logistics management information systems (LMIS)

Computerized LMISs can overcome the challenges of paper-based systems by standardizing data collection, allowing for vaccine tracking in real time, transmitting data quickly throughout the system for accurate vaccine forecasting and stock management, reducing errors, and automating reporting (182). There is some evidence that these systems can improve data use at the district level and above, as well as enhance the analysis, synthesis, interpretation, and review of data and assessments of data quality (88). LMIS interventions were most effective when they were combined with other data use activities such as dashboards (88).

Digitally-enabled supply chains allow all stakeholders, including manufacturers, distributors, NGOs, country officials and local health workers, to track the exact path vaccines take from the factory all the way to delivery, thus enabling the use of such data to monitor the number of doses that are administered. Additional technological innovations such as the use of block-chain — an incorruptible digital ledger that can be programmed to track individual vaccine doses from manufacturing to administration — also have the potential to increase data security and integrity, improve transparency and traceability along the system (183), and improve interoperability across immunization data systems (184). These initiatives are very recent and the evidence that they improve data quality is not yet available.

5.5 mHealth

While most commonly used in immunization to send SMS messages as reminders about vaccination sessions or appointments, mobile phone-based technologies (“mHealth”) have also been used for real-time data collection and monitoring of programme activities (Annex 17). When used to collect and report VPD surveillance data in real-time (including geolocation data), mHealth apps have the potential to improve the completeness, timeliness and precision of the data, as well as their integrity, since the data are only entered once. However, these systems can also lead to the over-reporting of cases and a high proportion of false positive cases, which have to be followed-up, resulting in increased workload. This is especially true when used as part of

community-based reporting (i.e., by unskilled informants) and/or there are incentives to report cases ([Annex 13](#)) (185).

Mobile applications can also be used to track health workers in the field and to supervise surveillance and immunization activities, as well as the management of the cold chain (e.g., using checklists). Such tools can improve data accuracy by, for example, ensuring adherence to case definitions during data collection, and can improve the completeness and timeliness of the data by reminding health workers to report (186). In addition, mHealth apps have been used to simplify the management of logistics data, such as in tracking vaccine stock levels and informing users of stockouts or low stocks at all levels of the system. There was evidence that the data generated from the e-VIN system used in rural parts of India informed actions and reduced periods of vaccine stockouts (187).

5.6 Media-based approaches

The main example of a media-based approach identified in the review is the AVADAR programme in Africa. The intervention involves sending videos to health workers and community informants on a weekly basis to remind them about case definitions and the type of cases to report as AFP and to send in their reports (see [Box 5.7](#)) (188). A similar approach could be considered for immunization activities to remind health workers about how to collect and report data, for example. The additional burden generated by applying this approach to VPD surveillance, as a result of over-reporting of cases, would not be seen for immunization data.

Box 5.7. AVADAR (Auto-Visual AFP Detection and Reporting)

AVADAR has been used in selected districts in 10 countries, including Liberia, Nigeria and the Lake Chad countries, to support the reporting of acute flaccid paralysis (AFP) by health workers and community informants.

The AVADAR application is installed on android-enabled mobile devices. A [30-second video](#) of a child with AFP is included in the app. A weekly reminder, including the video, is sent out to the community informants, who are asked to submit a “No” report or to report a case. Positive reports are investigated by a disease surveillance officer, who sends an investigation report by mobile phone, which goes to a database. The data can be viewed in real-time on a dashboard, or collated and presented to decision-makers.

The system has been very helpful in increasing the sensitivity of polio surveillance in remote and high-risk areas (188). At the same time, this increased sensitivity of suspected AFP cases has also led to increased reporting of cases that are not acute or flaccid. Since all reported cases have to be investigated, the high rate of false reports has resulted in a markedly increased workload for polio workers. AVADAR is also too expensive to use extensively beyond high-risk settings. Thus, while the extra workload and costs are acceptable during the last mile of the polio eradication programme, these factors would have to be weighed carefully when considering whether to apply this technology for the surveillance of other diseases.

5.7 Geospatial-based technologies

Geospatial technologies have been used in immunization programmes in two main ways: 1) to estimate better denominators, including migrating populations; and 2) in planning and monitoring immunizations and surveillance activities, including microplanning. Satellite imagery, geo-positioning and mobile phone call records have all been used on an experimental basis to estimate population size and the rate of migration at the local level ([Annex 13](#)) (185, 189-191). This reportedly has led to more accurate and precise population data, and even to population estimates in areas where no estimates previously existed. Processing such data requires a trained workforce, however “mapathons” are increasingly used, where volunteers are asked to identify individual structures (e.g., houses vs. schools or businesses) on satellite images, using a GIS application. This results in a detailed picture of individual structures, making it possible to

estimate population size in that area by using an assumed number of residents per structure (Annex 19).

GIS technologies have also been used to improve microplanning, identify missed or poorly covered settlements, more efficiently divide the workload among field vaccination teams, and track vaccination or surveillance teams (192). These uses of GIS can result in data that are more complete and accurate. More impact and economic studies of GIS technologies are needed to determine feasibility of broader programme use.

5.8 Predictive analytics

Predictive analytics in the context of immunization programmes can be described as the use of mathematical algorithms to estimate current and future patterns of vaccine coverage or VPD incidence. Such approaches have been proposed to estimate vaccine coverage in “coldspots” (193), reveal differences in coverage in large administrative areas and across administrative borders (193), or predict defaulters at the individual level (194). However, there is a disconnect between academia where the methodologies are being rapidly improved and refined, and country immunization and disease control programs who have been slower to adopt such tools (191). Such caution may be justified, as there is not much existing evidence of the public health impact and cost-effectiveness of predictive analytic methods. In addition, current algorithms may lack sufficient resolution and positive predictive value to be relevant for routine practice (194).

The use of “big data” for predictive analytics has also been explored in the field of disease surveillance, with mixed results. Consensus has not been reached on whether predictive approaches add value to traditional surveillance methods, or even that they are accurate or representative enough to inform public health action (195). Nevertheless, event-based surveillance based on big data mining is slowly becoming more common in the surveillance landscape (196) and there is some evidence that they can detect public health events earlier than traditional surveillance systems (197). When predictive analytics algorithms are combined with machine learning, the accuracy and precision, and consequently the usefulness, of these methods will increase with time and as increasing volumes of data are processed by these algorithms (Subash Chandir, personal communication). As their use is increasingly considered in routine immunization and surveillance programmes, predictive algorithms should be evaluated not only for the accuracy, precision and timeliness, but also for their added public health value, their cost-effectiveness, and their affordability and sustainability.

5.9 Conclusions

New technologies can have a positive impact on the quality and use of immunization and surveillance data, including their accuracy, completeness and timeliness (e.g. through real-time reporting). However, these interventions are not magic bullets, and are unlikely to be adopted by countries in the long-term or to lead to long-lasting data improvements unless other factors and conditions are in place (Table 5.1). These factors, identified repeatedly by different stakeholders and in guidance documents (60, 198), include sustainable financing, such as earmarked funding; interoperability with other health information systems; the flexibility to adapt to future needs; and their development within a broader national eHealth strategy (60). These factors, in turn, require the existence of strong governance structures to ensure that there is political will to adopt these technologies, the inclusion of key stakeholders and partners in developing and implementing them, and a sustainability plan (Annex 17). Thus, innovative technologies that are not integrated in the healthcare system and that do not take into consideration the infrastructure, human and material resources required to make them functional or the political climate they’re operating in are unlikely to succeed or to go beyond the pilot stage. Innovative approaches are also more likely to lead to improved data use when they include multiple components, when they address a specific need, and when they are considered within a whole systems approach.

Table 5.1. Factors determining the success of innovative technologies for collecting, analyzing and reporting surveillance and immunization data

Factors	Examples
Governance	Leadership, political will, legal framework (e.g. data protection)
Integration/ Interoperability	Data linkage potential, use of consistent data standards, integration of EIR in HIS
Capacity	Human resources (training, workforce), material resources (computers, phones)
Sustainability	Including financial sustainability, e-health strategy
Infrastructure	internet, electricity, technical support structures including effective troubleshooting, security (to store devices safely)

Adapted from the WHO (198) and PAHO (60) guidance documents, and A. Poy, personal communication

Rigorous evaluation of these tools is not systematically done and is essential because the outcome is not always obvious. Where evaluations have been done, they have shown that, for example, mobile-based reporting does not always improve timeliness, or that the implementation of a health management information system does not systematically lead to improved data use (88). In some of the polio examples, for a range of reasons, innovative approaches had low uptake by frontline workers and only made a small contribution to the number of reported cases. This required them to run in parallel with traditional data collection methods, thus further overburdening the already over-burdened frontline health staff ([Annex 13](#)) (185).

There are gaps in the existing literature in key areas, such as how to best integrate routine immunization data into an HMIS or how to identify key indicators that would assist in measuring the effect of a technological innovation on vaccination coverage rates. And although guidance exists on how to evaluate digital health interventions, there is an increasing need for real-life evidence, as well as guidance, on how and when to scale up innovations to ensure a sustained long-term benefit on data quality and use. The sharing of both best practices and challenges with less successful innovations would also assist in improving the overall global community's understanding of appropriate technologies to explore within the appropriate context.

6. Assessment and Improvement Planning: Data Use for Continuous Quality Improvement

Key messages

- New approaches to monitor the performance of EPI programmes are needed as coverage improves and programs shift their focus to life-course of vaccination, equity in service delivery, and disease elimination goals (e.g., measles). This includes new approaches to assessing numerators and denominators.
- The use of data has been shown to improve their quality.
- Better use can be made of existing information to supplement and validate administrative coverage data, such as VPD surveillance data; vaccine supply data; and rapid coverage monitoring data, as collected during activities such as supervisory visits and outbreak response.
- Opportunities should be found for greater coordination between EPI and other programmes and interventions for collecting data, as part of health systems strengthening.
- Data triangulation is helpful for synthesizing existing evidence across data sources and reaching deeper understanding of issues, and should become the default for public health analysis.
- Assessments of data quality and subsequent improvement efforts are most effective if conducted on an on-going basis, versus periodically, – down to the lowest level – as part of a Continuous Quality Improvement (CQI) approach.
- Such assessment should examine the root causes of poor data quality and use and inform the development of a data improvement plan, which are currently often not based on evidence.
- To assist countries in shifting from periodic to routine monitoring of data quality, standard data quality monitoring indicators and global guidance on routine data validation are needed.

Using data enables vaccination of the last child, appropriate responses to disease risk, more efficient allocation of resources, and accountability at all levels. Discussion around data quality and use needs to start from the key objectives in order to determine what data and what degree of data quality are required (“fit for purpose”). Historically, the approach to immunization data quality has been focused on detection of errors and assessing the scope and extent of the problem (the “what?”), rather than on performing an analysis of the root causes of data problems (the “why?”) that would feed into an overall cycle of improvement. Ideally, assessment of data quality should be a continuous process rather than episodic evaluations conducted every few years. And, as mentioned in earlier chapters, the quality of immunization data can only be improved significantly if the health systems organization and structure are taken into account, using a whole systems approach.

The findings of this chapter are based largely on the landscape analysis of data quality assessment approaches and indicators, the Data Triangulation Framework, and example of data triangulation analysis, and case studies (see online Annexes). The purpose of this chapter is to highlight how approaches to assessing data quality can become routine, how data analysis practices might be improved at all levels, and how use of data should feed into broader efforts to improve the immunization programme and the larger health system. The limitations of this review were that the data quality indicators and approaches to continuous quality improvement were not reviewed systematically.

6.1 Monitoring coverage as performance improves and the focus shifts towards an equity and life-course approach

The Decade of Vaccine's GVAP established ambitious goals for national and subnational immunization coverage, which require high-quality data to track progress towards success and reach all of the children left-out or dropped-out of the immunization system. In addition, the costs of the immunization program and demands of monitoring of evaluation are increasing as the number of available vaccines continues to expand. The introduction of new vaccines and a shift towards life-course vaccination targeting older age groups (e.g., school-age, adolescents, pregnant women, elderly) have increased the complexity of accurately monitoring coverage. Ensuring transparency and accountability regarding the appropriate use of resources and evidence-based decision-making around employing cost-effective strategies — all of which require high-quality data — are perhaps more critical than ever.

Maintaining accuracy as coverage increases

As seen in Chapter 2, high-quality coverage estimates are more difficult to measure through administrative measures as coverage increases (49). The effects of errors in target population estimates are amplified as the coverage level increases and can conceal differences in vaccination coverage across areas and over time (Figure 2.2). Even if national population targets for immunization remain relatively stable, the accuracy of population estimates has been noted to decrease when data are disaggregated (48). Few low- and middle-income countries have birth and civil registries for obtaining high-quality immunization targets and census estimates may be outdated or inaccurate due to political reasons (50, 51). Some of these issues may be addressed through better cross-unit coordination, advocacy or work-around solutions (53). Geospatial modeling of population denominators for administrative areas also shows promise, but further field validation is needed (199).

Migrants and other high-risk groups may be left out of population target estimates and require different approaches to estimate denominators and monitor coverage. Developing approaches to track coverage not only based on place of vaccination and but place of residence (or inside and outside catchment) may be helpful in this regard (Box 2.6). Tracking individual-level vaccination status through EIRs may be the gold standard, but may not be practical for every setting. Improving the design and functionality of paper-based registers (e.g., to track residence inside and outside catchment areas) and improving use/retention of home-based records should be more feasible. New approaches like electronic dashboards and automated analysis, Smart Paper (Box 5.5) are hybrid paper-digital solutions that show promise for addressing the demand for individual level tracking, while addressing the current limitations for eHealth at the peripheral levels. Continued innovation and stewardship in this area is needed.

Monitoring equity in vaccination coverage

While one can measure inequalities, the goal is to monitor equity in immunization, i.e., the fair reach of vaccines to all. Several global analyses of immunization inequalities have been published (200). However, to date, monitoring equity has often been equated with measuring differences in survey coverage across sub-populations (201). The Health Equity Assessment Toolkit ([HEAT](#)) is a software package that allows analysis and visualization of vaccination coverage by different dimensions of inequality (e.g., education, economic status, subnational region) (202). The software is available as an online or stand-alone version, and either comes preloaded with many years of survey data (from the DHS and MICS), or with the ability to upload and analyze other data. Interactive country profiles that contain these data are also available on the [WHO Global Health Observatory Health Equity Monitor](#) website (203). A limitation is that these surveys occur only approximately every five years and only in some LMICs.

A 2017 systematic review highlighted that existing approaches to monitoring equity towards achieving the SDGs have been sub-optimal in identifying and reducing gaps in immunization coverage for vulnerable groups or minorities, or by attributes such as education, specific religious

groups, or sexual orientation (201). The [Equity Reference Group \(ERG\) for Immunization](#) has written several discussion papers on how equity might be monitored by immunization programs, but associated guidance has not yet been developed. Triangulation of quantitative and qualitative data to validate or put information in context (e.g., surveys of caretakers or healthcare workers to identify reasons for non-vaccination), is also relevant for addressing coverage and equity issues (204). The collection and use of individual level vaccination data (i.e., EIR) can serve as the gold standard for identifying and targeting under-vaccinated groups (Box 6.1).

Box 6.1. Using routine immunization data to tackle inequalities in vaccine coverage in England

Public Health England (PHE), the executive agency of England's Department of Health, is responsible for collecting and reporting vaccine coverage for vaccines offered in the national vaccination schedule. PHE uses two Immunization information systems to monitor the vaccination programme across the life-course: 1) the Child Health Information Systems, which are local electronic registers of all children up to age 18 residing in an area, including migrants, and 2) data automatically extracted from electronic medical records from over 95% primary care health centres.

In addition to estimating vaccine coverage down to the facility level in real-time, these two systems record additional variables that enable PHE to describe vaccination inequalities in terms of geography, ethnicity, gender, co-morbidities, or socio-economic deprivation. The data have allowed the agency to identify and locate groups that are less likely to initiate and/or complete vaccine courses. Ultimately, these data led to changes in national and local strategies in order to improve coverage, such as vaccination catch-up campaigns for susceptible birth cohorts, and local vaccination efforts targeting specific under-vaccinated groups. These studies also inform the national immunization programme's Equity Impact Assessment, a comprehensive analysis of inequalities, and with recommendations on how to reduce them.

Measuring performance of life-course vaccination

Shifting towards a life-course approach of vaccination poses complex challenges in monitoring coverage for multi-dose vaccinations given beyond the first year of life. For administrative coverage data, issues arise with both accurately estimating denominators and accurately counting numerators (e.g., for doses received late). With coverage surveys, there are challenges in standardizing target age groups to assess vaccination coverage and in collecting accurate vaccination histories. For example, measuring TT vaccination coverage among pregnant women with at least two doses (TT2+) or protection at birth (PAB) rates has been long known to be a challenge due to poor retention of home-based records (vaccination cards), in addition to the lack of documentation of tetanus-containing vaccine doses received during childhood or through campaigns. The introduction of the second dose of measles, or measles-rubella, vaccine, HPV and other vaccines in pregnancy have also acutely highlighted the challenges in monitoring coverage associated with new age vaccination platforms and has resulted in many lessons learned. The challenges of estimating coverage beyond infancy will also need to be addressed with the upcoming support from Gavi for a DPT booster dose (85, 205).

Accurately assessing population immunity resulting from multiple-dose vaccination schedules poses another challenge, even for well-performing programmes. For example, TT2+ and PAB coverage rates are known to underestimate population immunity, especially as vaccination programmes improve (14). For this reason, the SAGE suggested in October 2016 that serosurveys could be useful (206). Routine serosurveillance programmes are common in higher-income settings (207-210), and a case has been made for greater use of serosurveys in LMICs to aid decision-making (12, 211). In settings with weak surveillance or unreliable vaccination coverage, or that rely heavily on vaccination campaigns, serosurveillance could potentially play an important role in deciding what interventions should be taken to improve population immunity. For example, repeated poliovirus serosurveys in Nigeria have been used to evaluate the effectiveness of campaigns and to guide programme interventions (212-215). Serosurveys have

also been useful in assessing the level of population immunity required for measles elimination (216, 217). However, questions remain about the role, usefulness and priority of serosurveys relative to other programme priorities, such as vaccination, especially given the various technical limitations with these studies (Box 6.2 and [Annex 20](#)) (216, 218, 219).

Box 6.2. The use of serosurveillance to guide immunization policies and strategies

Serosurveys provide an objective biological measure to estimate population immunity and monitor risk for VPDs. Serological data are increasingly desired to guide immunization policy and strategy — from support of vaccine introductions (e.g., rubella) to the verification of disease elimination (e.g., hepatitis B). In 2011, the SAGE recommended that WHO develop guidelines for collecting, analyzing and interpreting biomarkers to validate vaccination coverage and to support research (4).

Since then, serosurveys have been used in an increasingly number of different contexts. Disease-specific guidance on serosurveys for [dengue \(2017\)](#), [tetanus \(2018\)](#), and measles and rubella (in draft) has been added to the existing guidelines for [hepatitis B \(2011\)](#). Methods to reduce the costs of the surveys have also been explored. These include combining their implementation in the field with other surveys, and “multiplex laboratory testing”, which allows simultaneous detection of antibodies to multiple antigens in a single sample (220). However, the question of how useful serosurveys are as a tool to monitor immunization programmes and their relative importance in different contexts, especially in resource-limited settings, remains. The Working Group proposes that, going forward, SAGE provides a position on the role of serosurveys in monitoring immunization programmes across different VPDs and epidemiological situations ([Annex 20](#)).

6.2 Routine monitoring of data quality as part of a more robust programme monitoring approach

Monitoring progress, and allocating the resources needed to achieve immunization objectives, hinges on the use of high-quality data (114). The use of results-based financing mechanisms by major donors has created further demands for timely and reliable data for decision-making (56), though SAGE, in 2011, already warned against use of coverage data for performance based financing (4). It has also created the possibility of a perverse incentive to report over-estimated vaccination coverage data, especially in low-income countries with serious data quality challenges. This situation creates a case for shifting away from focusing exclusively on using targets as a basis for funding to a focus on improvement — both in terms of performance and data quality.

Monitoring data quality is crucial to support accountability and transparency (113) of the immunization programme, and helps in interpreting surveillance or coverage data and putting them in context. As discussed in Chapter 2, recent guidance documents (e.g., DQR, Handbook) outline helpful analysis approaches like examining trends in numerator and denominator separately, and assessing internal and external consistency. These guidance documents and other publications propose also possible indicators of data quality. However, there still lacks a robust framework for ongoing monitoring of data quality or a set of standard performance indicators for use at different levels ([Chapter 2.3.2](#)).

With the increasing use of electronic information systems, there are more opportunities to perform automated data validation checks and analyses to improve data quality and use. WHO/EURO recently developed a JRF data validation process ([Box 6.3](#)), and discussions are underway at the global level to incorporate automated JRF data validation checks and data analyses into the new WIISE platform. In AFR, automated analyses of immunization coverage and data quality were incorporated into DHIS2 monitoring dashboards for broad use in the Region (11). However, data validation checks are not used systematically, but are instead incorporated on an *ad-hoc* basis from country to country. The American Immunization Registry Association (AIRA) has issued guidance around data quality validations for to be added to EIRs in use in United States jurisdictions (19). An example of data validation checks from England is

included in Box 6.4 ([Annex 21](#)). It would be useful to develop guidance for countries in incorporating validation checks for immunization and surveillance data, as part of guidance on developing electronic information systems standards (*Chapter 2.3.1*).

Box 6.3 WHO Europe Regional Office (EURO) annual review of

immunization data reported through the JRF

Beginning in 2017, the EURO Immunization and Surveillance Data Team began to implement a series of quality checks on data submitted by countries for region-specific questions on the Joint Reporting Form. Data quality checks focus on the completeness of reported data; a comparison of the expected versus actual field data type (e.g., character vs. numeric); a check of the range of reported data against expected values; as well as an internal consistency check of reported data values for similar questions within the same country JRF. They also include consistency checks of reported values against recalculated values (e.g., 85% coverage is reported, but recalculating the coverage using the reported numerator and denominator data yields a different value). At present, the data quality checks are confined to a given JRF in a given year from a given country. Moving forward, the aim is to allow for time-series checks for reported data for region-specific questions.

Box 6.4 How England assures the quality of vaccination coverage data

Public Health England (PHE) is responsible for collecting and reporting coverage for vaccines offered in the national vaccination schedule. The quality assurance process for the data collected by its immunization information systems include both systematic manual and automated validation checks, as well as *ad hoc* analyses. When data fail validation checks, those providing the data are systematically queried. The data are then either corrected, notated with explanations for the validation failure or, in rare instances where the quality is too low, not published or delayed ([Annex 21](#)).

Automated validation checks examples

- Denominator is \geq numerator
- Coverage change within $\pm 5\%$ compared with previous quarter
- Denominator change within $\pm 10\%$ compared with previous quarter
- Dose 1 coverage \geq Dose 2 coverage

Manual validation checks examples

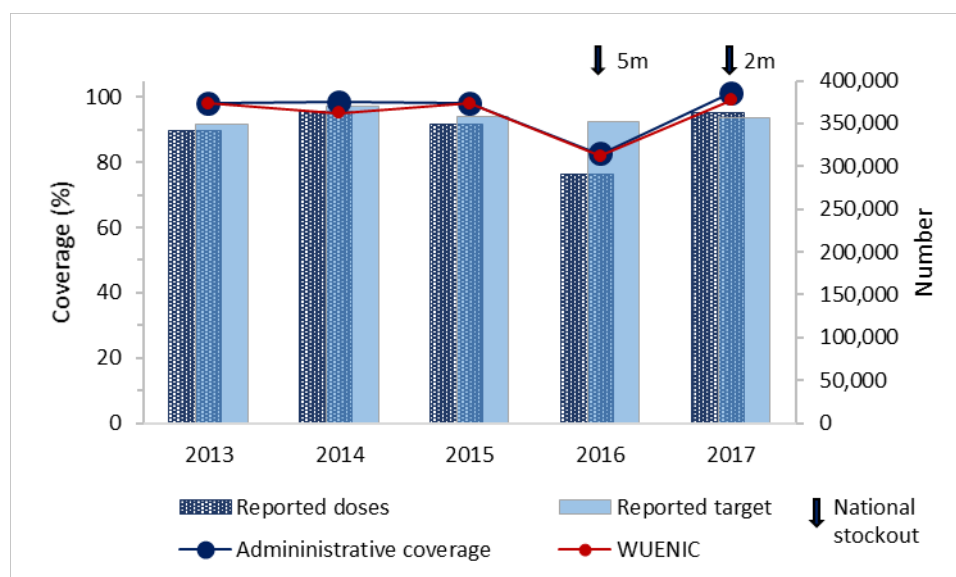
- Departure from expected on coverage trends over the previous 4 quarters
- Data extraction is for correct time period

Ad hoc analyses

- Triangulation of live births data with rotavirus and pre-natal pertussis coverage for denominator validation
- Triangulation of coverage in individual birth cohorts with age specific incidence

Shifting from periodic data quality assessments to routine monitoring of data quality would be a step in the right direction in terms of creating a cycle of data quality improvement, as discussed below and in *Section 2.3.2*. The approach would vary by level, but would entail an assessment of data quality alongside coverage. Currently at the global level, a graph of a single analysis relevant to data quality is published on the [WHO Monitoring Website](#) — comparing annual WUENIC estimates with reported administrative DTP3 coverage and reported number of doses by country over time (221). The addition of reported denominators and stock-outs would also be helpful in interpreting annual fluctuations in coverage and numerators (Fig. 6.1). Other unpublished analyses are performed as part of the annual WUENIC process. The routine publication of global desk reviews of immunization data quality should be considered, similar to joint MMWR and WER reviews that are conducted for polio, measles, rubella and routine immunization. At the regional and country level, incorporating data quality monitoring into feedback, monitoring bulletins, dashboards and other automated analyses would support the use of data and quality improvements (88).

Figure 6.1. Analysis of WUENIC estimates and reported administrative coverage with DPT-containing vaccine, vaccine doses administered, targets, and national vaccine stockouts for a country. (Source: WHO)



6.3 Building a data use culture: turning data into actionable intelligence at all levels

Strengthening routine health information systems involves building a data use culture that informs decisions at all levels of the health system (16, 222).⁵ In practice, this is challenging because it involves strengthening the entire health system (governance, tools, people, improvement processes) and changing aspects of a particular culture. To date, a lot of focus in this field has been devoted to interventions to assess and improve data quality. However, evidence from the IDEA review has highlighted the fact that interventions to improve the use of data may be a potential entry point for improving the quality of the data (88).

Two key ways of improving the use of data to inform programme planning and decision-making are: 1) making better use of existing data besides coverage data, including from other programmes; and 2) synthesizing different types of data through “triangulation”.

Making use of under-utilized data to supplement coverage data

The EPI programme has a lot of additional data that are under-utilized for programme planning and decision-making at all levels. For example, EPI programmes may not be making adequate use of VPD surveillance data because of a lack of coordination between the EPI and the surveillance unit, or because the surveillance data collected are not fit-for-use in managing EPI programmes. An example is aggregate reports that lack age stratification and laboratory data (see Chapter 2.2.2, Box 2.7, and Box 2.11). In these cases, either the coordination and sharing of data from different units needs to improve, or the decision to collect the relevant data from the beginning needs to be made, as part of a shift towards a comprehensive VPD surveillance strategy (see Box 2.4). There is also an increasing interest in using vaccine supply data to better understand the performance of immunization programmes (e.g., by comparing data on vaccine shipments with data on doses administered), but further research is needed to determine the usefulness of these comparisons at different levels (223).

⁵ [Data use culture](#) is defined as the customs, dispositions, and behaviors of a particular group or organization to support and encourage the use of evidence, including facts, figures, and statistics, to inform their decision-making.

Other examples of combining data from different sources to improve data quality as well as vaccination coverage include using rapid coverage monitoring data collected for different purposes, such as during supervisory visits, outbreaks, post-campaign evaluations, or data on vaccination status collected during surveillance (224-226). In Pakistan for example, children identified during polio vaccination campaigns who were incompletely immunized for other vaccines were followed up by the routine immunization programme, leading to improvements in coverage ([Annex 22](#) and [Box 6.5](#)).

Box 6.5 Use of polio campaign data to improve routine EPI coverage in Pakistan

The Expanded Program of Immunization (EPI) and Polio Eradication Initiative (PEI) in Pakistan developed an initiative called “EPI/PEI Synergy” to use PEI data and staff to support the EPI and improve routine immunization coverage. During polio vaccination campaigns, vaccinators collect data on children who have not been vaccinated through routine immunization (“RI Zero dose status”). The polio teams also identify unvaccinated children during surveillance activities (“AFP Zero dose status”). Through the EPI/PEI Synergy Initiative, the two programmes have worked together at all levels to improve routine coverage through the following activities:

1. Sharing of “RI zero dose” data collected during polio vaccination campaigns and “AFP zero dose” data from surveillance for children aged 0-23 months with EPI management at the district level;
2. Joint planning and implementation of routine outreach sessions for “RI zero dose” children;
3. Joint monitoring and supervision of outreach sessions by EPI and PEI staff;
4. Reporting on the number & percentage of 0-23-month-old children vaccinated through joint efforts.

Punjab is one of the first provinces to establish the EPI/PEI Synergy initiative. The province demonstrated excellent collaboration between EPI and Polio Teams, with coverage of RI zero-dose children who were vaccinated within 14 days following a polio campaign ranging between 92%–98% from January 2017- September 2018 ([Annex 22](#)).

Performing “data triangulation”

Data triangulation involves the critical synthesis of two or more existing data sources to address relevant questions for programme planning and decision-making. The process identifies and aims to address limitations of any one data source and/or data collection methodology, and also encourages deeper insights by examining complementary data and putting them into the broader context. A framework document for Data Triangulation for Immunization and Surveillance Programs was developed in collaboration with the WG ([Annex 2](#)) (10). As part of this process, the U.S. CDC conducted a landscape analysis that identified five types of triangulation analyses that have been used by EPI programmes:

- 1) check of consistency across data sources (e.g., coverage monitoring);
- 2) estimation of coverage, target populations or disease burden;
- 3) diagnostic for targeting program interventions (e.g., risk assessments, surveillance performance monitoring);
- 4) observational evaluation of the impact of interventions (e.g., vaccine introduction, campaigns); and
- 5) holistic assessment of programme adequacy (e.g., outbreak investigation, disease elimination verification).

To date, guidance on data triangulation for immunization (i.e., [DQR](#) and [JSI guide](#)) has focused exclusively on using this technique to assess data quality by, for example, checking the consistency of similar indicators across different data sources (e.g., administrative coverage vs. surveys). However, data triangulation can also be used to guide policy and strategies — from vaccine introduction to verification of disease elimination ([Annex 2](#)) (10). It has recently been suggested to the SAGE that data triangulation may be useful for identifying measles immunity

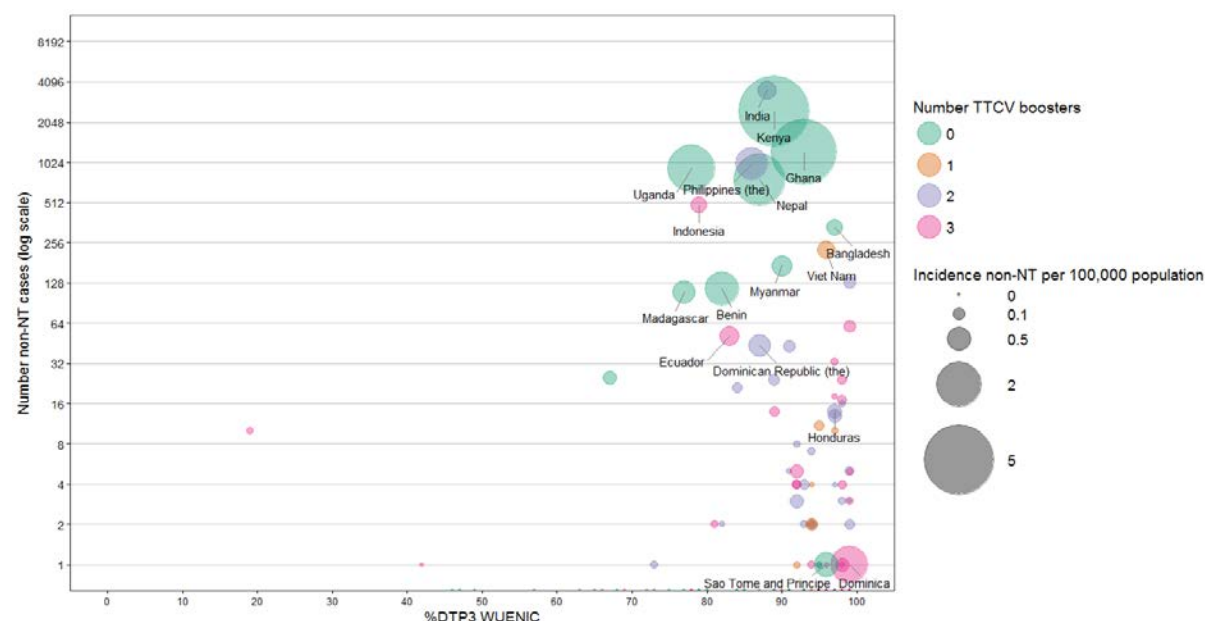
gaps (227). It is also relevant for addressing issues of equity (200), improving population denominators (53), and addressing other key issues. The perspective of the WG is that triangulation should really be the default for public health analyses to make the best use of existing data, despite the limitations of individual data sources, and because it has the potential for deeper understanding and improved confidence in decision-making (Annex 2) (10). As a proof of concept, the WG commissioned a global data triangulation analysis described in Box 6.6 (Annex 5) (37).

Box 6.6 Example of global data triangulation of tetanus vaccine coverage and incidence

In order to evaluate the feasibility of using non-neonatal tetanus (non-NT) surveillance data to monitor the coverage of DTP-containing vaccines (DTPCVs), the U.S. CDC conducted an analysis that triangulated three types of data for 194 countries reported to WHO: 1) tetanus vaccine schedules, 2) vaccination coverage (using WUENIC estimates), and 3) tetanus (neonatal and non-neonatal) incidence. The review found a high tetanus burden in low- and middle-income countries in Africa and Asia. This is in contrast to the pattern of reporting observed for pertussis, which tended to be reported from high-income countries with greater capacity for laboratory confirmation (36). Higher non-NT incidence was observed in countries with low DTPCV3 coverage and/or ones without booster doses in their vaccination schedule (see figure). However, there was evidence of unreliable non-NT reporting, likely resulting in the burden being underestimated (Annex 5) (37).

The review concluded that the ability to use non-NT incidence data to monitor DTP3 coverage is likely to vary from country to country, based on the quality of surveillance data. It also highlighted several limitations with the global availability and quality of JRF-reported data (Box 2.7).

Reported non-NT cases and incidence, DTP3 coverage estimates (WHO/UNICEF), and number of TTCV doses by country,* 2016



*Note: 129 countries not depicted because reporting zero non-NT (82) cases or not reporting (47)

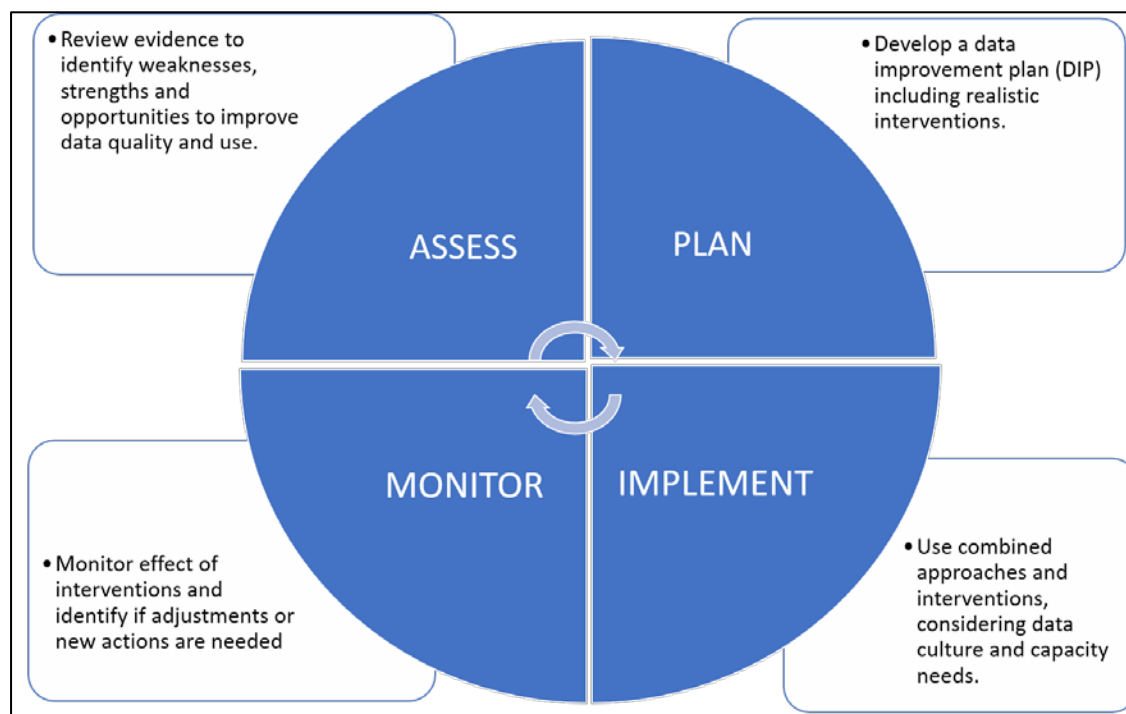
Encouraging the use of data triangulation methodologies, as has been done by HIV (228, 229), has the potential to promote a “data-use culture” by building capacity for critical thinking, data analysis and use within the context of an increasingly data-rich environment. The WHO, UNICEF and U.S. CDC have proposed to develop guidance on data triangulation that: 1) adapts the data triangulation process used for HIV and expands the desk review process described in the DQR as best practices for data analysis across topics relevant for EPI programmes, 2) is driven by

important questions relevant to immunization and surveillance programs (e.g., the identification of immunity gaps, and assessment of program impact, 3) includes the use of disparate data sources (e.g., VPD surveillance, vaccine supply/use, program management, serosurveys), and 4) attempts to reinforce critical thinking in processing data into information, including considering data limitations. The plan is to pilot-test draft guidance in two countries in 2019, and finalize the document in 2020 ([Annex 2](#)) (10).

6.4 Using an approach of continuous quality improvement and health systems strengthening

Continuous quality improvement (CQI) has been defined as the combined and continual efforts of everyone — healthcare professionals, patients and their families, researchers, payers, planners and educators — to make the changes that will lead to better patient outcomes (health), better system performance (care), and better professional development (230). CQI encourages stakeholders across the healthcare system — not only in the immunization programme — to continuously ask the questions: “How are we doing?” and “Can we do it better?” (231). It is a cyclical process of assessing performance, implementing improvement plans, and reassessing results to constantly strive to reach the best possible outcomes through data-driven decision-making (232) (Figure 6.2). Experiences in implementing a CQI approach for health system strengthening in LMICs have shown increases in ownership of the data and in the use of data for action (233). Ideally, this process occurs from the lowest (point of care) level all the way up to the highest level. Recent, guidance has been developed on how to develop a continuous immunization supply chain improvement plan: [How to Develop a Continuous Improvement Plan \(cIP\)](#) (2018). It would be helpful for WHO/UNICEF to develop a plan for how these principle could be applied more broadly to EPI.

Figure 6.2. Schematic of possible Continuous Quality Improvement (CQI) cycle to strengthen data quality and use



To date, assessments of immunization data quality in many settings has remained a top-down approach driven by the requirements of international agencies, rather than a country-led process focusing on improving healthcare delivery. As tools have been refined over time, including the latest DQR and *Handbook on the use, collection and improvement of immunization data*, increasing emphasis has been placed on performing a root-cause analysis of poor data quality to

inform the development of a Data Improvement Plan (DIP) (15, 234) (see *Chapter 2.3.2*). The review findings can be used to identify barriers and propose tailored solutions that would be most effective. However, the reality shows that many DIPs are not evidence-based and do not include actionable recommendations and appropriate indicators to monitor progress on data quality. Preliminary findings from 34/40 (85%) DIPs systematically reviewed show that <45.5% included indicators, only 30% estimated the budget; 60% indicated the agency responsible for carrying out the activity and only 24% identified a responsible person (Davis L, King A. personal communication). The review is ongoing.

Since 2000, Gavi has used vaccination coverage targets as part of its performance-based incentive schemes, in which countries become eligible for financial support for new vaccine introductions when national vaccination coverage levels meet or exceed a specified threshold (77). These pressures of crossing minimum thresholds to obtain financial support are often substantial and may encourage programmes to either game the system or falsify the data (235), potentially creating false reassurance about population protection against VPDs, as well as undermining data quality (see *Governance Chapter 3*).

To differentiate between a “measurement culture” and a “performance culture” (236), recent efforts have explored monitoring coverage of multiple vaccines doses (e.g., including BCG, DTP1, DTP3 and MCV1) rather than just one antigen (DTP3), as well as and monitoring relative immunization service delivery improvements (e.g. % improvement since previous period) alongside achievement of absolute vaccination coverage performance targets (89, 237) ([Annex 9](#)). Another benefit of assessing relative change is that some types of data quality issues, such as consistently inaccurate denominators, could be partially overcome (237). Aside from publications that have used such relative measures (89, 237), we are unaware of any research on the utility and effectiveness of relative measures of performance improvement compared to absolute targets as a way to improve immunization service delivery, while avoiding undesirable consequences such as data fabrication.

To maximize the impact of immunization strategies, CQI must focus not only on fixed targets but also on process evaluation, supervision and monitoring. Priority should be given to setting up mechanisms and processes that are institutionalized and sustainable to improve data quality and use at all levels of the health system. Examples of a long-standing institutionalized CQI programme from the U.S. immunization program and a CQI intervention in the health system in Peru are described in Boxes 6.7 and 6.8, respectively ([Annex 23](#)). When trying to address improvements over different areas of the health system, the use of a “maturity grid” to assess country capacities may be helpful in prioritizing and coordinating technical support for improvement. The use of maturity grids for immunization programmes and VPD surveillance have recently been proposed for Africa (238). A draft WHO technical package to strengthen country health data for universal health coverage and the health-related SDGs called SCORE (Survey, Count, Optimize, Review, and Enable) also features a maturity grid. The WG advises optimizing coordination of the global and regional EPI programs with such health systems approaches to create synergies and improve efficiency.

Box 6.7 AFIX Program in the U.S. for continual improvement of the immunization program

[AFIX](#) (Assessment, Feedback, Incentives, eXchange) is a strategy started in the U.S. during the 1980s focused on improving child and adolescent coverage at health clinics providing free vaccines to low income families by reducing missed opportunities to vaccinate and improving immunization delivery practices. The AFIX program consists of four components:

- Assessment involves generating reports on vaccination coverage levels of selected health care providers and examining the effectiveness of providers’ immunization delivery practices.
- Feedback provides an opportunity to share assessment results with each provider, discuss practice procedures and barriers, and collaborate to develop customized improvement strategies.

- Incentives recognize provider accomplishments and can be powerful motivation for providers to improve vaccination coverage rates.
- eXchange is the regular follow-up with providers to monitor their quality improvement progress and offer support through guidance and Incentives.

AFIX supports health care providers by identifying low immunization rates, determining opportunities for improving immunization delivery practices, and ensuring that providers are:

- Aware of their immunization rates and missed opportunities to vaccinate
- Motivated to incorporate changes into their current practices
- Ready to try new immunization service strategies
- Capable of sustaining improvements to their vaccination delivery services

Source: [AFIX website](#).

Box 6.8 Continuous quality improvement intervention in Peru

In Peru, with support from USAID, a continuous quality assurance program was created covering child and maternal health services in half of the country, centered on an accreditation system of 90 major hospitals heading regional networks of health services. The accreditation was based on process indicators, rather than on fixed outcomes. Teams of healthcare staff engaged in a peer problem-solving methodology to develop a quality improvement plan in the areas of: data to make decisions, essential equipment and supplies, standardization of care, patient satisfaction and working with the health service network and with community health workers.

To monitor and catalyze the quality improvement system, indicators were established based on each quality areas described. A team was trained in independent assessment and made at least two visits to each hospital. Impressive improvements were observed across most indicators, reaching >80% of approval in all categories. All hospitals were able to be accredited, the main reward of which was a diploma signed by the MoH officials given to all members of the quality assurance team. Utilization of health services improved dramatically, as measured by the proportion of children and pregnant women covered by programs, and a significant drop in maternal mortality was observed only in the regions of Peru where the program worked, documented by the country DHS surveys. Importantly, when several variables not used in the accreditation system were measured, important improvements in all of them also existed, including immunization practices and coverage ([Annex 22](#)).

6.5 Conclusion

There is a dynamic and cyclical relationship between data quality and data use. Although poor data quality has been reported as an important barrier to data use, the evidence to date suggests that greater availability of high-quality data, on its own, is insufficient to ensure that the data are actually used (8). On the contrary, limited evidence suggests that data quality improves through its use (88). Presumably, as decision-makers start using their data and identifying inconsistencies with the quality of the data, they will take corrective actions to improve data quality. Increasing and improving the use of data — and ultimately the performance of the immunization programme — can come about both by strengthening the data-related skills and knowledge of health workers (see *Workforce Chapter 4*) and by making better use of a diverse range of available, often-underused data, including by performing data triangulation. In addition, shifting from periodic assessments to the routine monitoring of data quality, as part of monitoring the performance of the immunization programme, will provide a stronger framework for accountability and confidence in the data. It is also critical that efforts to improve immunization data quality and use be part of broader efforts to improve the overall performance of the immunization programme and larger health system.

7. Evidence

7.1 Gaps in evidence

The WG's scope of this work included vaccine coverage, immunization program process indicators (e.g., vaccination sessions), vaccine supply, and VPD surveillance data. We did not assess evidence or make recommendations outside these areas.

In relation to “data quality”, an important challenge encountered by the WG included the lack of a consensus definition on the term and a lack of an agreed approach to monitoring data quality. To address these fundamental gaps, the WG proposed adopting a working definition and outlining attributes of data quality and associated indicators, as well as uses of data by level in order to advance the discussion. Further field-testing and feedback from users are needed before key indicators can be adopted as part of any global monitoring framework, e.g., for the next Global Immunization Strategy. Of note, relevant data quality indicators are likely to differ by context and level.

Another fundamental challenge is sparse evidence on how better data quality and use leads to better decision-making and better immunization programme performance. While these relationships have been demonstrated in the field of healthcare quality improvement, further work to examine the relationship between data quality, data use, and immunization program improvement would be useful. The IDEA project created an evidence gap map that highlights that more evidence exists on the impact of interventions on improved data quality and availability, but less evidence on what works to support decision-making informed by data, particularly at the facility level (Gap Map, [IDEA Report](#) [Precis Annex](#) in Yellow Book) (88). Nevertheless, and reassuringly, “data-driven” impact has been demonstrated in other sectors from leadership guiding their managerial decisions using data (239, 240).

This report highlights that ultimately data quality at all levels is underpinned by the quality of data collection and processing at the local level (facility or community), but also affected by errors that may occur during data entry and aggregation as data is reported up. Comprehensive evidence on the relative contribution of different types of data errors, at different levels, and the relative impact of different types of interventions to increase data quality is lacking. More evidence is needed around what the motivating and demotivating factors are for using data and producing data of high quality.

The WG noted that much of the evidence reviewed regarding interventions designed to increase data quality and use were generally lacking robust evaluations. There is very limited evidence on the effectiveness, cost-effectiveness and sustainability of interventions which aim to improve data quality and use. For example, despite the many pilots of novel ICT approaches to data collection, processing and reporting, few documented examples exist of evidence-based decisions on when and how to scale interventions.

The issue of denominator deserves a special mention. Better evidence around how to improve immunization targets (denominators), especially at local levels and in the context of mobile populations, was also identified as a fundamental gap. This issue was repeatedly highlighted as a key issue in most informant interviews, and also highlighted in the reviews; more guidance is desired. Denominator challenges include both technical and political dimensions, and each needs their own solutions. To address the gaps in this area, conducting further research, collaborating with other health programmes facing similar denominator issues, and considering how to move innovations from the research phase into programmatic use would be worthwhile.

GVAP adopted equity targets, but related monitoring has been hindered by the insufficient quality of subnational immunization data. Methods like data triangulation and geospatial modeling of subnational immunization coverage are some of the promising approaches for addressing this issue. As with denominator data, collaborating with stakeholders in other programmes that also

monitor equity (HIV, malaria, maternal health) may be beneficial to outline a common research agenda around measuring inequalities and developing strategies to improving equitable immunization coverage.

Serosurveys aim at measuring population immunity. However, serosurveillance was another area where gaps exist, though they have been conducted in high-income countries for years and are being increasingly conducted in middle and low-income countries. These surveys may also contribute to improving immunization data quality through triangulation with vaccination coverage data. WHO has produced guidelines for conducting serosurveys for hepatitis, measles and rubella, dengue, and tetanus. Yet, more needs to be done to summarize the evidence regarding the utility of serosurveys by disease and different epidemiologic/country contexts and comment on the role of serosurveys as part of immunization program monitoring (e.g., relative to other programme priorities).

Finally, the WG is proposing greater emphasis on continuous quality improvement approaches. Closer evaluation of existing approaches from other health fields would be useful, as well as conducting immunization program research in different contexts. One specific question is whether moving targets, or relative increases in performance over baseline, in combination with a focus on targeted strategies to reach unvaccinated persons might generate greater success than focusing on absolute performance targets.

7.2 Research Agenda

The section below summarises specific research topics based on the identified gaps in the evidence. It should be noted that based on the objectives and situation of data quality and use in each country, local evidence should be considered, and a research agenda developed.

Data quality and use

- Documenting which data are most useful at different levels in different contexts
- Field testing different data quality attributes and related indicators at different levels
- Better evaluating data quality and use interventions- monitoring of impact on indicators, cost effectiveness and time efficiency This includes the systematic collection of case studies from countries that succeeded or failed to improve data quality and use in a systematic and/or sustainable manner
- Identifying and characterizing the technical and non-technical barriers to denominator estimation and numerators and how can they be overcome
- Defining data quality assessment/validation approaches for VPD surveillance data

Workforce

- Better characterizing the evidence around effectiveness, cost effectiveness and sustainability of interventions aimed at strengthening data-related workforce capacities: training strategies (virtual, face to face, etc), supervision, mentoring, etc. This includes field testing of immunization competency assessment and training
- Identifying enabling factors to help health workers collect and use data to improve vaccination delivery

Information systems and tools

- Better defining what tools are actually needed and helpful for health workers to do job in different contexts E.g., are register books relevant in today's context, both in rural and urban areas?
- Documenting the impact of transition from immunization information systems to integrated ones. What is needed for integrated systems to meet needs of immunization and VPD surveillance programs? What are the opportunities and efficiencies created?
- Evaluating effectiveness and cost-effectiveness of novel technologies to improve data quality and use in different contexts

- Documenting evidence and decision-making processes around scaling of novel technologies
- Documenting experiences where novel technologies have actually replaced the conventional data collection tools (HMIS forms), to better understand if are systematically integrated into the existing health system structure for example.

Data triangulation, including modeling

- Field testing of data triangulation guidance (in particular triangulating coverage with VPD surveillance and vaccine supply data)
- Validating modeled subnational coverage data, and evaluation of usefulness in overcoming data quality issues with reported subnational administrative coverage
- Exploring modelling approaches and incorporation of other inputs, such as stock data, as part of WUENIC

Monitoring and accountability- or CQI

- Exploring what are the most appropriate incentives leading to both improved data quality and programme performance
- Evaluating the role of CQI in improving data quality and use
- Evaluating the impact of relative vs. absolute targets on program improvement and avoiding perverse incentives that may lead to inflated reported coverage.
- Defining how best use provider assessment and feedback interventions effective to improve data quality and use.
- Conducting an evidence review of taking health system approaches to improving data quality and use.

Other topics (denominator, equity, life-course, surveys)

- Developing a research agenda around denominators to better understand technical and non-technical barriers to denominator estimation and how can they be overcome
- Determining the effectiveness and cost of GIS and other methods for improving population denominators
- Exploring how to enumerate special populations such as migrants, asylum seekers and age groups beyond infancy, etc. (lessons learned from NGOs, polio) and then monitor vaccination in these groups
- For coverage equity, developing standardized equity monitoring indicators and approaches
- For coverage surveys, implementing the research that has been identified, notably around:
 1. Validity of respondent recall,
 2. Utility of facility traceback to improve documentation of vaccination vis-à-vis costs,
 3. Feasibility of different household sampling methods (e.g., GIS grids),
 4. Analytic approaches to dealing with missing information, and
 5. Easier proxies to wealth questions and computation
- Serosurveys
 1. Research on the feasibility of integrating immunization coverage and VPD serosurveys with other large surveys/serosurveys (HIV, malaria),
 2. Triangulation of seroprevalence, coverage estimates and other data
 3. New laboratory technologies with improved performance characteristics (point-of-care, multiplex, capture ELISAs with improved sensitivity and specificity)

8. Moving Forward

There is no shortage of immunization and VPD surveillance data, at all levels — local, national, regional, and global. The global strategic drive towards better quality data is based on the assumption that use of quality data is a catalyst for improving programme performance and efficiency. Yet despite tremendous progress, coverage has plateaued and the EPI programme still has the potential to reach more and more people with lifesaving vaccines. A number of possibilities therefore exist:

- Quality data, i.e., fit for purpose, exists but is not sufficiently accessible where needed to inform public health action;
- Data is not of sufficient quality for use; or
- Data is available, but not used.

This report highlights that the current situation is a likely result of a combination of these three factors. Though evidence that high data quality improves data use is lacking, use seems to improve quality. Using better data will ultimately contribute to better identifying and targeting those who are eligible for vaccination.

A barrier to evaluating the importance of data quality in improving programme performance may be a lack of common operational definition and monitoring framework for assessing data quality. This report suggests a definition for data quality as well as a list of attributes contributing to quality data. This report takes a pragmatic approach and suggests a definition of data quality as “good enough for the intended purpose,” such as monitoring performance, supporting efficient program management, or providing evidence for decision-making. We recommend that SAGE endorses this definition and that WHO agrees on data quality attributes using those suggested in the report as a starting point to including data quality as part of a comprehensive immunization monitoring framework in the near future.

Historically, the data quality debate has been too focused on vaccine coverage accuracy at the global level and the monitoring needs of global stakeholders, rather than producing data of sufficient quality to accomplish to goals (e.g., finding un or under vaccinated persons and preventing disease). This report recognizes that data quality at all levels ultimately depends on the quality of data collection at the point of vaccination. Thus, *data quality interventions must target the local level where data collection occurs*. In addition, the use of data at the national level downwards, down to the level where individuals are vaccinated, is modest at best. In order to achieve impact, we need to refocus the data quality debate on underlying causes of insufficient data quality and use at national and subnational level, and in particular at the facility level.

Even where the local level collects and reports quality data, more often than not there is no feedback of analyzed data from the higher levels to enable facilities to use these data to address gaps in the immunization programme. Creating a strong “data use culture” where data is collected, reported, analysed and fed-back as intelligence relevant to improving the delivery of an immunization programme would go a long way in driving data quality upwards. Such a data use culture emphasizes moving beyond sporadic data quality reviews and assessments (often perceived as “tick box” requirements) that treat quality data as an outcome, to supportive continuous quality improvement interventions that demonstrate the public health impact of better data to those who use it.

This report suggests consideration of several complementary approaches to optimize the use of existing data in order to move beyond the exclusive use of vaccine coverage data as the hallmark of immunization programme performance and immunization data quality: (i) Triangulation, or synthesizing existing data from two or more sources (e.g., coverage and surveillance data), is a pragmatic approach that is commonly (but not systematically) used in the public health field. This report suggests triangulation should become the default approach for EPI data analysis and use; (ii) giving prominence to other data sources such as surveillance data; (iii)

moving away from evaluating programme performance exclusively against absolute performance targets. While achieving targets can be important in an eradication, elimination or disease control context, it can create perverse incentives, in particular when reaching these targets have financial implications. This report proposes that data quality be monitored alongside data used to monitor performance (e.g. mainly vaccine coverage) using a panel of indicators, and that gradual improvement of performance and data quality are rewarded alongside reaching coverage targets.

Optimal data quality and use ultimately requires a skilled workforce. Currently, capacity, capabilities and, in many cases, structural factors are limiting factors. It is crucial to understand that data are collected by individuals at the local level who often have to balance clinical duties with data related activities. It is assumed that at the local level healthcare workers will collect, input, report and sometimes analyse the data on top of their clinical activities. In practice, data related activities compete with clinical duties for staff time, and data is often an afterthought. To improve data quality and use, data related activities need dedicated time, and staff need to be equipped and motivated to perform the data-related activities expected of them. Creating capacity and capability requires including dedicated data-related time in workforce planning at all levels, and a multi-pronged training approach that includes both pre-service and in-service components, with regular reinforcement through supervision and feedback. This report attempts to define what the data-related expectations are at each level, which can help inform staff time and training requirements. In addition to the often overlooked workforce, this report also highlighted important issues related to governance, such as having enough financing for data collection and analysis, government leadership, coordination with partners to prevent fragmented data systems, setting data and information system standards, and data sharing agreements.

Technology and innovation are often used to non-specifically to compensate for the root causes of insufficient data quality highlighted above. The plethora of pilot projects that fail, are never scaled up or never evaluated is testament to the fact that while technology can solve technological problems, it is not a magic bullet that solves all data quality and use issues. Certain applications of technology such as the combination of global information systems (GIS) and predictive analytics to generate population estimates i.e., denominators, could prove to be genuine advances in our ability to better monitor vaccine programmes. Not all innovations will prove to add public health value and the limited data available regarding the effectiveness and costs of digital health solutions is telling of how much more we need to learn before we can properly make evidence-based decisions regarding the use of new technologies. Innovation such as health information systems, in the right context, can improve the quality of immunization and surveillance data quality, and decision-making tools such as dashboards have the potential to drive data use, and as such the WG is supportive of the development of WIISE.

Despite most countries gradually transitioning to electronic health information systems, the tension between standalone and integrated systems remains unresolved. In theory, integrated approaches are generally more efficient, both from the country perspective and from the perspective of the frontline healthcare worker doing all the data collection for various program areas. But, in practice this requires coordination across programme areas and developing and integrating EPI programme standards into a whole-systems approaches to data management. In some cases, standalone tools continue to exist because integrated systems do not adequately address the needs of the EPI program. The utilization of well-planned and coordinated integrated information systems, training, and assessment approaches has the potential to create greater synergy on health system strengthening that can be cost-saving and time efficient. Regardless of the approach, the successful use of digital health interventions still requires the right contextual factors to be in place – infrastructure, resources, connectivity, governance, clear processes and a skilled and motivated workforce – to use well-designed user-centered tools.

Improving data quality in itself is necessary but not sufficient to improve vaccine programmes. Users must be able to find the data they need and guidance on how to use it in an optimal way. This report highlights the plethora of available data and related guidance on various aspects of data use, collection, monitoring, and quality assessment. However, these data and guidance are not necessarily easily discoverable or accessible. WHO, UNICEF and global must ensure that global data collection continues and is strengthened so that those who need data at the global

level can find it and those who manage and use data to deliver the immunization programme can easily find relevant guidance. The latter can be done by making guidance easily discoverable on relevant communication channels such as websites and apps, and by analyzing carefully where guidance is needed in order to prevent duplication. In addition, immunization and surveillance data must be shared in way that is proportionate to public health needs and in a manner that ensures the benefits of the data are shared equitably.

As the global EPI matures and coverage improves, the growing number of immunized individuals increasingly requires enhanced use of better quality data. As vaccine coverage has increased dramatically in most settings since the beginning of the 21st century, closing the immunization gap will require to use data to answer questions such as: How equitable is immunization service delivery? Are we reaching underserved populations such as migrant populations or those living in slums? What about those who use private healthcare facilities? How are vaccines targeting groups outside infancy reaching their goals and what is their impact in those populations? Alongside strengthening the quality and use of what is considered routine data, it is time to consider what data is needed to answer these questions at the different levels, how to collect it in a cost-effective manner, and more importantly how to ensure it achieves the objective of improving the delivery of the immunization programme in terms of effectiveness and efficiency. This report suggests answering these questions should be prioritized as part of the research agenda.

Finally, while this report focuses on immunization data, this report recognizes that data quality and use issues encountered in the EPI are not unique. It also acknowledges that in many cases, and in particular at the most local level, individuals responsible for immunization data will also manage data from other public health programmes, who will commission similar reviews on data quality and use. While the structure of public health programmes precludes an exclusively whole health systems approach, there is value in the global immunization programme working through a whole health systems approach, collaborating more closely with other programmes on data quality and use issues, as well as data initiatives that are not programme specific, within WHO or outside.

9. Recommendations

Achieving equitable immunization coverage and timely detection of VPDs requires high-quality programme data. Concerns about the quality and use of immunization and VPD surveillance data have been highlighted on the global agenda for more than two decades. As countries strive to meet the ambitious goals of GVAP and future goals Post-2020, improved information systems and more precise and finer types of measurements will be required to achieve improvements in equity of service delivery across the life-course and reductions in disease burden for an expanded set of VPDs.

The WG defined “data quality” as the degree to which data are fit for the intended purpose (i.e., accurate, precise, relevant, complete, and timely enough for use). Following a 1.5-year review, the SAGE WG on the Quality and Use of Global Immunization and Surveillance Data recommended the following actions at various levels to be considered by SAGE.

1. Embed monitoring of data quality into global, regional and country monitoring of immunization and VPD surveillance performance.⁶

	<u>Relevant levels</u>	<u>Chapters providing evidence</u>
a) SAGE to endorse data quality definition proposed by the WG as the “degree to which data are fit for the intended purpose”.	G	2
b) WHO to update, finalize and disseminate the <i>Global Framework to Strengthen Immunization and Surveillance Data for Decision-making</i> so it can be considered in post-2020 immunization strategy	G	2
c) WHO to develop a common lexicon, including defining the attributes of data quality, using the definitions proposed in this report as a starting point	G	1, 2, 6
d) WHO to propose (and SAGE to endorse) appropriate data quality indicators corresponding to the different data quality attributes (i.e., small panel of indicators, rather than one), using the indicators identified in this report as a starting point	G	2,6
e) Integrate ongoing monitoring of data quality indicators alongside other routine programme performance (e.g., coverage) and impact indicators	G R N	2,6
f) Develop and utilize data quality assessment approaches for immunization program data other than coverage (i.e., VPD surveillance, stock data, etc.)	G R N	2,6
g) Conduct impact and economic evaluations of interventions which aim to improve data quality, management, and use to inform decisions on scale-up	G R N	7

2. Increase workforce capacity and capability for data quality and use, starting at the lowest level where data collection occurs.⁷

	<u>Relevant levels</u>	<u>Chapters providing evidence</u>
a) WHO to review and revise their <i>Standard Competencies Framework for the Immunization Workforce</i> document to ensure comprehensive consideration of data collection, management, analysis and use at all levels, especially considering that the facility/ community level has critical shortages of people and time in most settings	G	2,4
b) Develop and disseminate data-related competencies guidance and capacity building tools to implement assessment of workforce at country-level	G R N	4

⁶ The recommendation builds on a SAGE recommendation to “continuously review the Progress on GVAP and the need for reformulation of the indicators or mechanisms for collection and reporting of data” (Nov. 2012).

⁷ This recommendation builds on a SAGE recommendation to “create tools to assist countries in different aspects of immunization human resources management including: staff turnover and rotation policies, performance evaluations, and design of training” (April 2017).

- | | | |
|---|------------|-----|
| c) Ensure data functions (collection, analysis, and use) are accounted for and resourced in workforce management plans, e.g., devoting adequate person-time equivalents, staff recruitment, retention | N | 4 |
| d) Build data capabilities with training across various levels and career stages (pre-service, refresher, supportive supervision, etc.), considering new approaches (e.g., e-Learning) potential efficiencies created by coordination across programs | GRN | 4 |
| e) WHO to finalize & publish <i>Handbook on the Use, Collection and Improvement of Immunization Data</i> , and continue disseminating through Immunization Monitoring Academy and other approaches. Regions and countries should adapt context-specific guidance and training approaches as needed. | GRN | 2,6 |

3. Take actions to improve the accuracy of immunization programme targets (denominators).

- | | <u>Relevant levels</u> | <u>Chapters providing evidence</u> |
|---|------------------------|------------------------------------|
| a) WHO IVB to increase coordination with other programs and broader data initiatives (e.g., Health Data Collaborative, WHO IER programme) around improving the quality of denominators as part of health systems strengthening. | GR | 3 |
| b) WHO and UNICEF to revising and finalize the draft guidance on <i>Assessing and Improving the Accuracy of Target Population Estimates for Immunization Coverage</i> (2015), including proposing practical and evidence-based solutions | G | 2 |
| c) Increase immunization programme coordination with national statistics office, birth/civil registration offices, and other relevant programmes/organizations for improving the quality of denominators | N | 3 |
| d) Identify and attempt to address the technical (e.g., resident vs non-resident) and non-technical barriers (e.g., political) to accurate denominators in countries, including the use of operational denominators | GRN | 2,3,5,6 |
| e) Document best practices and country experiences about using different sources of denominators (birth cohorts, vital registries and census estimates) or methods for improving denominators. | GRN | 2,3,5,6 |
| f) WHO, global immunization partners, and other programmes/initiatives to collaborate in developing fora for new research approaches and validation of existing research for improving denominators (e.g., spatial modelling) to inform guidance for program use. | GRN | 3,5,6 |

4. Enhance the use of existing data at all levels for tailored action, including immunization programme planning, management, and decision-making.

- | | <u>Relevant levels</u> | <u>Chapters providing evidence</u> |
|--|------------------------|------------------------------------|
| a) Increase the use of data sources beyond administrative coverage for monitoring, planning and decision-making at all levels (e.g., numerators, denominators, surveys, surveillance, vaccine supply, service delivery, serosurveys) | GRN | 6 |
| b) Develop guidance and training on data triangulation for immunization and surveillance programmes at the national and subnational level | GRN | 2,6 |
| c) Support the development and use of decision-support tools (e.g., monitoring charts, dashboards), as needed, for better planning and program management | GRN | 5,6 |
| d) Document instances where data use has led to increased programme performance | GRN | 8 |

- | | | |
|--|--------------|-----|
| e) SAGE to recommend further work on defining the role of serosurveys for immunization program management at different levels, across different diseases and different epidemiological contexts ⁸ | G | 7 |
| f) Research on the relevance of data sources beyond coverage to evaluate and improve data quality (e.g., stock) and use for program management and decision-making. | G R N | 2,6 |

5. Adopt a data-driven continuous quality improvement (CQI) approach as part of health system strengthening at all levels.

	<u>Relevant levels</u>	<u>Chapters providing evidence</u>
a) Shift from identifying data quality issues to root cause analysis and improvement planning, as outlined in the draft <i>Handbook on the Use, Collection and Improvement of Immunization Data</i>	G R N	6
b) Monitor the implementation and impact of previous recommendations to improve accountability and inform new recommendations (e.g. create data-driven improvement cycles)	G R N	6
c) Strengthen data collection and use by implementing multi-component strategies, which may include capacity-building activities, tools, supportive supervision, actionable feedback, staff recognition (e.g. certificates, awards) and accountability mechanisms	G R N	3,4,5,6
d) Recognize that perverse incentives may have led to overestimation in reported coverage, and ensure that data quality improvements leading to lower coverage are not penalized (i.e., promote accurate reporting)	G R N	3,6
e) Develop a vision for a CQI approach for EPI, including measuring relative changes, in addition to achieving absolute indicator targets	G R N	6

6. Strengthen governance around piloting and implementation of new information, communication, and technology (ICT) tools for immunization and surveillance data collection and use.

	<u>Relevant levels</u>	<u>Chapters providing evidence</u>
a) Design and pilot/implement systems and tools based on clearly defined needs/objectives, user requirements, local context, and potential health system sustainability in mind ⁹	G R N	3,5
b) Review existing evidence on cost, impact and effectiveness when considering pilot or scale up new tools for data collection/ management	G R N	5,7
c) Plan for and ensure integration and interoperability of any newly introduced tools within the existing information system	G R N	3,5
d) Ensure any new system is accompanied by guidance, standards and specification	G R N	2,3,5
e) Evaluate the impact, costs, sustainability, and added value of new tools for data collection, management and use	G R N	3,5,7

⁸ This would strengthen previous SAGE recommendations “that WHO identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage...as well as support new research for biological specimen collection including rapid on-site diagnostics that could improve coverage and susceptibility estimates” (November 2011) and “Where feasible, the use of (tetanus) 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” (October 2016).

⁹ [PAHO Electronic Immunization Registries \(eIR\) Guide \(2018\)](#)
[Planning and Information Systems Project \(2013\)](#)

7. Improve data sharing and knowledge management across areas and organizations (e.g., private sector) for improved transparency and efficiency.

	<u>Relevant levels</u>	<u>Chapters providing evidence</u>
a) Include best practices on data management (archiving, migration, sharing, and security) in immunization monitoring and surveillance guidance and training	GRN	3
b) Ensure new information systems include historical data and support all data management functions, including archiving, security, and linkage of relevant data	GRN	3
c) Build and maintain websites, mobile apps and other communication tools where data, guidelines, documentation, and reports are available and readily discoverable to relevant users	GRN	2
d) Improve routine coordination between program units (epidemiologic surveillance, laboratory, and immunization), private providers, and partners, with regards to reporting/sharing of relevant data and information	GRN	3,6
e) Recognize that data issues are similar across health programs, share experiences and look for areas of collaboration, as part of whole systems approach	GRN	3

8. WHO and UNICEF to strengthen global reporting and monitoring of immunization and surveillance data through a periodic needs assessment and revision process.

	<u>Relevant levels</u>	<u>Chapters providing evidence</u>
a) Continue development and implementation of global (WIISE) and regional information systems and electronic JRF for coverage and surveillance data	GR	2
b) Collect and monitor disaggregated coverage (e.g., subnational) and surveillance data (e.g., by age group, vaccination status, lab confirmation) ¹⁰	GR	2,6
c) Develop a comprehensive approach for collection of relevant data to support robust monitoring of vaccination across the life-course	G	2,3,4, 5, 6
d) Develop approaches for improving immunization coverage monitoring and disease incidence among migrants /mobile populations who move across borders	G	2
e) Develop approaches on how to manage and monitor qualitative data (e.g., reasons for non-vaccination, recommendations from assessments)	G	2,6
f) Collaborating and convening around new research and validation of existing research for improving subnational coverage (e.g., spatial modeling) and approaches to equity monitoring to inform guidance for program use.	G	2, 6

9. WHO SAGE should review in 5 years which WG recommendations have been implemented i.e., when, where and how with outcomes of this strengthening and lessons learned.

¹⁰ This recommendation reinforces earlier SAGE recommendation “that additional disaggregation was needed in the analysis of the progress achieved on the ground, and in identifying bottlenecks for progress, and recommended that reports display disparities observed at subnational levels” (April 2015) and “that the accumulation of susceptible persons at both the national and subnational level should continue to be monitored to identify and address immunity gaps” (October 2016).

10. Table of Annexes

Annex in Yellow Book

Precis from IDEA realist review report ([full report¹¹](#)) (TOR 4b)

Online Annexes

1. Global Framework to Strengthen Immunization and Surveillance Data for Decision-making
2. Framework for Triangulation for Immunization and Surveillance Data (TOR3)
3. Table of data quality attributes (TOR3)
4. Summary of key informant interviews on EPI data availability (TOR1)
5. Triangulation analysis of tetanus vaccination and surveillance data (TOR3)
6. *Case study*: Electronic immunization registry, Chile
7. Literature review: Barriers limiting quality of VPD surveillance data (TOR 4a)
8. Summary table of global EPI guidance (TOR2)
9. Summary table from review of data quality indicators (TOR3)
10. *Case study*: Improving vaccination coverage data quality, China
11. *Case study*: Utilization of data for evidence-based decision-making, India
12. *Case study*: Efforts to improve data quality and use, Nigeria
13. Literature review: Novel methods for polio surveillance (TOR5)
14. Scoping review: Factors limiting immunization data quality in LMIC (TOR 4a)
15. Scoping review: Pre- and in-service training on immunization data in LMIC
16. Summary table of innovations for immunization and surveillance data (TOR5)
17. Literature review: Novel approaches for immunization data (TOR5)
18. *Case study*: Integration of VPDs into communicable disease surveillance, Vietnam
19. *Case study*: Polio map-athon — using georeferenced data to strengthen microplans
20. Proposal to SAGE on role of serosurveillance for immunization monitoring
21. *Case study*: Improving the quality and use of vaccine coverage data, England
22. *Case study*: Using polio campaign data to improve EPI Coverage, Pakistan
23. *Case study*: Continuous quality assurance processes, Peru
24. References for this report

¹¹ <https://findyourfinding.org/>

11. Acknowledgments

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Finally, this report is dedicated to Anthony (Tony) Burton (retired from WHO), a public health and data champion who passed away in July 2018. Tony was an inspiration to many of us working on immunization in general and immunization data in particular.



A Realist Review of What Works to Improve Data Use for Immunization

Evidence from low- and middle-income countries

PRÉCIS

Introduction

Within global health, it is widely acknowledged that a cornerstone of well-functioning health systems is data of high enough quality to guide decision-making. Yet despite international efforts to improve the quality of health data, including in the immunization field, increasing data use for making decisions remains a challenge, especially at the level of health care delivery.¹ There is a need to take stock of the evidence from existing efforts to strengthen immunization data and identify effective and ineffective approaches, as well as any knowledge gaps.

The goal of the Immunization Data: Evidence for Action (IDEA) project is to identify, review, synthesize, and disseminate *what works* to improve use of immunization data and *why* it works. To this end, we conducted a realist review with these objectives:

- ▶ Articulate a Theory of Change (TOC) that illustrates key mechanisms and outcomes related to strengthening data use.
- ▶ Synthesize existing evidence (published and unpublished) related to strengthening the use of immunization data, and evidence on strengthening data quality in relation to data use.
- ▶ Provide information and evidence so that various stakeholders may select approaches with the highest potential for improving the use of routine immunization data.

This review was a collaborative effort between PATH and the Pan American Health Organization (PAHO). The review team included health systems researchers with expertise in immunization, measurement and evaluation, and evidence-informed policymaking from PATH's Health Systems Analytics team, as well as immunization and data use experts from PAHO. To ensure the review's relevance for multiple agencies, countries, and decision-making bodies, a steering committee of ten global and regional senior leaders in the areas of immunization, data quality, and use guided the work of the review team.

¹ Karuri J, Waiganjo P, Orwa D, Many A. DHIS2: The tool to improve health data demand and use in Kenya. J Health Inform Dev Ctries [Internet]. 2014 Mar 18 [cited 2018 Sep 9];8(1). Available from: <http://www.jhidc.org/index.php/jhidc/article/view/113>

Methods

The review sought to answer two principal research questions:

01. *What are the most effective interventions to improve the use of data for immunization program and policy decision-making?*
02. *Why and how do these interventions produce the outcomes that they do?*

Realist Review Approach

To answer our research questions, we conducted a realist review of the evidence on what works to improve data use. This approach allowed us to include multiple types of evidence, such as experimental and nonexperimental study designs, grey literature, project evaluations, and reports.

Much of the immunization sector's knowledge on data quality and use interventions has not been rigorously evaluated or published. In addition to including studies and evaluations that applied scientific research methods or evaluation design in our review, which we referred to as "evidence," we considered grey literature that did not qualify as a study or evaluation but had strong theoretical plausibility of improving data use, as judged by our TOC. We referred to these records as "promising strategies": strategies that have not yet proven successful but have potential for future success.

Realist reviews are typically driven by a theoretical understanding of how the context and causal mechanisms interact to produce certain outcomes.² By providing explanations for why interventions may or may not work and under what circumstances, realist reviews can lead to more pragmatic, actionable conclusions. The approach also gave us the flexibility to orient our data collection iteratively to fill gaps.

Review Process

The review included eight steps:

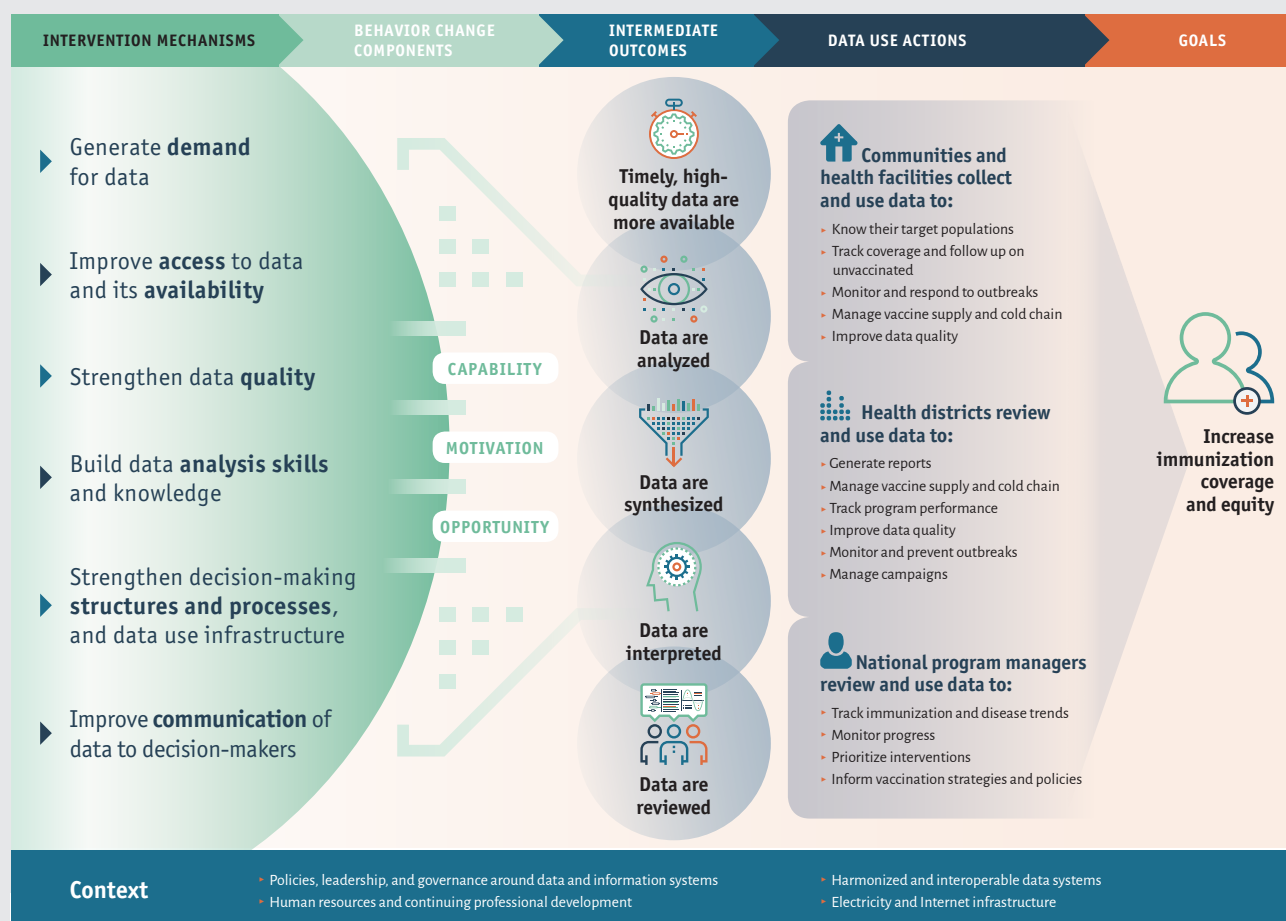
01. *Develop a TOC based on our analysis of systematic reviews and related literature.*
02. *Conduct a systematic review of effectiveness (peer-reviewed and grey literature).*
03. *Review promising strategies to inform why and how the interventions work.*
04. *Extract and code text data based on the TOC.*
05. *Conduct a quality assessment of studies and evaluation of effectiveness.*
06. *Synthesize preliminary data and validate findings with the IDEA steering committee and other immunization stakeholders.*
07. *Conduct a second round of data collection and review literature on data use interventions in other health sectors.*
08. *Synthesize the final data and develop an evidence gap map.*

To guide the review, we developed a TOC (see Figure 1) based on our analysis of existing health information and data use frameworks and logic models, as well as reviews on topics related to health information system strengthening and evidence-informed decision-making. The TOC framed our hypothesis of the theorized mechanisms and contextual factors that work together to help decision-makers translate data into information and, ultimately, action. In order to be effective, we hypothesized that any intervention must incorporate one or more of these mechanisms: demand, access and availability, quality, skills, structure and process, and communication. We also included behavioral drivers: capability, motivation, and opportunity.

2 Pawson R, Greenhalgh T, Harvey G, Walshe K. Realist review—a new method of systematic review designed for complex policy interventions. *J Health Serv Res Policy*. 2005 Jul;10 Suppl 1:21–34.

FIGURE 1.

Theory of Change for supporting data-informed decision-making for immunization programs



We identified intermediate outcomes as the necessary precursors to data use: data quality and availability; and analysis, synthesis, interpretation, and review of data. The ultimate outcomes of interest are the data use actions, which are based on the World Health Organization's Global Framework to Strengthen Immunization and Surveillance Data for Decision-making.³ The TOC guided our analysis of how interventions led to improved data use and, ultimately, to increased immunization coverage.

The review focused on studies, evaluations, reports, and descriptions of interventions to improve use of routine data by an immunization program for service delivery (which excluded surveillance, financial, and human resources data). We excluded documents that were not specific to a particular intervention or where the outcome examined was something other than data use. We considered health care

professionals to be the principal users of routine health data and did not examine use of data by recipients of health care services. We primarily focused on interventions implemented in low- and middle-income countries (LMICs); however, in a limited number of cases, we considered relevant publications from high-income countries (n=7). Much of the literature we collected had been published within the last 15 years.

Although we primarily focused on evidence related to strengthening the use of immunization data, we also examined interventions to strengthen data quality in relation to improving data use. Our TOC recognizes data quality as both a driving mechanism of data use and a measurable intermediate outcome of data use interventions. We therefore included literature on data quality that allowed us to examine these relationships.

3 World Health Organization. Global Framework to Strengthen Immunization and Surveillance Data for Decision-making. Geneva, Switzerland: WHO; 2018 Jan.

We searched PubMed, POPLINE, CABI (Centre for Agriculture and Biosciences International) Global Health, and African Journals Online for published evidence. We obtained grey literature by searching vaccine and digital health conference, implementer, and technical agency websites, as well as through targeted outreach to entities such as TechNet-21, the Global Digital Health Forum, BID Learning Network webinars, other key stakeholders, and members of the steering committee to identify projects and interventions. We assessed the quality of records that qualified as evidence using the Mixed Methods Appraisal Tool (MMAT), a checklist for systematic literature reviews.⁴

We examined the characteristics of the interventions: designs and strategies; targeted types of health care professionals and levels of the health system; implementation settings; and outcomes. We looked at how the interventions functioned and what mechanisms made them successful. We also sought to understand the reasons why interventions did not show evidence of effectiveness.

We presented a synthesis of our preliminary findings to the IDEA steering committee and other immunization stakeholders in May 2018 and identified gaps in the literature. For intervention categories that had limited evidence and were applicable outside of immunization, we expanded the review to include evidence from other health sectors, specifically HIV and maternal and child health. We coded the included records, synthesized the evidence according to outcomes in the TOC, and rated the certainty of evidence.

Assessing Certainty of Evidence

Realist reviews generally do not exclude evidence based on study design or quality. We took this approach but adapted various methods of quality appraisal. We considered certainty of evidence of the evaluated intervention's effect on data quality and use by analyzing (1) design and (2) quality of the included studies, (3) number of studies and their agreement, and (4) context dependence of the evidence. The certainty of evidence rating of high, moderate, low, or very low was a subjective estimation based on these four constructs.

Literature Findings

We initially reviewed 426 documents from published and grey literature and in the second round of data collection reviewed another 123 documents. Ultimately, we included 103 of these documents in the full-text review. We determined that 69 of the articles were research evidence, as they reported results from a study or evaluation, and 34 were promising strategies. Most included literature came from LMICs, although seven pieces of literature were from high-income countries. Africa was the most represented region in the review, and electronic immunization registries were the most reported primary intervention type.

- ▶ 48% of reports from Africa
- ▶ 13% from the Americas
- ▶ 9% from South East Asia
- ▶ 6% from Western Pacific
- ▶ 5% from Eastern Mediterranean
- ▶ 2% from Europe
- ▶ 17% of reports were not related to a single region

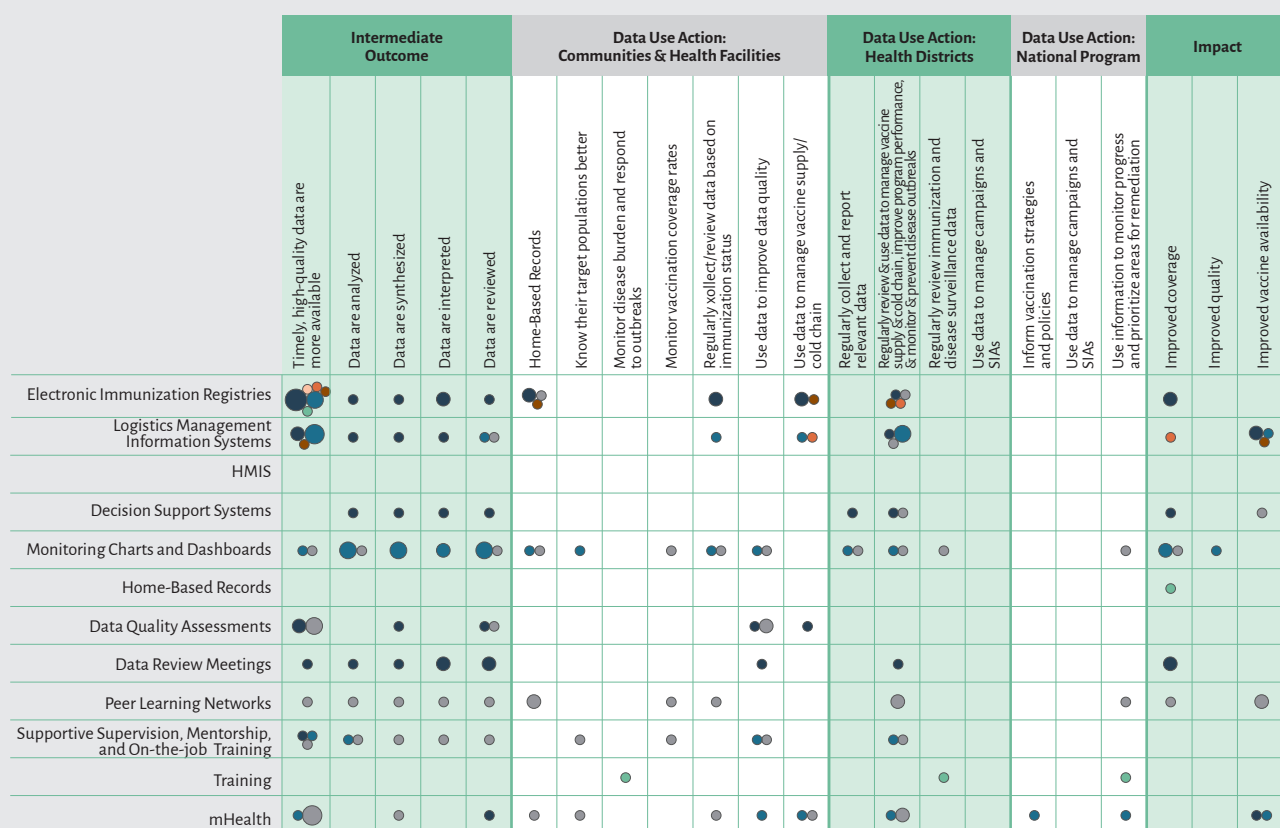
Most documents described projects with multiple intervention components and tended to report on multiple intermediate outcomes and data use actions.

We developed a gap map to visualize all the pieces of evidence and promising strategies included in the review, which illustrates the relatively small number of records pertaining to many data use actions and impact indicators (see Figure 2). Many gaps exist regarding national-level data use actions.

4 Pace R, Pluye P, Bartlett G, Macaulay AC, Salsberg J, Jagosh J, et al. Testing the reliability and efficiency of the pilot Mixed Methods Appraisal Tool (MMAT) for systematic mixed studies review. *Int J Nurs Stud*. 2012 Jan;49(1):47–53.

FIGURE 2.

Evidence Gap Map



Evidence presented in the gap map includes studies and evaluations of immunization data use interventions that applied scientific research methods or evaluation design, as well as literature that did not qualify as a study or evaluation but had strong theoretical plausibility of improving data use, as judged by our TOC. We referred to these records as promising strategies, which we define as strategies that have not yet proven successful, but have potential for future success.

Strong, Moderate, and Weak categories apply only to the study quality. Reviewers appraised each study using the Mixed Methods Appraisal Tool (MMAT) checklist, which translates into a percentage score. 'Strong'-quality studies scored 75-100%; 'Moderate'-quality studies scored 50-74%; 'Weak'-quality studies scored 0-49%.

To access the interactive gap map, please visit public.tableau.com/profile/path5412#!/vizhome/IDEAgapmap/FORPUBLICPUBLISH

The color of a circle indicates the strength and directionality of the evidence

- Strong quality evidence
- Moderate quality evidence
- Weak quality evidence
- Promising strategy
- Weak quality counterevidence
- Moderate quality counterevidence
- Strong quality counterevidence

The size of a circle indicates the amount of evidence available

- One piece of evidence reviewed
- Two pieces of evidence reviewed
- Three pieces of evidence reviewed

A blank square on the gap map indicates no evidence from immunization data use interventions was identified

Categories of Data Use Interventions

We grouped the interventions into ten primary intervention categories, as well as multicomponent interventions (see Table 1). Although not all interventions were digital, we aligned most of the intervention categories with the WHO Classification of Digital Health Interventions.⁵

TABLE 1.

Descriptions of immunization data use intervention categories

Intervention Category	Description
Electronic immunization registries (EIR)	Store data on administered vaccine doses in computerized, individual-level databases
Logistics management information systems (LMIS)	Collect data on vaccine inventory and demand to support managing the vaccine supply chain; often computerized
Health management information systems (HMIS)	Store aggregated health data and can facilitate converting data into useful information for decision-making; we focused on computerized HMIS
Decision support systems	Help users interpret data and use data for decision-making; include computerized decision support systems (CDSS) and noncomputerized tools (e.g., monitoring charts, dashboards, and home-based records)
Data quality assessments	Range from interventions that train program managers how to routinely audit data quality to external audits of data quality
Data review meetings	Employ adult-learning techniques (e.g., peer learning and knowledge sharing) to build skills in data analysis
Peer learning networks	Connect health workers so they can share information and discuss data; increasingly accessed through social networking platforms online
Supportive supervision, mentorship, and on-the-job training	Build health workers' skills, foster performance and motivation, and identify and resolve problems
Training	Strengthen the capacity of health workers responsible for managing and using data at all levels of the health system through workshops, classroom-based learning, and hands-on approaches
Multicomponent interventions	Leverage many of the intervention categories but lack a clearly identifiable primary intervention type

⁵ World Health Organization. Classification of Digital Health Interventions v1.0 [Internet]. Geneva, Switzerland: WHO; 2018. Available from: <http://apps.who.int/iris/bitstream/handle/10665/260480/WHO-RHR-18.06-eng.pdf?sequence=1>

Results

We identified data use actions at the community and health facility, district, and national levels and analyzed the effects of interventions on those actions, as well as on intermediate outcomes according to our TOC.



Intermediate Outcomes

Timely, high-quality data are more available. Computerized interventions (EIR, LMIS, and HMIS) improved data quality, especially when combined with other data use activities. While evidence suggested that these systems made data more available, inconsistent use undermined this availability. Tools used to digitize paper immunization records and mHealth solutions applied to LMIS interventions helped increase data availability. Countries that conducted repeat data quality assessments or that held data review meetings as part of broader efforts to develop health information infrastructure saw improved data quality. These efforts were more effective when combined with supportive supervision and other forms of feedback, so that health workers developed the skills to address issues.

Data are analyzed, synthesized, interpreted, and reviewed. Health workers reported increases in their ability to synthesize and interpret routine data as a result of using computerized systems (EIR, LMIS, HMIS, and CDSS), especially at the district and provincial levels. Simple paper-based monitoring charts and dashboards increased tracking of immunization coverage; these tools are most effective when integrated within established data review and decision-making processes (such as monthly review meetings) and when reinforced through supportive supervision and other forms of feedback. Evidence suggests that peer learning networks increase collaborative data review and problem-solving by health workers.



Data Use in Communities and Health Facilities

There was little evidence that health facilities used data from computerized data collection and management systems (EIR, LMIS, and HMIS) to make decisions and take action, especially when implemented as stand-alone interventions with no

support mechanisms. At this level, improving data quality was often emphasized more than improving data use. Challenges such as additional data-entry burdens, poor infrastructure, and workers' lack of motivation contributed to inconsistent use. Digitizing paper immunization records helped improve data quality and relieve the burden of manual data entry. Peer learning networks, training, and decision support interventions (monitoring charts) bolstered facility performance. Data quality assessments prompted health facilities to improve data quality, and such improvements in turn generated more data use in facilities.



Data Use at the District Level

When used consistently, computerized data collection and management systems had more impact on using data to make decisions at the district level than at the facility level, likely as a result of fewer operational challenges. LMIS interventions in particular improved vaccine stock management. Health districts used monitoring charts and dashboards to strengthen facility performance and data quality, but the effect of computerized decision support systems that employed algorithm-based software was uncertain. Data review meetings at the district level increased the use of data to understand and solve issues. Training of district monitoring and evaluation personnel also improved the quality and use of data.



Data Use at the National Level

There was little evidence on how interventions improved data use by national programs. However, anecdotal evidence suggested that a data quality assessment led to the use of data to inform national vaccine strategies and policies. Evidence also suggested that training contributed to more use of data at the national level to strengthen systems and implement policies. National-level participants in peer learning networks reported becoming more data oriented in their work and making decisions based on data. Peer learning networks are likely most effective when they bring together individuals from across departments and levels of the health system and adopt structured approaches for continuous quality improvement.



Impact on Overall Immunization Programs

Few evaluations and studies measured improvements in immunization coverage, equity, and vaccine availability resulting from data use interventions. Among the evaluations and studies that measured overall impact on the immunization program, the results were difficult to attribute to improvements in data use because other interventions were often implemented at the same time.

Improved coverage: Some interventions, such as EIRs, contributed to increased vaccination rates, however it was difficult to assess the EIR's effectiveness in isolation since complementary activities such as text message immunization

reminders may have contributed to the improvements.

Decision support systems (monitoring charts) contributed to improvements in coverage in low-performing regions. Data review meetings and supportive supervision also contributed to increases in coverage.

Improved vaccine availability: Both use of LMIS and participation in peer learning networks improved vaccine stock management, leading to more consistent stock availability.

Improved equity: We found no evaluations that examined whether or how data use interventions led to improvements in immunization equity.

Key Findings

Summarizing across all evidence and promising strategies, and informed by our TOC, we reached the following broad conclusions:

- **(1) Multicomponent interventions were the most prevalent and were often more effective.** Nearly all the interventions we reviewed used more than one strategy. More comprehensive strategies that addressed barriers at various stages of data use were more likely to achieve results.
- **(2) Interventions that took a health systems approach to institutionalizing data use were more likely to succeed and be sustained over the long term.** This occurred by routinely conducting data review meetings, creating national guidelines and protocols on data use, hiring data managers at all levels of the health system, and incorporating training in data use in national curricula.
- **(3) Although we found limited evidence on the effectiveness of health management information systems (HMIS), including electronic immunization registries (EIR), on data use, they remain promising interventions when accompanied by complementary activities.** Transitioning from paper to computerized HMIS across all levels of the health system
- has made higher-quality data more available to decision-makers. Phasing in computerized systems incrementally after establishing reliable infrastructure and human resource capacity improves their likelihood for success.
- **(4) Computerized logistics management information systems (LMIS) have made higher-quality data more available to decision-makers to improve supply chain management, especially at district levels and higher.** Although implementing computerized LMIS as a single intervention improves data quality and use, even greater gains were made when other data use activities complemented the LMIS.
- **(5) There is a dynamic, cyclical relationship between data quality and data use.** Although results of this review confirm that data quality is a necessary precursor to data use, we found limited evidence that single-component interventions increased data quality and improved data use. Conversely, we found stronger evidence that data quality improved as a result of increased use of data. More data use generated demand for higher-quality data, which in turn drove actions to improve data quality; as data quality improved, users were able to better trust the data, thus reinforcing data use.

Discussion

The state of the evidence around what works to improve data use is still nascent. Few data use interventions have been rigorously studied or evaluated. We found more evidence on intermediate outcomes within our TOC, such as improved data quality and availability, but less evidence on what works to support decision-making informed by data, particularly at the facility level. More emphasis on building skills and a culture of data use at the facility level may have a greater effect, but this should be tested in future research.

Many of the HIS interventions pointed to challenges with operational barriers and administrative burdens on health workers. Health workers' concerns about sustainability and data loss also limited their acceptance of these systems. We propose additional research and suggest considering the human transaction costs associated with the intervention, as well as any potential unintended consequences for service delivery.

We recommend that data use interventions be designed to address multiple mechanisms in the TOC. Implementers should define the specific data use actions that the intervention will reinforce. Monitoring and evaluation strategies should measure whether data are being used as defined by the data use actions. To strengthen data use throughout the health system, national guidelines for data collection, analysis, and use should be developed and effective support, tools, and training provided to health workers at the facility and district levels. Especially at the facility level, efforts to improve data quality should be balanced with strategies to improve data use. To reduce administrative burdens, health facilities should be equipped with sufficient human resources, including dedicated staff to perform data-related tasks.

Both monitoring and evaluation of interventions could be strengthened: monitoring primarily through better indicator definitions and evaluation through more appropriate evaluation designs. There is a need to develop better measures for assessing data use in decision-making to better understand the effectiveness of these interventions. Measuring data use is possible but requires a firm understanding of the mechanisms that drive data use behaviors and actions and how the use of

data may change health outcomes. Evaluations should consider the cost-effectiveness of interventions. Supplementing long-term evaluations with iterative approaches to improving effectiveness of interventions will enable problems and their solutions to be identified more quickly.

Strengths of the Review

The strengths of this review were its inclusiveness and methodological flexibility, afforded by the realist review approach, its focus on data use interventions in LMICs, and its emphasis on understanding how the interventions functioned, what made them successful, for whom, and under what conditions. A majority of the evidence we reviewed was from the non-peer-reviewed literature; although of lesser quality, it provided important evidence and learnings that more traditional systematic reviews would overlook.

Limitations of the Review

Several factors limited this review. Our findings relied on what the literature reported, which sometimes did not thoroughly describe the factors that contributed to an intervention's success or failure and may have caused us to miss important contextual considerations. We likely missed some interventions, especially in regions where English is not the dominant language. Our focus on routine immunization data helped contain the scope of the review but risks further isolating immunization programs or missing lessons from surveillance, financial, and human resource data use interventions that were excluded from the review. Although we expanded the review to include literature from other health sectors, these efforts likely failed to capture all the available evidence. Few studies and evaluations analyzed cost-effectiveness, so we were unable to examine the cost-effectiveness of interventions included in this review. Likewise, we did not find any examination of the outcomes of data use interventions over the long term, which makes it challenging to determine how to ensure lasting results.

Conclusion

By synthesizing the evidence and learnings from 69 studies and evaluations and the promising strategies from 34 papers, this review contributes to our understanding of what interventions improve the quality and use of routine immunization data and why. Although presented primarily through the lens of using data to make decisions in immunization programs, our findings are relevant for other health sectors. The evidence on the most effective practices detailed in this review will help program implementers, policymakers, and funders choose approaches with the highest potential for improving vaccine

coverage and equity. We anticipate that these findings will also be of interest to researchers and evaluators to prioritize gaps in the existing knowledge. However, the state of the evidence does not lend itself to recommending which specific interventions or packages of interventions are most effective. Improving immunization data use greatly depends on designing a package of interventions that is theoretically sound and contextually driven, addresses technical and behavioral barriers, and can be sustained outside a project setting.

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IDEA

**IMMUNIZATION DATA:
EVIDENCE FOR ACTION**



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P O A O D I I O

Executive Summary Immunization stress-related response

Reports of clusters of anxiety-related reactions following immunization that had an impact on immunization programmes by drawing negative attention from the media and public was discussed at the Global advisory committee on vaccine safety (GACVS) in December 2015. Following the meeting, GACVS convened an expert working group to explore and understand the etiology of such events and their characteristics, and prepare a guidance document that would help guide public health efforts and programme managers and immunization staff in prevention and management. The expert working group systematically reviewed the available literature along with information gathered from social media, and used the findings to initiate discussion with subject experts.

During the expert working group discussions, it became clear that the term, “immunization anxiety-related reaction” would not cover the entire spectrum of these events and that a broader term was required. After several iterations the term “immunization stress-related responses (ISRR)” was proposed, as it encompasses the broad range of responses that can be experienced in relation to immunization, without implying that they are causally related. The WHO causality assessment process should then be followed to determine the relationship between immunization and the event.

The group prepared a draft guidance document aimed to equip immunization programme managers and health-care providers at local, regional and national levels with the knowledge to manage both individual and clusters of such events. The emphasis was to obtain clarity on the spectrum of anxiety-related manifestations, including their epidemiology and associated risk factors, and to better understand the context of their occurrence. The objective was to produce a document providing a framework and guidance to understand, prevent, diagnose and manage such events; to explain the context of their occurrence; to clarify the reporting mechanisms and the communication approaches when such events occur; and to identify research gaps and strategies to move forward.

GACVS made additional recommendations, in particular that the manual should address not only programme managers but all health care professionals, that use of “responses” rather than “reaction” in the new term would be appropriate, and that postural orthostatic tachycardia syndrome, chronic fatigue syndrome and complex regional pain syndrome are not part of the ISRR spectrum as there is currently insufficient evidence to include them in ISRR.

GACVS agreed that the manual should be prominently featured in the vaccine safety landscape, as prevention, diagnosis and management of ISRR are fundamental to avoid mistrust in immunization programmes. The comprehensive manual will be made available in several languages on the WHO website, and a synopsis will be proposed for publication in an international, peer-reviewed journal to increase awareness among health care professionals of the existence of ISRR, with a link to the full manual. Publication of the ISRR manual will also be accompanied by appropriate training materials. Currently the manual is being reviewed by WHO and awaiting official clearance.

Documents in Yellow Book:

GACVS report December 2018 meeting.

Synopsis of the final ISSR draft manual.

Documents on the SAGE website:

Full final ISSR draft manual.



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Global Advisory Committee on Vaccine Safety, 5–6 December 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 39th meeting in Geneva, Switzerland, on 5–6 December 2018,² when it examined the safety profile of a conjugate typhoid vaccine. It also reviewed 4 generic issues: the status of no-fault vaccine injury compensation programmes (VICPs), immunization stress-related reactions, the development of an updated global vaccine safety strategy and case studies of safety communication in the case of errors in the administration of measles-containing vaccines.

Safety of typhoid conjugate vaccine

GACVS previously reviewed the safety of typhoid vaccines, including the newer generation of typhoid conjugate vaccines (TCVs), in December 2016.³ The Committee noted that its conclusions and recommendations formed part of the evidence reviewed by the Strategic Advisory Group of Experts (SAGE) on immunization for a revised policy and an updated WHO position paper on the use of typhoid vaccines, issued in March 2018.⁴ The new position paper includes the first recommendation for routine use of TCV as a single intramuscular dose for primary vaccination of

Comité consultatif mondial pour la sécurité des vaccins, 5-6 décembre 2018

Le Comité consultatif mondial pour la sécurité des vaccins (GACVS) est un organe consultatif indépendant composé d'experts cliniques et scientifiques qui fournissent à l'OMS des conseils d'une grande rigueur scientifique sur des problèmes de sécurité des vaccins susceptibles d'avoir une portée mondiale.¹ Le GACVS a tenu sa 39^e réunion à Genève (Suisse) les 5 et 6 décembre 2018.² À cette occasion, il a examiné le profil d'innocuité d'un vaccin antityphoïdique conjugué et a abordé 4 questions génériques: la situation des programmes d'indemnisation hors faute en cas de préjudice lié à la vaccination (VICP, de l'anglais «vaccine injury compensation programmes»), les réactions vaccinales liées au stress, la mise à jour de la stratégie mondiale pour la sécurité des vaccins et des études de cas sur la communication en matière de sécurité lors d'erreurs commises avec des vaccins à valence rougeole.

Innocuité du vaccin antityphoïdique conjugué

En décembre 2016, le GACVS avait étudié l'innocuité des vaccins antityphoïdiques, y compris des vaccins antityphoïdiques conjugués (VTC) de nouvelle génération.³ Le Comité a indiqué que les conclusions et recommandations qu'il avait émises ont fait partie des éléments examinés par le Groupe stratégique consultatif d'experts sur la vaccination (SAGE) pour formuler une politique révisée et une note de synthèse OMS actualisée sur l'utilisation des vaccins antityphoïdiques, laquelle a été publiée en mars 2018.⁴ Cette nouvelle note de synthèse contient la première recommandation émise concernant l'utilisation systéma-

¹ See No. 41, 1999, pp. 337–338.

² GACVS invited additional experts to present and discuss evidence on particular topics, who included experts affiliated with: Monash Children's Hospital, Melbourne, Australia; Centre for Disease Control, Beijing, China; Centers for Disease Control and Prevention, Atlanta (GA), USA; Women's and Children's Hospital, Adelaide, Australia; Dalhousie University, Halifax, Canada; University of Siena, Italy; University of Oxford, United Kingdom; Aga Khan University, Karachi, Pakistan.

³ See No. 92, 2017, pp. 17–19.

⁴ See No. 93, 2018, pp. 153–172.

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. Ces experts étaient affiliés entre autres aux organismes suivants: Monash Children's Hospital, Melbourne (Australie); Centre for Disease Control, Beijing (Chine); Centers for Disease Control and Prevention, Atlanta, GA (États-Unis); Women's and Children's Hospital, Adelaide (Australie); Dalhousie University, Halifax (Canada); Université de Sienne (Italie); Université d'Oxford (Royaume-Uni); Aga Khan University, Karachi (Pakistan).

³ Voir N° 92, 2017, pp. 17–19.

⁴ Voir N° 93, 2018, pp. 153–172.

infants and children from 6 months of age and adults ≤45 years of age and in catch-up campaigns in children ≤15 years of age in typhoid-endemic regions. Further, TCV is recommended for the control of typhoid in epidemic settings.

GACVS received newly available data on the Vi-tetanus toxoid conjugate vaccine Typbar-TCV™ (produced by Bharat Biotech International Limited), currently the only licensed TCV available internationally and pre-qualified by WHO. The data comprised preliminary safety data on Typbar-TCV™ from 3 ongoing trials of effectiveness in the field conducted by the Typhoid Vaccine Acceleration Consortium (TyVAC), data from early public sector use of the vaccine in India and Pakistan and data from private sector use in India reported to the manufacturer.

The Committee reviewed the preliminary results of individually randomized control trials by the TyVAC in Malawi and Nepal (with Group A meningococcal vaccine as the control) and a cluster randomized trial in Bangladesh (with Japanese encephalitis SA14-14-2 vaccine as the control). While only blinded data could be presented to GACVS, they represent adverse events data for approximately 24000 children and serious adverse events data for 99000 children aged between 9 months and 15 years in the TCV and control arms in the 3 trials. Solicited local and systemic adverse reactions were reported with a similar frequency in the 2 arms at all trial sites, and most events were of mild or moderate severity. Specifically, fever and pain were reported in 3–8% and 1–7% of vaccinees in each arm, respectively, while other non-specific local and systemic reactions occurred in 0–3% of vaccinees in each arm. The occurrence of serious adverse events was similar in the 2 arms.

Additional data were presented on passive and active surveillance of adverse events in 2 mass immunization campaigns with TCV in 2018: (i) in response to a typhoid outbreak caused by an extensively drug-resistant strain of *Salmonella* Typhi in Hyderabad, Pakistan; and (ii) for introduction of the vaccine into the routine childhood immunization programme in Navi Mumbai, India. Approximately 110 000 doses of TCV were administered in each campaign to children aged 6 months to 10 years in Pakistan and aged 9 months to <15 years in India. Preliminary results from the 2 campaigns showed an adverse event profile similar to those of other routine injectable vaccines, with low rates of mild-to-moderate local and systemic events overall. Fever, pain and swelling at the injection site were the commonest adverse events in both settings. Data from passive surveillance suggested underreporting of adverse events; however, active surveillance was robust, as supported by the use of Brighton Collaboration case definitions. At 5 sentinel hospital sites in Navi Mumbai, 43 cases of thrombocytopenia were observed among vaccine recipients, and 299 cases were observed among unvaccinated children (no statistically significant difference between the 2 groups). The large number of thrombocytopenia cases among unvaccinated children and a final diagnosis of

tique du VTC, sous forme de dose intramusculaire unique, pour la primovaccination des nourrissons et des enfants à partir de l'âge de 6 mois et des adultes de ≤45 ans, ainsi que dans le cadre de campagnes de rattrapage chez les enfants de ≤15 ans, dans les régions d'endémie de la fièvre typhoïde. Le VTC est en outre recommandé pour combattre la fièvre typhoïde dans les situations d'épidémie.

Le GACVS a reçu de nouvelles données sur le vaccin Typbar-TCV™ (vaccin conjugué Vi-anatoxine tétanique fabriqué par Bharat Biotech International Limited), qui est actuellement le seul vaccin VTC homologué disponible à l'échelle internationale et préqualifié par l'OMS. Parmi ces données figuraient des données préliminaires sur l'innocuité du Typbar-TCV™ provenant de 3 essais d'efficacité sur le terrain, encore en cours, mené par le Typhoid Vaccine Acceleration Consortium (TyVAC), ainsi que les premières données issues de l'utilisation du vaccin dans le secteur public en Inde et au Pakistan et les données transmises au fabricant dans le cadre de l'utilisation du vaccin dans le secteur privé en Inde.

Le Comité a pris connaissance des résultats préliminaires des essais contrôlés randomisés menés par le TyVAC au Malawi et au Népal (utilisant le vaccin antiméningococcique du groupe A comme témoin) et d'un essai randomisé par grappes au Bangladesh (utilisant le vaccin SA14-14-2 contre l'encéphalite japonaise comme témoin). Bien que seules des données en aveugle aient pu être présentées au GACVS, ces dernières représentaient des données concernant les manifestations indésirables pour environ 24000 enfants ainsi que les manifestations indésirables graves pour environ 99000 enfants âgés de 9 mois à 15 ans dans les groupes vaccinés par TCV et les contrôles des 3 études. Sur tous les sites, les réactions indésirables locales et systémiques signalées sur demande étaient de fréquence comparable dans les 2 bras d'étude et étaient généralement bénignes ou modérées: l'apparition de fièvre et de douleur a été signalée par 3-8% et 1-7% des personnes vaccinées dans chaque bras, respectivement, et d'autres réactions locales et systémiques non spécifiques sont survenues chez 0-3% des sujets vaccinés dans chaque bras d'étude. La fréquence des manifestations indésirables graves était semblable dans les 2 bras.

Le Comité a pris connaissance de données supplémentaires issues de la surveillance passive et active des manifestations indésirables lors de 2 campagnes de vaccination de masse par le VTC menées en 2018 i) en riposte à une flambée de fièvre typhoïde imputable à une souche de *Salmonella* Typhi ultra-résistante aux médicaments à Hyderabad, au Pakistan et ii) aux fins de l'introduction du vaccin dans le programme de vaccination systématique de l'enfant à Navi Mumbai, en Inde. Environ 110000 doses de VTC ont été administrées à des enfants dans le cadre de chacune de ces campagnes, la tranche d'âge ciblée allant de 6 mois à 10 ans au Pakistan et de 9 mois à <15 ans en Inde. Les résultats préliminaires de ces 2 campagnes indiquaient que le profil des manifestations indésirables était analogue à celui d'autres vaccins injectables du programme de vaccination systématique, avec un taux globalement faible de manifestations locales et systémiques bénignes à modérées. Fièvre, douleur et œdème au point d'injection étaient les manifestations indésirables les plus courantes dans le cadre de ces deux campagnes. Les données de la surveillance passive semblaient indiquer une sous-notification des manifestations indésirables; cependant, la surveillance active était solide, s'appuyant sur les définitions de cas établies par la Brighton Collaboration. Dans 5 hôpitaux sentinelles de Navi Mumbai, 43 cas de thrombopénie ont été observés parmi les sujets vaccinés et 299 cas chez les enfants non vaccinés (pas de différence statistiquement significative entre les

dengue reported in more than half the cases suggested ongoing transmission of dengue viral infection unrelated to the TCV campaign.

Post-licensure safety data for Typbar-TCVTM reported to the manufacturer (with approximately 8 million doses marketed), based on approximately 9000 reports received from paediatricians in the private sector in India and through periodic safety reports, showed an acceptable safety profile (similar to that in public sector use) and did not raise any safety signals.

On the basis of the available data from a variety of settings, GACVS concluded that the safety profile of the Typbar-TCVTM vaccine is reassuring, and no signals of serious adverse events were presented. The Committee also noted the absence of prior theoretical safety concerns for this TCV in the safety profile of its components. Nonetheless, GACVS recommends that countries that introduce TCV into their routine immunization schedule or into campaigns make every effort to ensure robust monitoring of safety (as for any new vaccine) in order to add data on co-administration of TCV with other routine childhood vaccines or in special populations, to detect any signals that require further investigation and to maintain public confidence in the immunization programme.

Further analysis of unblinded safety data from the ongoing TyVAC trials and from the campaigns in Pakistan and India, including the safety profile of TCV in malnourished children, are expected and will be considered by the Committee when they become available. GACVS will also consider future reviews of safety data as warranted, in particular for special populations, including pregnant women. It recommends examination of concomitant administration with other vaccines, such as that against measles, mumps and rubella (MMR), in large-scale campaigns with the currently available TCV and with additional TCVs with different carrier proteins, which are in development.

Vaccine injury compensation programmes

Vaccine injury compensation programmes (VICPs) are no-fault schemes established to compensate individuals who experience a vaccine-related injury due to the inherent risks of vaccination. These programmes do not require injured parties or their legal representatives to prove negligence or fault by the vaccine provider, the health care system or the manufacturer before compensation. They serve to waive the need for accessing compensation through litigation. As of 2010, compensation schemes for vaccine-related injuries had been identified and characterized in only 19 WHO Member States,⁵ none of which were low- or middle-income countries. With improved global capacity for vaccine safety surveillance, including more reporting and investigation of “adverse events following immunization”

2 groupes). Le nombre important de cas de thrombopénie chez les enfants non vaccinés et le fait que la dengue ait été diagnostiquée dans plus de la moitié des cas semblent signaler une transmission en cours de l'infection par le virus de la dengue, sans lien avec la campagne de vaccination par le VTC.

Les données d'innocuité post-homologation du vaccin Typbar-TCVTM communiquées au fabricant (après commercialisation d'environ 8 millions de doses), fondées sur quelque 9000 notifications provenant de pédiatres du secteur privé en Inde et sur des rapports de sécurité périodiques, ont révélé un profil d'innocuité acceptable (semblable à celui observé dans le secteur public) et n'ont mis en évidence aucun signal de sécurité.

Au vu des données disponibles, provenant d'origines multiples, le GACVS a conclu que le profil d'innocuité du vaccin Typbar-TCVTM est rassurant, notant qu'aucun signal de manifestations indésirables graves n'a été constaté. Le Comité a également observé que le profil d'innocuité des composants du VTC ne suscitait pas d'inquiétude théorique a priori quant à la sécurité du vaccin. Toutefois, le GACVS recommande aux pays souhaitant introduire le VTC dans leur calendrier de vaccination systématique ou dans des campagnes vaccinales de déployer tous les efforts nécessaires pour garantir une surveillance rigoureuse de l'innocuité (comme pour tout nouveau vaccin) afin de recueillir des données supplémentaires sur la coadministration du VTC avec d'autres vaccins du programme de vaccination systématique de l'enfant ou sur son utilisation dans des populations particulières, d'identifier tout signal exigeant une enquête complémentaire et de préserver la confiance du public à l'égard du programme de vaccination.

Lorsque les données d'innocuité sans insu des essais du TyVAC et des campagnes menées au Pakistan et en Inde deviendront disponibles, notamment celles portant sur le profil d'innocuité du VTC chez les enfants malnutris, elles feront l'objet d'une analyse plus approfondie et seront examinées par le Comité. À l'avenir, le GACVS envisagera également d'examiner d'autres données d'innocuité selon les besoins, en particulier pour certaines populations spécifiques, dont les femmes enceintes. Le Comité recommande que la coadministration avec d'autres vaccins, comme le vaccin antirougeoleux-antiourlien-antirubéoleux (ROR), soit étudiée dans le cadre de campagnes à grande échelle, tant pour le vaccin VTC actuellement disponible que pour d'autres VTC en cours de développement qui utilisent des protéines porteuses différentes.

Programmes d'indemnisation en cas de préjudice lié à la vaccination

Les programmes d'indemnisation en cas de préjudice lié à la vaccination (VICP) sont des régimes hors faute établis pour indemniser les personnes qui ont subi des préjudices liés à l'administration d'un vaccin du fait des risques inhérents à la vaccination. Les parties lésées ou leurs représentants légaux ne sont pas tenus de fournir la preuve qu'une négligence ou une faute a été commise par le prestataire, le système de santé ou le fabricant pour être indemnisés. Ces programmes visent à permettre un accès à l'indemnisation sans qu'il soit nécessaire de recourir à une procédure judiciaire. En 2010, des programmes d'indemnisation en cas de préjudice lié à la vaccination avaient été identifiés et caractérisés dans seulement 19 États Membres de l'OMS,⁵ dont aucun n'était un pays à revenu faible ou intermédiaire. Grâce au renforcement des capacités mondiales de surveillance de la sécurité vaccinale,

⁵ Looker C, Kelly H. No-fault compensation following adverse events attributed to vaccination: a review of international programmes. Bull World Health Organ 2011;89:371–378.

⁵ Looker C, Kelly H. No-fault compensation following adverse events attributed to vaccination: a review of international programmes. Bull World Health Organ 2011;89:371–378.

(AEFI) in low- and middle-income countries, WHO Member States are identifying and documenting reactions, with scientific evidence of causal associations with vaccination. This has led to increased interest and discussion of the need for national no-fault compensation policies for vaccine injuries.

GACVS was presented with the results of a global survey of the status of no-fault VICPs in WHO Member States, the main objective of which was to update the inventory of such programmes, evaluate current practices and update the characteristics of programmes. Further details of VICPs in China and USA were also presented and discussed. The survey identified 25 jurisdictions with no-fault VICPs, including 2 low- and lower-middle-income countries, although most countries with these programmes are categorized as high-income countries, mainly in the European Region, with 5 in the Western Pacific Region and 2 each in North America and the South East Asia Region. There is currently no such programme in Latin America or in the African or Eastern Mediterranean regions of WHO.

The no-fault VICPs in most jurisdictions are implemented and funded at central or federal government level. The eligibility criteria for vaccine injury compensation varied considerably among the schemes evaluated. Most programmes cover injuries arising from vaccines that are registered in the country and are recommended by the authorities for routine use in children, pregnant women and adults (e.g. influenza vaccines) and for special indications. In most programmes, a claim process is initiated once injured parties or their legal representatives file for compensation with a special administrative body. All the no-fault VICPs reviewed require proof of a causal association between vaccination and injury. Once a final decision has been reached, claimants are compensated with a lump sum of money; monetary compensation calculated from medical care costs and expenses, loss of earnings or earning capacity; and/or non-monetary compensation calculated on the basis of pain and suffering, emotional distress, permanent impairment or loss of function. In most jurisdictions, claimants have the right to seek damages either through civil litigation or from a compensation scheme but not both.

GACVS acknowledged that, as countries continue to extend the use of vaccines and strengthen their safety surveillance and investigative capacity, occasional severe vaccine-associated reactions will continue to be identified. No-fault VICPs are considered a measure to maintain confidence in immunization programmes, as they increase the adequacy and fairness of compensation by providing clear criteria and processes to access compensation for vaccine injuries. GACVS encourages and will support WHO in developing guiding principles for countries ready to develop VICPs.

et notamment l'amélioration de la notification et de l'investigation des «manifestations postvaccinales indésirables» (MAPI) dans les pays à revenu faible ou intermédiaire, les États Membres de l'OMS s'emploient désormais à identifier et à documenter les réactions, en recueillant les données scientifiques susceptibles de démontrer un lien de causalité avec la vaccination. De ce fait, une attention accrue a été portée à la nécessité d'instituer des politiques nationales d'indemnisation hors faute en cas de préjudice lié aux vaccins.

Le GAVCS a pris connaissance des résultats d'une enquête mondiale sur les programmes VICP hors faute existants dans les États Membres de l'OMS, dont l'objectif principal était de dresser un inventaire actualisé de ces programmes, d'en décrire les caractéristiques et d'évaluer les pratiques actuelles. Des détails supplémentaires sur les programmes VICP de la Chine et des États-Unis ont également été présentés et examinés. L'enquête a identifié 25 territoires dotés de programmes VICP hors faute; 2 d'entre eux étaient des pays à revenu faible ou à revenu intermédiaire de la tranche inférieure, mais la majorité étaient des pays à revenu élevé, appartenant principalement à la Région européenne, avec 5 pays dans la Région du Pacifique occidental, 2 en Amérique du Nord et 2 dans la Région de l'Asie du Sud-Est. Il n'existe actuellement pas de programme de ce type en Amérique latine, ni dans les Régions OMS de l'Afrique et de la Méditerranée orientale.

Dans la plupart des territoires concernés, les programmes VICP hors faute sont mis en œuvre et financés par le gouvernement central ou fédéral. Les critères à remplir pour bénéficier d'une indemnisation en cas de préjudice lié à la vaccination variaient considérablement entre les différents programmes évalués. La plupart d'entre eux couvraient les préjudices résultant de l'administration de vaccins homologués dans le pays et recommandés par les autorités aux fins de la vaccination systématique des enfants, des femmes enceintes et des adultes (par exemple, vaccins antigrippaux) ou pour des indications particulières. Dans la majorité des programmes, une procédure de réclamation est lancée lorsque les parties lésées ou leurs représentants légaux déposent une demande d'indemnisation auprès d'un organe administratif spécial. Tous les programmes VICS hors faute étudiés exigeaient une preuve du lien de causalité entre la vaccination et le préjudice subi. Une fois qu'une décision finale est prise, les demandeurs sont indemnisés par le versement d'un montant forfaitaire, par une compensation financière calculée sur la base des coûts et dépenses de santé et de la perte de revenus ou de la capacité de gain, et/ou par une compensation non financière calculée sur la base de la douleur subie, de la souffrance, de la détresse émotionnelle et de la perte ou de l'altération permanente des capacités fonctionnelles. Dans la plupart des territoires, les demandeurs ont le droit de réclamer des dommages par le biais d'une procédure civile ou du programme d'indemnisation, mais pas des deux.

Le GACVS a reconnu qu'à mesure que les pays continuent d'étendre la vaccination et de renforcer leurs capacités d'enquête et de surveillance de l'innocuité, des réactions graves liées aux vaccins seront occasionnellement identifiées. Les programmes VICP hors faute sont un moyen de préserver la confiance à l'égard des programmes de vaccination, car ils permettent une indemnisation plus juste et plus appropriée en définissant des critères clairs et en offrant une procédure d'accès à l'indemnisation en cas de préjudice. Le GACVS encourage l'OMS à établir des principes directeurs à l'intention des pays qui sont prêts à instituer des programmes VICP et s'engage à soutenir l'OMS dans cette démarche.

Immunization stress-related responses

In December 2015, GACVS received reports from mainstream and social media in several countries in which clusters of anxiety-related reactions after immunization had adversely affected immunization programmes.⁶ Subsequently, GACVS commissioned a group of experts to explore and determine the etiology and characteristics of those events and to prepare a guidance document to help guide public health programmes to prevent, recognize and manage them.

During the meeting in December 2017, the expert group presented the findings of a systematic review of the literature and social media and the outcome of discussions with subject experts.⁷ GACVS reviewed a draft manual to support programme managers in preventing, identifying and responding to stress-related events associated with immunization. It had become clear that the term, “immunization anxiety-related reaction” would not cover the entire spectrum of these events and that a broader term was required; initially “immunization-triggered stress response” was proposed, as it would incorporate all the stress-related symptoms and signs that manifest just before, during and after immunization.

GACVS recommended that the draft manual be circulated for review to relevant stakeholders, which was conducted in several rounds during 2018. Feedback was incorporated into a revised manual, which was presented to GACVS for discussion. A new term was proposed, as it was considered that “immunization -triggered stress response” would strongly assign causality to the immunization, whereas such responses are not specific to immunization. The term “immunization stress-related responses (ISRR)” was considered more appropriate, as it encompasses the broad range of responses that can be experienced in relation to immunization, without implying that they are causally related. The WHO causality assessment process should then be followed to determine the relation between immunization and the event.⁸ GACVS made additional recommendations, in particular that the manual should address not only programme managers but all health care professionals, that use of “responses” rather than “reaction” in the new term would be appropriate, and that postural orthostatic tachycardia syndrome, chronic fatigue syndrome and complex regional pain syndrome are not part of the ISRR spectrum. As the relation of these entities with some vaccine products has been discussed recently, GACVS concluded that the fact that there is currently insufficient evidence to include them in ISRR should be explicitly stated.

GACVS agreed that the manual should be prominently featured in the vaccine safety landscape, as prevention, diagnosis and management of ISRR are fundamental to

Réponses liées au stress dans le cadre de la vaccination

En décembre 2015, des informations provenant de médias traditionnels et de médias sociaux de plusieurs pays ont été communiquées au GACVS, faisant état de grappes de réactions anxieuses postvaccinales qui avaient eu une incidence négative sur les programmes de vaccination.⁶ Le GACVS avait alors demandé à un groupe d'experts d'étudier ces manifestations, d'en déterminer l'étiologie et les caractéristiques et de préparer un document d'orientation destiné à guider les programmes de santé publique pour les aider à prévenir, reconnaître et prendre en charge ces réactions.

Lors de la réunion de décembre 2017, ce groupe d'experts a présenté les résultats d'une revue systématique de la littérature et des médias sociaux, ainsi que les conclusions de discussions menées avec des spécialistes du domaine.⁷ Le GACVS a examiné un projet de manuel visant à soutenir les administrateurs des programmes dans leurs efforts de prévention et d'identification des manifestations de stress associées à la vaccination et dans la mise en œuvre d'interventions adaptées. Il est apparu clairement que le terme de «réaction vaccinale liée à l'anxiété» ne couvrirait pas tout l'éventail des manifestations concernées et qu'un terme de portée plus large devait être adopté. Dans un premier temps, il a été proposé d'utiliser «réponse de stress déclenchée par la vaccination», une expression qui avait l'avantage d'inclure tous les symptômes liés au stress qui se manifestent juste avant, pendant et après la vaccination.

Le GACVS a recommandé que le projet de manuel soit distribué aux parties prenantes concernées aux fins d'examen, ce qui a été accompli en plusieurs cycles pendant l'année 2018. Les commentaires reçus ont été incorporés à la version révisée du manuel, qui a été présentée au GACVS pour discussion. Une nouvelle expression a été proposée car il était estimé que l'expression «réponse de stress déclenchée par la vaccination» impliquait un fort lien de causalité avec la vaccination, alors que ce type de réaction n'est pas spécifique à la vaccination. L'expression «réponses liées au stress dans le cadre de la vaccination» (ISRR, de l'anglais «immunization stress-related responses») a été jugée plus appropriée car elle englobe le large éventail de réactions pouvant se manifester en lien avec la vaccination, sans supposer de relation de causalité. Le processus OMS d'évaluation du lien de causalité doit alors être employé pour déterminer la nature de la relation entre la vaccination et la manifestation observée.⁸ Le GACVS a émis d'autres recommandations, stipulant en particulier que le manuel ne devrait pas s'adresser uniquement aux administrateurs des programmes, mais à tous les professionnels de santé, qu'il était acceptable d'employer le terme de «réponse» plutôt que «réaction» dans la nouvelle expression, et que le syndrome de tachycardie orthostatique posturale, le syndrome de fatigue chronique et le syndrome douloureux régional complexe ne devaient pas être inclus dans le spectre des ISRR. Au vu des récentes discussions portant sur le lien éventuel entre ces syndromes et certains produits vaccinaux, le GACVS a conclu à la nécessité d'énoncer explicitement que les données actuellement disponibles sont insuffisantes pour les inclure parmi les ISRR.

Le GACVS a convenu qu'une place de premier plan devrait être accordée à ce manuel dans le domaine de la sécurité vaccinale car la prévention, le diagnostic et la prise en charge des ISRR

⁶ See No. 91, 2016, pp. 21–23.

⁷ See No. 93, 2018, pp. 27–28.

⁸ Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification. Second edition. Geneva: World Health Organization; 2018. (<https://apps.who.int/iris/bitstream/handle/10665/259959/9789241513654-eng.pdf>, accessed December 2018).

⁶ Voir N° 91, 2016, pp. 21-23.

⁷ Voir N° 93, 2018, pp. 27-28.

⁸ Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification. Second edition. Genève, Organisation mondiale de la Santé, 2018. (<https://apps.who.int/iris/bitstream/handle/10665/259959/9789241513654-eng.pdf>, consulté en décembre 2018).

avoid mistrust in immunization programmes. Communication strategies were also discussed. The comprehensive manual will be made available in several languages on the WHO website, and a synopsis will be proposed for publication in an international, peer-reviewed journal to increase awareness among health care professionals of the existence of ISRR, with a link to the full manual. Publication of the ISRR manual will also be accompanied by appropriate training materials.

Vaccine safety strategy post-2020

GACVS held a session to review the findings of the 7th meeting on the Global Vaccine Safety Initiative (GVSI) and to propose a process for preparing a second version of the Global Vaccine Safety Blueprint, aligned with WHO's post-2020 immunization strategy. The GVSI was prepared by a collaborative group of partners from national programme and regulatory agency staff, technical agencies, donors and industry as a mechanism for implementation of the blueprint.⁹ Since its launch in 2012, the GVSI has held 7 meetings in all 6 WHO regions. The network has contributed new resources for vaccine pharmacovigilance, including tools, methods, training packages, standard reporting forms and tools and e-learning packages. A network of websites has been developed (Vaccine Safety Net), the content of which has been verified for reliability and presentation.¹⁰ A first indicator of vaccine safety surveillance has been developed (AEFI reporting ratio of 10 cases per 100 000 surviving infants per year).¹¹ Steady improvement in meeting this goal has been observed since the launch of the GVSI. It was recognized that the roles of GACVS, which is involved in risk assessment, and GVSI, which is a capacity-building forum, are complementary and their interaction could be increased. Vaccine safety systems have improved greatly worldwide but still require dedicated resources and better reporting, data management, signal identification and investigation. In addition, closer collaboration is needed between immunization programmes and regulatory systems.

Progress in the Global Vaccine Safety Observatory was also reviewed. The role of the Observatory is to enhance surveillance capacity by improving access to indicators of national and regional systems through WHO partners. It is a clearing-house for vaccine safety data relevant to GVSI members. Specifically, it presents WHO-held data, allowing tracking and comparison of indicators over time and aggregation of region-sensitive data; notifies alerts of recalls or safety signals from national regulatory authorities; provides global mapping of reported vaccine safety events; and includes links to relevant "lessons and stories", expert sources and relevant data sources.

sont d'une importance vitale pour éviter la méfiance envers les programmes de vaccination. Les stratégies de communication ont également fait l'objet de discussions. Le manuel complet sera publié dans plusieurs langues sur le site Web de l'OMS et un résumé sera proposé pour publication dans une revue internationale à comité de lecture afin de sensibiliser les professionnels de santé à l'existence des ISRR, avec un lien vers le manuel complet. Des supports de formation appropriés seront également publiés en complément du manuel sur les ISRR.

Stratégie pour la sécurité des vaccins après 2020

Le GACVS a tenu une session visant à examiner les conclusions de la 7^e réunion sur l'Initiative mondiale pour la sécurité des vaccins (GVSI) et à proposer un processus de préparation d'une deuxième version du Projet mondial pour la sécurité des vaccins (GVSB), alignée sur la stratégie vaccinale de l'OMS pour l'après-2020. L'initiative GVSI a été élaborée par un groupe de collaboration réunissant divers partenaires – personnel des programmes nationaux et des instances nationales de réglementation, organismes techniques, bailleurs de fonds et représentants de l'industrie – afin de servir de mécanisme de mise en œuvre du GVSB.⁹ Depuis son lancement en 2012, 7 réunions de la GVSI se sont tenues dans les 6 Régions de l'OMS. Ce réseau a contribué de nouvelles ressources aux fins de la pharmacovigilance des vaccins, notamment des outils, des méthodes, des modules de formation, des formulaires et outils standard de notification et des programmes d'apprentissage en ligne. Un réseau de sites Web a été établi (Réseau pour la sécurité des vaccins) et le contenu de ces sites a été vérifié pour en contrôler la fiabilité et la présentation.¹⁰ Un premier indicateur de surveillance de la sécurité des vaccins a été élaboré (taux de notification des MAPI de 10 cas pour 100 000 nourrissons survivants par an).¹¹ Depuis le lancement de la GVSI, des progrès constants ont été accomplis dans la réalisation de cet objectif. Il a été noté que le GACVS, en tant qu'entité contribuant à l'évaluation des risques, et la GVSI, en tant que forum de renforcement des capacités, jouent des rôles complémentaires et qu'il serait opportun d'intensifier leurs échanges. Les systèmes de sécurité vaccinale se sont considérablement améliorés à l'échelle mondiale, mais il reste nécessaire de leur consacrer des ressources spéciales et d'améliorer la notification, la gestion des données, l'identification des signaux et l'investigation. En outre, une collaboration plus étroite est nécessaire entre les programmes de vaccination et les systèmes de réglementation.

Les progrès de l'Observatoire mondial de la sécurité des vaccins ont également été examinés. L'Observatoire a pour mission de renforcer les capacités de surveillance en améliorant l'accès aux indicateurs des systèmes nationaux et régionaux par l'entremise des partenaires de l'OMS. Il s'agit d'une centrale d'information regroupant des données de sécurité vaccinale pertinentes pour les membres de la GVSI. Il fournit en particulier des données détenues par l'OMS, permettant le suivi et la comparaison des indicateurs au cours du temps, ainsi que l'agrégation de données spécifiques selon la région; il diffuse des alertes en cas de rappels de produits ou de signaux de sécurité émis par les autorités nationales de réglementation; il présente une cartographie mondiale des événements signalés en matière de sécurité vaccinale; et il contient des liens pertinents pour accéder à des «expériences et enseignements», à des ressources expertes et à des sources de données.

⁹ Global vaccine safety blueprint (WHO/IVB/12.07). Geneva: World Health Organization; 2012 (https://apps.who.int/iris/bitstream/handle/10665/70919/WHO_IVB_12.07_eng.pdf, accessed December 2018).

¹⁰ Vaccine Safety Net: www.vaccinesafetynet.org/

¹¹ Lei et al. Use of a new global indicator for vaccine safety surveillance and trends in adverse events following immunization reporting 2000–2015. *Vaccine*. 2018;36:1577–1582.

⁹ Global vaccine safety blueprint (WHO/IVB/12.07). Genève, Organisation mondiale de la Santé, 2012 (https://apps.who.int/iris/bitstream/handle/10665/70919/WHO_IVB_12.07_eng.pdf, consulté en décembre 2018).

¹⁰ Vaccine Safety Net: www.vaccinesafetynet.org/

¹¹ Lei et al. Use of a new global indicator for vaccine safety surveillance and trends in adverse events following immunization reporting 2000–2015. *Vaccine*. 2018;36:1577–1582.

During the session, the SAGE Chair presented plans for the post-2020 WHO immunization strategy. It was noted that vaccine safety is part of such planning. The discussion moved toward preparation of the next Global vaccine safety blueprint during 2019. The previous GVSI meeting recommended greater attention to several areas: communication about increased rates of reported AEFI, identification of actual serious vaccine reactions, strategies to respond to and maintain public confidence and no-fault VICPs. In addition, enabling actions, such as dissemination of AEFI surveillance methods, vaccine safety training to local level, regional advisory mechanisms for vaccine safety and novel reporting tools would be valuable.

The WHO Secretariat presented a proposed programme of work for the blueprint during 2019, to be conducted in alignment with the Global Vaccine Action Plan. A landscape analysis was conducted in preparation for the first blueprint, and it was proposed to start by updating that analysis. GACVS discussed some of the proposed programme of work and made many suggestions. For instance, in addition to the goals of the original blueprint, which included minimum capacity for vaccine safety in all low- and middle-income countries and expanded capacity in some middle-income countries, the next safety strategy should apply to all countries. Timelines should be proposed to meet the main strategic goals. Additional indicators and sub-indicators of progress in establishing effective vaccine pharmacovigilance systems should be considered for development and integration into the plan. The partnerships of the GVSI and the Observatory might benefit from expansion to include groups such as the National Immunization Technical Advisory Group network, SAGE and others. Communication case studies could be useful to guide ways to address true safety issues. Communication in general is vitally important, and GACVS has a significant role to play in composing scientific messages for use by risk communicators. Guidance on injury compensation would be useful. Approaches to ensure appropriate safety reporting should be determined and emphasized, and national authorities should commit themselves to establish vaccine safety monitoring as part of the quality assurance of immunization programmes to ensure appropriate reporting. The next Global vaccine safety blueprint should also include preparedness for crisis communication about vaccine safety. The Vaccine Safety Network should be acknowledged as the living network that it has become and would benefit from continued review of clear priorities.

Report of the sub-committee on vaccine safety communication

Vaccine safety issues can lead to crises, erosion of public trust and even collapse of immunization programmes if communication is not properly handled. Safety concerns may have widespread consequences, even outside the country in which they occur. Preparedness and proactive rather than reactive communication are essential for maintaining confidence in vaccines.

Au cours de cette session, le Président du SAGE a présenté les plans relatifs à la stratégie OMS de vaccination pour l'après-2020. Il a été observé que la sécurité des vaccins faisait partie intégrante de ces plans. Les discussions ont ensuite porté sur la préparation du prochain GVSB au cours de l'année 2019. Les participants à la dernière réunion de la GVSI avaient recommandé qu'une plus grande attention soit dévolue à certaines questions, notamment la communication sur l'augmentation des taux de MAPI signalées, l'identification des réactions vaccinales graves effectives, les stratégies à adopter pour préserver la confiance du public et répondre aux situations de méfiance, et les programmes VICP hors faute. D'autres mesures favorables, comme la diffusion des méthodes de surveillance des MAPI, la formation locale à la sécurité vaccinale, la mise en place de mécanismes consultatifs régionaux en matière de sécurité vaccinale et l'adoption de nouveaux outils de notification, seraient également d'un apport précieux.

Le Secrétariat de l'OMS a présenté une proposition de programme de travail pour l'élaboration du GVSB en 2019, en harmonie avec le Plan d'action mondial pour les vaccins. Il a été proposé de commencer par une mise à jour de l'analyse générale de la situation qui avait été effectuée lors de la préparation du premier GVSB. Le GACVS a étudié certaines parties du programme de travail proposé et a émis de nombreuses suggestions. Par exemple, outre les objectifs du premier GVSB, qui comprenaient des capacités minimales en matière de sécurité vaccinale dans tous les pays à revenu faible ou intermédiaire et des capacités renforcées dans certains pays à revenu intermédiaire, il faudrait que la prochaine stratégie de sécurité soit applicable à tous les pays. Des calendriers devraient être proposés pour la réalisation des principaux objectifs stratégiques. Il conviendrait en outre de définir des indicateurs et des sous-indicateurs supplémentaires pour mesurer les progrès accomplis dans l'établissement de systèmes efficaces de pharmacovigilance des vaccins et de les intégrer au plan. Il pourrait être avantageux d'élargir les partenariats de la GVSI et de l'Observatoire pour inclure des groupes tels que le réseau de groupes consultatifs techniques nationaux sur la vaccination, le SAGE et d'autres. Des études de cas sur la communication pourraient être utiles pour mieux comprendre comment aborder les problèmes réels de sécurité. De manière générale, la communication revêt une importance cruciale et le GACVS a un rôle important à jouer dans la mesure où il contribue à formuler des messages scientifiques pouvant être utilisés par les responsables de la communication sur les risques. Il serait utile d'élaborer des orientations concernant l'indemnisation en cas de préjudice. Il convient par ailleurs d'identifier et de promouvoir des approches susceptibles de garantir une notification appropriée concernant la sécurité des vaccins et les autorités nationales devraient s'engager à mettre en œuvre une surveillance de la sécurité vaccinale dans le cadre des activités d'assurance de la qualité des programmes de vaccination pour veiller à une notification adéquate. Le prochain GVSB sur la sécurité des vaccins devrait également aborder la préparation aux communications de crise sur la sécurité vaccinale. Le rôle du Réseau pour la sécurité des vaccins, devenu un véritable réseau vivant, devrait être reconnu et ses priorités devraient être régulièrement examinées et clairement définies.

Rapport du sous-comité chargé de la communication en matière de sécurité vaccinale

Les problèmes de sécurité vaccinale peuvent entraîner des situations de crise, une érosion de la confiance du public et même l'effondrement des programmes de vaccination si la communication n'est pas convenablement assurée. Les inquiétudes liées à la sécurité peuvent avoir des conséquences majeures, même en dehors de leur pays d'origine. Pour préserver la confiance à l'égard des vaccins, il est essentiel de se préparer et de favoriser une communication proactive, plutôt que réactive.

A GACVS subgroup on vaccine safety communication continuously reviews and provides advice on strategies for vaccine safety communication. It was asked to prepare a series of case studies of vaccine safety communication,¹² to contribute to a common framework for vaccine safety crisis communication and capacity-building in Member States. During the meeting, the Committee examined communication about immunization errors involving measles-containing vaccines. Such errors have been reported occasionally in the medical literature. For example, at least 15 children died after being vaccinated against measles during a catch-up campaign, all of whom were aged 6–18 months. A published report indicated that the vaccine had been accidentally diluted with atracurium, a muscle relaxant used in anaesthesia, with packaging similar to that of the vaccine diluent.¹³ Contamination of multi-doses vaccine vials of measles-containing vaccine is known to have occurred in India in the 1990s.¹⁴ As such events require programme adjustment and frequently disciplinary action, communication channels become blurred and could lead to the mistaken conclusion that the vaccine itself was responsible.

GACVS reviewed case histories from global vaccine safety websites. It also discussed 2 recent events in which children died because of programme errors during immunization with measles-containing vaccines, in routine immunization and during a mass immunization campaign. In the first instance, 2 infants aged 1 year died within minutes of receiving routine MMR during a routine immunization session. In the other instance, at least 15 deaths resulted from contaminated vaccine during a mass immunization campaign in a medically underserved population. As these events reflect real challenges to immunization programmes, the committee discussed the need for (i) a concerted focus on training, supervision and support of national authorities and partners during planning of mass immunization campaigns; (ii) acknowledgement of programme errors and prompt proposal of corrective measures; (iii) preparedness for crisis management; and (iv) high-quality communication about the safety of immunization, both routine and during mass campaigns.

Vaccine safety issues have multiple dimensions. The GACVS case studies should reveal those aspects, including errors that reflect systemic issues. The Committee unanimously acknowledged that vaccine safety communication should address a broad range of scenarios. Further case studies will address both common and unique problems related to vaccine safety and will be used to prepare guidance for various scenarios, in collaboration with communication experts. ■

Le sous-groupe du GACVS chargé de la communication sur la sécurité vaccinale examine en continu les stratégies de communication mises en œuvre dans le domaine de la sécurité vaccinale et émet des conseils en la matière. Il lui a été demandé de préparer une série d'études de cas concernant la communication sur la sécurité vaccinale,¹² qui contribueront à un cadre commun de communication de crise sur la sécurité vaccinale et de renforcement des capacités dans les États Membres. Lors de la réunion, le Comité a examiné les communications relatives à des erreurs de vaccination par le vaccin à valence rougeole. De telles erreurs ont occasionnellement été signalées dans la littérature médicale. Par exemple, au moins 15 enfants, tous âgés de 6 à 18 mois, sont décédés après avoir été vaccinés contre la rougeole lors d'une campagne de rattrapage. Selon un rapport publié, le vaccin avait été dilué par inadvertance avec de l'atracurium, un relaxant musculaire employé en anesthésie, dont l'emballage était semblable à celui du diluant indiqué pour le vaccin.¹³ On sait que dans les années 1990, des flacons multidoses de vaccin à valence rougeole ont été contaminés en Inde.¹⁴ Étant donné que de tels incidents exigent un ajustement des programmes de vaccination et souvent des mesures disciplinaires, il peut y avoir un flou dans les canaux de communication, risquant de conduire à la conclusion erronée que le vaccin lui-même est responsable de l'incident.

Le GACVS a examiné des dossiers issus de sites Web mondiaux sur la sécurité des vaccins. Il a également étudié 2 incidents récents dans lesquels des enfants sont décédés en raison d'erreurs programmatiques commises lors de l'administration du vaccin à valence rougeole, dans le cadre de la vaccination systématique ainsi que pendant une campagne de vaccination de masse. Dans le premier cas, 2 nourrissons âgés de 1 an sont décédés dans les minutes qui ont suivi l'administration du ROR lors d'une visite de vaccination systématique. Dans le second cas, au moins 15 décès sont survenus par suite de l'administration d'un vaccin contaminé dans le cadre d'une campagne de vaccination de masse au sein d'une population mal desservie par les services médicaux. Ces incidents sont le reflet de réelles difficultés des programmes de vaccination et le Comité a donc fait état de la nécessité de: i) mener une action concertée pour mettre l'accent sur la formation, la supervision et le soutien aux autorités nationales et aux partenaires lors de la planification des campagnes de vaccination de masse; ii) reconnaître les erreurs programmatiques et proposer rapidement des mesures correctives; iii) mener des activités de préparation à la gestion des crises; et iv) assurer une communication de qualité concernant la sécurité de la vaccination, tant dans le cadre de la vaccination systématique que pendant les campagnes de masse.

Les problèmes de sécurité des vaccins revêtent plusieurs dimensions. Les études de cas du GACVS devraient mettre en lumière ces différents aspects, y compris les erreurs qui sont révélatrices de problèmes systémiques. Le Comité a unanimement reconnu que la communication sur la sécurité vaccinale se doit d'aborder un large éventail de scénarios. D'autres études de cas traiteront à la fois de problèmes communs et de problèmes uniques liés à la sécurité des vaccins et seront utilisées pour élaborer des orientations applicables à divers scénarios, en collaboration avec des experts en communication. ■

¹² See No. 93, 2018, p. 395.

¹³ Cousins S. Contaminated vaccine deaths a serious setback for Syria. *Lancet*. 2014;384:1172.

¹⁴ Sood DK et al. Adverse reactions after measles vaccination in India. *Natl Med J India*. 1995;8(5):208–10.

¹² Voir N° 93, 2018, p. 395.

¹³ Cousins S. Contaminated vaccine deaths a serious setback for Syria. *Lancet*. 2014;384:1172.

¹⁴ Sood DK et al. Adverse reactions after measles vaccination in India. *Natl Med J India*. 1995;8(5):208–10.

Immunization stress-related response (ISRR) - A synopsis

A quick reference to the ISRR manual for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization

Immunization stress-related response

The response to a stress encompasses a range of manifestations (symptoms and signs) that may include an acute stress response which includes a vasovagal reaction (fainting), hyperventilation or a dissociative neurological symptom reaction which includes non-epileptic seizures (formerly known as a conversion reaction).

“Immunization stress-related response” (ISRR) is a response to the stress some individuals may feel about getting an injection, and encompasses the spectrum of manifestations mentioned previously. Formerly, this spectrum was described as “an AEFI arising from anxiety about the immunization”. ISRR was necessitated since the term “anxiety” does not adequately capture all the elements of how these AEFI may present. In contrast to other AEFI, the symptoms of an ISRR may also occur immediately *prior* to immunization. In addition, an ISRR may only affect an individual or groups of individuals resulting in a cluster which is often referred to as mass psychogenic illness.

The biopsychosocial model of ISRR

A stress response is complex. It involves a combination of physiological (biological) factors occurring within individuals interacting within their own psychological strengths, vulnerabilities and knowledge/preparedness and within a particular social context.

For example, certain biological factors may facilitate a vasovagal reaction following immunization. These include age (adolescence is risk period), gender (females are more predisposed), weight (lower body mass index increases risk), etc. Psychological factors include an individual’s temperament (personality), ability to understand and reason, preparedness for the immunization event, and underlying anxiety which is influenced by previous experience. These all may affect the perception of pain symptoms following the injection of a vaccine.

Social factors around the immunization injection such as community trust in healthcare, community perceptions, norms, and values around immunization, community and family support for immunization and false or misleading news reports (TV, print, radio, online) are also important. Social media messages around immunization have an impact on the behavior of healthcare workers, family or friends and others such as peers being vaccinated (such as may occur in mass or school campaigns). Thus, stress responses can occur with stressors other than the actual immunization.

Manifestation of ISRR

Most symptoms and signs of an ISRR are transient and resolve spontaneously manifesting just before, during, or immediately after immunization. It is important to remember that an initial acute stress response (which is consistent with fight or flight response) may be followed by an over compensatory parasympathetic reaction in which heart rate and blood pressure fall precipitously. Thus, an acute stress response in some individuals may lead to physiological overcompensation and a vasovagal reaction.

An acute stress response may range from mild feelings of worry and "butterflies" in the stomach to those of sympathetic nervous system stimulation – increased heart rate, palpitations and difficulty breathing.

Vasovagal reactions (known as fainting in lay-terms) manifest with symptoms from mild dizziness to a brief loss of consciousness (syncope) because of insufficient blood flow to the brain resulting from low blood pressure due to a decreased heart rate, vasodilatation of blood vessels or both. It can be

associated with prodromal symptoms such as nausea, sweating or pallor. Rarely it can be associated with a syncopal seizure and/or can result in injuries from falling.

Hyperventilation syndrome (rapid and fast breathing) may be part of an acute stress response and include features of a dissociative neurological symptom reaction. The presenting features are dyspnoea (shortness of breath), chest pain, paraesthesia (tingling sensation) in fingers, light-headedness, dizziness, and headache. In some individuals this may be a recurrent symptom and is not necessarily associated with recent provocative stress. Syncope and non-epileptic seizures characterised by pseudo-absence spells may occur. Adolescent girls are usually affected and episodes are associated with anxiety or be a component of an anxiety disorder. Episodes may often recur and the diagnosis may be missed and ascribed to cardiac or other life-threatening disorders.

Importantly, ISRR can sometimes manifest with dissociative neurological symptoms such as weakness or paralysis, abnormal movements or limb posturing, gait irregularities, speech difficulties, and/or non-epileptic seizures with no apparent neurological basis. The symptoms and signs may be delayed, especially in cases where such symptoms occur in clusters involving many vaccine recipients. Dissociative neurological symptom reactions appear to be more common in females. They are not typically diagnosed in infants. In children, dissociative neurological symptom reactions more typically manifest with a single symptom. Dissociative neurological symptom reactions are thought to be the result of numerous factors interacting at different levels which can be understood within the biopsychosocial context

One form of a dissociative neurological symptom reaction presents with non-epileptic seizures which are less common in early childhood (youngest age reported is 5 years) and appear to increase in adolescence. This is typically a diagnosis of “exclusion”. Non-epileptic seizures are also often referred to as pseudo-seizures or psychogenic seizures. Non-epileptic seizures are events resembling an epileptic seizure, but without the characteristic neural discharges (detected in EEG) associated with epilepsy. Non-epileptic seizures are seen as involuntary and affected individuals may or may not report feeling fearful or anxious before the event.

What is NOT an ISRR

A variety of delayed and ongoing AEFI have been reported post-immunization where the symptoms and signs are unexplained after appropriate medical investigations and the causal association with immunization, after review of the current evidence, has not been established. These include, complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS) and chronic fatigue syndrome (CFS). In some countries these conditions have been reported as AEFI and have been of significant concern to the public and health authorities.

Prevention of ISRR

A trained, competent and compassionate immunizer with good communication skills utilizing a friendly, confident and relaxed approach with a trusting relationship is more likely to minimize emergence of an ISRR. Prior to immunization, it is helpful to identify individuals with predisposing risk factors such as adolescent age group (10-19 years), history of vasovagal syncope, previous negative experience with immunization, an expressed fear of injections/needles, and pre-existing conditions such as an anxiety disorder or, a developmental disorder such as autism spectrum disorder.

General preventive interventions, include taking the parent or caregiver present into confidence who have hopefully not instilled fear of needles and fear of health care professionals. Preventative interventions also include using an age- and developmentally-appropriate evidence-based approach focusing on immunization environment, health care provider and family communication, physical position, and psychological strategies like distraction to reduce pain. As far as possible, all immunizations should be administered in a calm, private and planned environment even when administered to a large group such as a school setting. If syncope is anticipated, it can be avoided by using specific additional measures such as immunizing the individual seated or in the supine position and using “muscle tension”.

Communication should be directed towards the vaccine recipient but also any accompanying parent or caregiver (as relevant). Prior to mass vaccination, especially for adolescents, targeted messages and awareness sessions might help to alleviate some concerns.

Diagnosis of ISRR

An acute stress response could occur with a variety of cardiovascular (tachycardia - an increased heart rate, palpitations - feeling the heart beat), respiratory (shortness of breath, hyperventilation i.e. breathing fast and deep) and neurological/sensory (dry mouth, hot or cold sensation, tingling or numbness of limbs and sweating) manifestations. Some individuals may have a parasympathetic nervous system response with bradycardia (slow heart rate) and blood vessel dilatation both of which can result in hypotension (low blood pressure).

Differentiating anaphylaxis from an acute stress response - general and vasovagal reaction with syncope

	Acute Stress Response		
	Anaphylaxis	General	Vasovagal reaction with syncope
Onset	Usually occurs after 5 minutes but maybe delayed up to 60 minutes	Sudden, occurs before, during, or shortly after (< 5 minutes) immunization	Sudden, occurs before, during, or shortly after (< 5 minutes) immunization. May present after 5 minutes if individual changes position – stands suddenly
Systems			
Skin	Generalized urticaria (hives) or generalized erythema, angioedema, localized or generalized, generalized pruritus with or without skin rash, generalized prickle	Pale, sweaty, cold, clammy	Pale, sweaty, cold, clammy

	sensation, localized injection site urticaria, red and itchy eyes		
Respiratory	Persistent cough, noisy breathing as airway constriction: wheeze, stridor. If very severe respiratory arrest.	HYPERVENTILATION Rapid and deep breathing	Normal to deep breaths
Cardiovascular	↑ heart rate, ↓ BP, circulatory arrest	↑ heart rate, normal or elevated systolic Blood Pressure	↓ heart rate, +/-transient ↓ BP
Gastrointestinal	Nausea, vomiting Abdominal cramps	Nausea	Nausea, vomiting
Neurological and other symptoms	Uneasiness, restlessness, agitation, Loss of Consciousness (LOC), little response once supine /flat	Fearfulness, light-headedness dizziness, numbness, weakness tingling around lips, spasm in hands, feet	Transient Loss of Consciousness (LOC), good response once supine/flat +/- tonic-clonic seizure

It is important to remember that if sudden loss of consciousness is delayed and occurs more than 5-10 minutes after immunization, anaphylaxis should be considered as a possible diagnosis in addition to vasovagal syncope. Since anaphylaxis may be life-threatening, it requires immediate management with intramuscular adrenaline. Thus, it is important to exclude anaphylaxis and secondly define the manifestation of the ISRR to guide proper onsite case management, which is critical to preventing further concerns and possible development of a cluster. Clusters of anaphylaxis have NOT been reported. Therefore, **a cluster of multiple individuals presenting with these symptoms and signs, including collapse, is likely to be an ISRR and not anaphylaxis.**

Clues that a patient has a dissociative neurological symptom reaction include the disappearance of symptoms or signs when the patient is distracted, signs or symptoms which are not consistent with known neurological disorders, and no response to pharmacological interventions. Symptoms and signs maybe intermittent and vary between presentations. For example, there may be inconsistent neurological findings such as unusual gait or postures. The limb power and sensation may be normal lying down but the patient may exhibit an inability to stand and walk. If presenting as seizure, it is important that non-epileptic seizures be differentiated from seizures due to other causes such as epilepsy, meningitis and encephalopathy.

Management of ISRR

The key is to differentiate an ISRR from anaphylaxis and other diagnoses. If a vasovagal reaction has developed, the individual should remain in the supine position. Once an ISRR has been identified, the vaccine provider should clearly ascertain and exclude a vaccine product-related reaction and immunization error-related reaction. The nature of the symptoms, the fact that they are expected and

not harmful and will resolve spontaneously without any need for medications, should be explained.

Medication and hospitalization should be avoided as much as possible as experience has shown that they may aggravate the situation and cause additional cases.

Management of a dissociative neurological symptom reaction including a non-epileptic seizure involves a multi-disciplinary approach including medical and psychological assessments that focuses on interventions to reduce the functional disability. As a primary measure, reassure the affected person and others, assist the person to lie down in a calm and well-ventilated place, **and importantly, keep calm and confident**. Encourage returning to “normal activity”. In general, referral to a health practitioner or a health centre with expertise will be required. Treatments need to be tailored to the symptom constellation and may include physiotherapy, cognitive behavioral therapy and/or pharmacological interventions.

ISRR occurring as clusters of cases

In social situations, such as schools or in places where people congregate, one person’s syncope may trigger syncope in others in what is often referred to as “mass psychogenic illness” or “mass hysteria” in the literature. This pattern can be exacerbated when children or adolescents waiting to be vaccinated can observe others post-vaccination who may be experiencing stress responses.

Clusters of these events following immunization have occurred in both rural and urban settings, as well as in high-, middle- and low-income countries across the world and the extent of the cluster has varied widely from 7 affected individuals in one school to over 800 in multiple schools. Individuals in clusters described similar symptoms of dizziness, headache, and syncope with rapid onset after vaccination. Sometimes abdominal symptoms were reported. Vaccination programs have been negatively affected (and in some instances entire programs suspended) especially when these events are reported in the traditional and/or social media.

Investigations have demonstrated the absence of vaccine product or immunization error. Both males and females were affected, and most published clusters involved adolescents. Different vaccines were implicated; although some of the clusters involved a new vaccine introduction or a change in the routine vaccination program, including a novel vaccine, new age group, or new setting for vaccination.

In some instances, clinical management of cases within the clusters involved invasive testing or treatment that led to even more harm, as the link to stress was not recognized. Small clusters occurring in one group setting (typically a school) have spread quickly to a larger number, often escalated by media reports.

It is also important to keep in mind that, as previously mentioned, **it is extremely rare and almost impossible for anaphylaxis to occur in clusters**. However, in some instances, making a wrong diagnosis of clusters of anaphylaxis has resulted in mismanagement of ISRR clusters resulting in hospitalizations with inappropriate treatment and caused further worsening of the patients’ condition.

ISRR during mass immunization campaigns

In the case of mass immunization, health care workers should anticipate and take measures to avoid or minimize ISRR. During the planning phase itself, the “local setting” of mass vaccine administration including the waiting areas prior to vaccination should be assessed.

Emergency kits and information, education and communication (IEC) messages should be readily available. Of importance, job aids or posters differentiating anaphylaxis from an acute stress response including vasovagal syncope should be available to health workers. Planning should also incorporate the different primary responders (with address, phone numbers and transportation plans) to an individual event as well as a cluster of events and ensuring that they are aware of the possibility of being called in the event of an ISRR and responding appropriately. Mitigation of environmental factors known to contribute to clusters such as an overheated and crowded waiting area, prolonged standing, lack of privacy and availability of e-communication tools amongst those being immunized (e.g., for text messaging, social media) needs to be considered.

If vaccination requires injections, privacy needs to be offered to individual vaccine recipients keeping in consideration the local culture and sensitivities regarding dress code and gender. Individuals with risk factors for ISRR should especially be separately immunized. General pain management techniques should also be used. If a cluster of cases has already occurred, de-escalation by separating affected individuals from each other and from healthy vaccine recipients is key.

Having local community leaders and local health workers familiar to the vaccine recipients is helpful. This can increase calmness and comfort in the vaccine recipients and thereby support the immunization team. After vaccination, the vaccine recipients should be advised to wait for a period of 30 minutes to an hour at a waiting area that is well illuminated, providing basic distractions and a relaxing ambience.

ISRR as a component of AEFI surveillance

In general, individual cases of acute stress responses do not need to be notified or reported as part of AEFI surveillance with the exception of a vasovagal reaction with syncope, especially if an injury results. Dissociative neurological symptom reactions including non-epileptic seizures that may develop later may be reported if the patient seeks the intervention of a health care provider and attributes the symptoms to immunization.

The standard country AEFI reporting form should be used and the signs and symptoms observed, and the basic clinical features should be documented. Clusters of such events should be reported immediately to higher authorities by the fastest means possible (e.g., telephone). Depending on the seriousness of the event or the presence of a cluster, responsible authorities should initiate a detailed investigation of the concerned event or cluster of events. During investigation, it is important to ask probing questions of the relevant stakeholders and collect evidence on the biopsychosocial aspects to determine if the event could be a stress response related to immunization.

Causality for all ISRR should be assessed using the WHO causality assessment classification for AEFI. The first step should be to see if the reported symptoms and signs fulfill a case definition for an acute stress response, vasovagal reaction or dissociative neurological symptom reaction. If so, the causality assessment process should be followed. The next step is to formulate the causality question. However unlike other adverse events, for an acute stress response, symptoms may sometimes precede the actual administration of the vaccine. When assessing causality, after excluding coincidental events, such cases may be currently classified as “consistent with causal association to immunization” under the category of ISRR.

Communication aspects of ISRR

It is essential for countries to have a strong communication plan in place to anticipate, prepare for, and respond effectively to ISRR. Based on an assessment of background information, communication interventions to help prevent ISRR may be broadly divided into ‘primary prevention’ or ‘secondary prevention’ strategies.

Primary prevention strategies are implemented at a population level, at a very early stage when risk factors are present. Strategies include continuing to explain the importance and safety of vaccines and immunization, gathering and analyzing ongoing data on the situation and developing and testing key messages and tools. Simultaneously, health care providers should be trained in communication and interpersonal skills, and the importance of staying calm in the case of any event. They should be provided refresher courses on AEFI and ISRR and be urged to plan immunization sessions to avoid long waiting periods for a person being vaccinated and avoid persons watching those being vaccinated. In addition, they should emphasize techniques for relaxing vaccine recipients by connecting with and increasing their confidence prior to vaccination. They should also be trained on the processes and timelines for reporting events and follow-up actions.

Secondary prevention strategies are implemented at a local level on detecting and responding to ISRR. In addition to the components outlined in primary prevention strategies, secondary prevention strategies include activating the communications team and deciding if, when, and what to communicate and implement according to the crisis communication plan. It is important to simultaneously provide ongoing information to stakeholders, especially the media when necessary, and also monitor public sentiment that would include both the media coverage and social media where applicable, and then counteract any spread of rumors. Health care providers need to share lessons from experience with previous ISRR and review the structure of the immunization environment looking for any immediate adjustments that may be needed such as increased privacy, less waiting times etc.

When individual cases occur, the major goal of communication is rapid on-site management and local de-escalation of the situation to avoid increasing the number of affected individuals. Health care providers and other staff should be ready and able to take all the necessary steps to tactfully isolate the person concerned (“index case”) in order to help prevent the transmission of fear and anxiety to others, and to reduce stress. It is important to remember that ISRR are NOT the patient’s “fault” nor are they “crazy”. The reactions are responses to the stress of the event as perceived by the patient. It is absolutely critical to ensure that patients with stress-related AEFI are managed by professionals who are qualified and experienced in diagnosis and managing such reactions. Cultural sensitivities also need to be taken into consideration during case management as this can vary from one context to another.

Monitoring and evaluation are complementary to the communication plan and should include a system to monitor the process, outputs, and outcomes, and evaluate the results. The documentation of lessons learnt, good practices, and innovations in ISRR related communications and other AEFI will benefit many aspects of immunization programmes. It is important to continue to maintain relationships built with key stakeholders and media long after events have taken place to ensure that these groups continue to be strong programme partners and contribute to sustaining trust in vaccines and in the health authorities delivering them.

Global vaccine action plan (GVAP) review and lessons-learnt. Preliminary report 11 March 2019

*Background document for the post-2020 immunization partners' consultation:
'Co-Creating the Future of Immunization', 19-21 March 2019*

Executive Summary

- The ongoing GVAP review aims at supporting the development process of the next global immunization strategy by providing analyses and lessons learnt from the current plan. Preliminary results are summarized in this document. The full review will be prepared for the October 2019 SAGE session.
- Three surveys of GVAP stakeholders have been carried out from 2017-2018. Key findings include that GVAP is seen as a powerful tool to align global immunization actors but difficult to implement. Progress has been made on many GVAP's goals and strategic objectives but the only one that is on track is introduction of new vaccines. Advocacy and communication about GVAP have been weak links.
- The 2019 survey of GVAP stakeholders suggests that GVAP added value in a number of ways, including through the Monitoring and Evaluation/Accountability framework; and by building political will for immunization through setting global goals, supporting National Immunization Technical Advisor Groups (NITAGs), the development and implementation of regional vaccine action plans (RVAPs), and the Addis Declaration on Immunization. It contributed to improving equity through a focus on subnational data and access to new vaccines, and to immunization systems. It also added value by highlighting the issue of vaccine pricing. Overall, GVAP made moderate to slight contributions to meeting its 6 strategic objectives.
- Ongoing interviews reveal a range of views on the importance and success of GVAP. The following quotes reflect some of the perspectives shared thus far:
 - "GVAP was more about goals and less about how to get to the goal, markers on the road, rather than which road to take."
 - "Some countries take the goals very seriously and work very hard. India is a good example of how GVAP has influenced action."
 - "M&E has been mainstreamed and countries have been contributing data. This has led to comparisons across countries, regional plans and annual reports. It has been a benefit."
- The global context in which immunizations occur has changed significantly over past decade, including: additional vaccines and expanding target groups; strengthening of immunization systems and improving data quality; growth in Gavi support, and Gavi and polio transition; demographic changes and population movement.

Background

WHO is coordinating a review of the Global Vaccine Action Plan (GVAP) to inform the development of a post-2020 strategy for vaccines and immunization. The technical oversight of the review is provided by the SAGE Decade of Vaccines Working Group (DOV WG). The review assesses five topics:

1. Evaluation of the GVAP partnership and collaboration;
2. Evaluation of the plan itself (with a specific focus on the added value of GVAP);

3. Evaluation of the monitoring and evaluation (M&E) framework;
4. Overall assessment of progress of immunization over the decade; and
5. Comparative background analysis of the changes in the global immunization arena between 2010 and 2018.

This document provides some preliminary analyses to contribute to the development of the next global immunization strategy as a background document for the immunization partners' stakeholder consultation 'Co-Creating the Future of Immunization', 19-21 March 2019 in Geneva. A consolidated final report will be submitted to SAGE for endorsement at its October 2019 meeting. The information presented includes summary of findings from prior work and initial results from the first phase of the current project.

WHO is assisted by the Task Force for Global Health (TFGH) and MM Global Health Consulting (MMGH) in this review.

GVAP survey 2017-2018

Three surveys relating to GVAP were carried out in 2017-2018. In 2017, forty key stakeholders were interviewed¹ on the development, implementation and impact of GVAP (what worked well and what could have worked better), and suggestions for the development of the post-2020 strategy. Another survey² in 2017 and 2018 assessed the utility and application of GVAP and explored ways to strengthen the next 10-year plan. Finally, following the June 2018 Global Immunization Meeting, a survey³ was sent to all participants with 10 questions about the "why, what, and how?" of a post-2020 global immunization strategy.

Although the three surveys took place at different times, had slightly different objectives, and targeted different respondents, there was considerable concordance in their findings. In total, information was gathered from approximately 300 persons. A summary of the main findings relating to the development of GVAP (Past), current situation (Present), and post-2020 strategy (Future) follows. Of note, the value/impact of the M&E framework has not been specifically addressed in those surveys.

Past (development)

- The development of GVAP was a large-scale undertaking seen as having limited structure and vision of execution (no clear process goals and terms of reference, missing links with the preceding Global Immunization and Vaccine Strategy). Though the consultative phase for the development of the GVAP was open and inclusive, the development of the plan itself was driven by a handful of agencies. The latter took a top-down approach with limited engagement and ownership of stakeholders delivering immunization (country governments, non-state actors and regions), and very limited involvement of people from outside the field of immunization.
- There was a lack of clarity on process ownership and leadership.
- The development process made it difficult for GVAP workgroup outputs to be reflected in the final plan.
- Inadequate involvement of implementing parties (countries) resulted in plans with limited operational focus.

¹ Survey carried out by MMGH

² Survey carried out by TFGH and the Emory Vaccine Center, with support from CDC

³ Survey carried out by WHO

Present (implementation)

- GVAP is viewed as a first-time all-encompassing plan for immunisation with large and diverse stakeholder engagement.
- GVAP is seen as a powerful tool to orient global immunisation actors, but difficult to implement (as too high level and not fully costed). It provides the "what" but not the "how."
- Aspirational goals and objectives led to limited accountability by many stakeholders.
- Progress has been made on GVAP's strategies and targets but the only one that is on track is introduction of new vaccines.
- Disease-specific targets are seen as too ambitious to reach by 2020.
- The M & E/Accountability Framework has provided a useful mechanism for monitoring progress but there has been limited accountability for actions to increase progress toward goals.
- Advocacy and communication about GVAP have been weak links – despite the plan's quality, knowledge of GVAP is still limited outside the immunization community.

Future

- A post-2020 strategy should be developed using a bottom-up approach, with a limited number of globally-agreed goals/targets and details developed at regional and national levels.
- A post-2020 strategy should be integrated into larger strategies/goals, such as the Sustainable Development Goals (SDGs) and the 13th WHO General Programme of Work.
- A post-2020 strategy should take into account the changing context of immunization and of global health in general, such as climate change and migration.

Ongoing evaluation of the GVAP (with a specific focus on the added value of GVAP) and of the GVAP monitoring and evaluation framework

A new survey relating to the added value of GVAP and to the GVAP Monitoring and Evaluation/Accountability framework has been conducted querying 110 individuals representing a range of perspectives. Respondents were given a list of 36 specific actions relating to GVAP and asked to score for each of the items their contribution to improving global immunization. Options for scoring were 3 for "important contribution of GVAP", 2 for "moderate contribution of GVAP", 1 for "slight contribution of GVAP", and 0 for "GVAP did not contribute".

GVAP-related action items were grouped under the following headings:

- Monitoring and Evaluation/Accountability (M&E/A) Framework
- Strategic Objective (SO) 1: All countries commit to immunization as a priority.
- SO 2: Individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility.
- SO 3: The benefits of immunization are equitably extended to all people.
- SO 4: Strong immunization systems are an integral part of a well-functioning health system.
- SO 5: Immunization programs have sustainable access to predictable funding, quality supply and innovative technologies.
- SO 6: Country, regional, and global research and development (R&D) innovations maximize the benefits of immunizations.

In addition, respondents were asked to score each GVAP Strategic Objective in terms of its contribution to improving global immunization, using the same scoring rubric.

Survey Results

Preliminary results as of 1 March 2019 are based on 55 responses (50% response rate). Of the respondents, 53% represented global perspectives and 47% represented regional or country perspectives. The average score for the contribution of each item to global immunization was calculated: of the 36 GVAP-related action items, 15 had average scores between 2 and 3, indicating that respondents believed they had made ***moderate to important*** contributions to improving global immunization. These items are shown in Table 1 below. None had an average score ≤ 1 , indicating that all were considered to have made at least some contribution to improving global immunization. Scores for all 36 action items are shown in Annex 1.

Table 1 Preliminary results of stakeholder responses rating the perceived GVAP contribution to improving global immunization, by GVAP action items (only the 15 highest scoring items presented)

Average Score	Area	Action items
2.4	M&E/A	<u>Regional and National Annual Reports.</u> Since 2016, all WHO regions and some countries have published annual progress reports of their regional vaccine action plans developed in conjunction with the GVAP Secretariat Report. These reports have been presented in regional committee (RC) meetings each year.
2.3	M&E/A	<u>Independent monitoring and review.</u> The Strategic Advisory Group of Experts (SAGE) reviews the Secretariat report and issues a concise Assessment Report that highlights key issues and recommends actions to accelerate progress
	SO 1: Political will	<u>Regional Vaccine Action Plans.</u> By 2016, all the WHO regions had adopted regional vaccine action plans aligned with the GVAP. These plans include robust monitoring and evaluation (M&E) frameworks that contribute to global GVAP M&E.
2.2	SO 3: Equity	<u>Subnational data collection and reporting.</u> GVAP reviews have contributed to a greater appreciation of the need for subnational data to evaluate progress in immunization and to efforts to collect, share, and use subnational data. As of 2018, 141 member states have reported subnational immunization data.
	SO 3: Equity	<u>New vaccine introduction target.</u> GVAP called for at least 90 low and lower-middle income countries to introduce one or more new or underutilized vaccines by 2015, and for all such countries to introduce one or more new or underutilized vaccines by 2020.
	M&E/A	<u>Independent oversight.</u> As called-for by the World Health Assembly (WHA), the WHO Executive Board (EB) and the WHA review progress on an annual basis to foster accountability at the highest levels.
2.1	SO 1: Political will	<u>Global Goals.</u> The GVAP set forth 5 Goals: Achieve a world free of poliomyelitis; Meet global and regional elimination targets; Meet vaccination coverage targets in every region, country and community; Develop and introduce new and improved vaccines and technologies; and Exceed the Millennium Development Goal 4 target for reducing child mortality.
	SO 1: Political will	<u>National Immunization Technical Advisory Groups (NITAGs).</u> GVAP called for an increase in the number of countries with functioning NITAGs and Assessment Reports have recommended that NITAGs contribute to monitoring the implementation of national vaccine action plans.

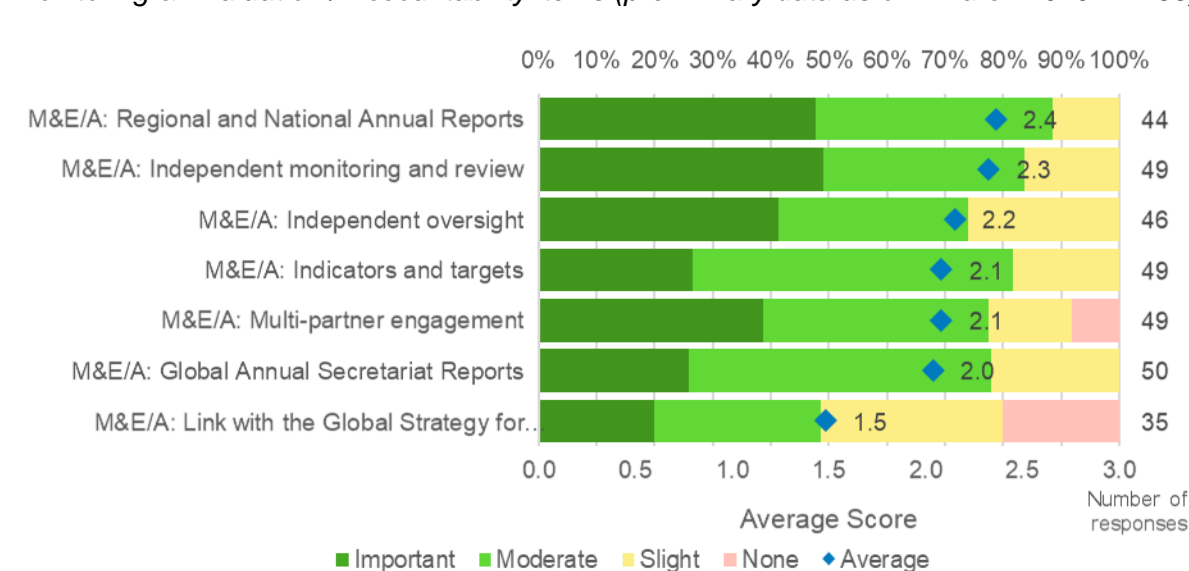
Average Score	Area	Action items
2.1	M&E/A	<u>Indicators and Targets.</u> The GVAP Monitoring and Evaluation/Accountability Framework reinforced or enhanced existing global targets and established a wide range of new indicators and targets for issues such as financing, integration, and research and development. Since 2017, progress against key indicators has been available online at the GVAP Indicators Portal.
	M&E/A	<u>Multi-partner engagement.</u> The GVAP was developed under the auspices of 5 major global health institutions (WHO, UNICEF, Gavi, BMGF, and NIAID (USA)), and these organizations engaged actively in the monitoring process, including serving as the secretariat for preparing annual reports.
2.0	SO 5: Funding and Supply	<u>Vaccine price transparency.</u> At the 2015 World Health Assembly, countries raised their concerns about vaccine prices and adopted a landmark resolution calling for price transparency and greater affordability. This created momentum for the V3P platform, which facilitates the appropriate comparison of price information and provides countries with accurate, reliable and useful data on vaccine product, price and procurement.
	M&E/A	<u>Global Annual Secretariat Reports.</u> The GVAP Secretariat describes global progress toward GVAP targets each year in a comprehensive Secretariat Report.
	SO 1: Political will	<u>Guiding Principles.</u> Six principles were adopted to guide the elaboration of GVAP: 1) Country ownership, 2) Shared responsibility and partnership, 3) Equity, 4) Integration, 5) Sustainability, and 6) Innovation.
	SO 1: Political will	<u>Addis Declaration on Immunization.</u> At the 28th African Union (AU) Summit in 2017, Heads of State from across Africa endorsed the Addis Declaration on Immunization (ADI), committing to advance universal access to immunization across Africa. This was accompanied by a roadmap for its implementation.
	SO 4:	<u>Joint Reporting Form (JRF) and data quality workshops.</u> As a result of data quality concerns raised by the first GVAP report, JRF workshops are now being held in all regions to improve the quality of the reported data. Regional workshops for data quality are also being held.

In general, respondents representing regional and national perspectives gave similar or slightly higher scores than those representing global perspectives (see Annex 2).

These results show broad recognition of the value of the GVAP Monitoring and Evaluation/Accountability framework and of similar measurement and evaluation conducted at the regional level. GVAP contributed to SO 1: Building political will for immunization through setting global goals, NITAGs, regional vaccine action plans, and the Addis Declaration on Immunization. It contributed to SO 3: Equity, through a focus on subnational data and access to new vaccines and to SO 4: Immunization systems, through JRF workshops. GVAP also added value by highlighting the issue of vaccine price transparency.

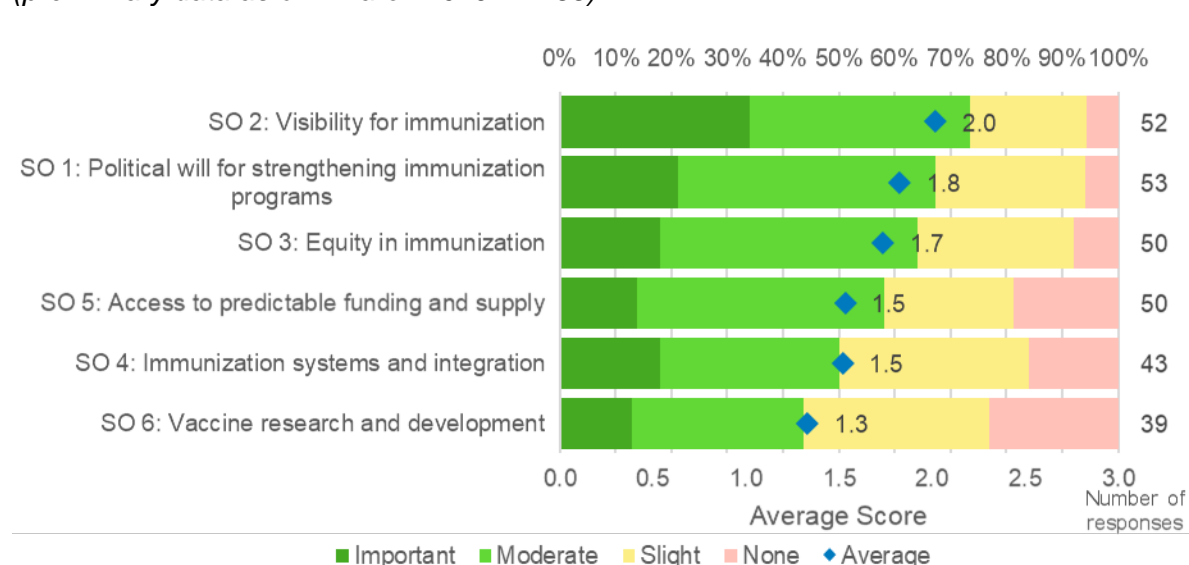
Looking specifically at actions relating to the Monitoring and Evaluation/Accountability framework, 6 of the 7 action items received scores between 2 and 3, reflecting a moderate to important contribution, and only one received an average score between 1.0 and 2.0, reflecting a ***moderate to slight*** contribution to global immunization (Figure 1). This was the link with the Global Strategy for Women's, Children's and Adolescents' Health. Overall the M&E/A average score was 2.1.

Figure 1: GVAP review survey: perceived GVAP contribution to improving global immunization – Monitoring & Evaluation / Accountability items (preliminary data as of 1 March 2019 - N=55)



When respondents were asked to score the contribution of GVAP to meeting each strategic objective, all of the 6 SOs received average scores between 1.0 and 2.0, indicating that GVAP had made **moderate to slight** contributions to achieving each one (Figure 2). Overall the average SO score was 1.7. Score differences according to respondent's global or regional/country perspective are shown in Annex 3.

Figure 2: GVAP review survey: perceived GVAP contribution to achieving Strategic Objectives (preliminary data as of 1 March 2019 - N=55)



Interview results

Additional interviews to gain a more nuanced view of the GVAP partnership and collaboration and the added value of GVAP are being conducted with individuals who were involved in the development, implementation, and monitoring of GVAP. A selection of responses to date from current and former interviews follows, reflecting a range of views. A complete summary and analysis will be included in the final report.

- “GVAP was more about goals and less about how to get the goal, markers on the road, rather than which road to take.”
- “GVAP was an excellent technical document and no doubt GVAP 2.0 will be the same. But it hasn’t changed the dynamic at the country level. We need to put enabling factors at the center, not technical approaches.”
- “Some countries take the goals very seriously and work very hard. India is a good example of how GVAP has influenced action.”
- “M&E has been mainstreamed and countries have been contributing data. This has led to comparisons across countries, regional plans and annual reports. It has been a benefit.”
- “We need more interim measures that show progress to keep countries motivated.”
- “GVAP raised the profile of the supply chain and provided a focus on coverage and equity, but did not help much in the creation of demand”
- “We are not sure how much GVAP has improved accountability per se, but the indicators and targets, as well as the reports, serve as a benchmark, guidelines and a reminder for every level of what is important, what we have to focus on, and how far we have come.”
- “The ongoing dialogue among GVAP stakeholders has surfaced issues such as vaccine hesitancy that must be addressed.”
- “There was a lot of expectation on funding availability, but ultimately funds were not there. Funding requirements need to be much more precise and link to sources of funding.”
- “GVAP was most successful in areas such as new vaccine introduction, where funding was made available.”
- “My view is that the joint stewardship role of WHO, UNICEF, Gavi, NIAID/CDC, BMGF was among the most disappointing aspects of the DoV/GVAP overall...largely not convened at leadership levels, silent, or weak when a joint voice eventually came forward....”
- “There was close to zero communication around GVAP and no advocacy at the country level. I have not heard the work ‘GVAP’ once in three years here.”

- “GVAP contributed to R&D: The GVIRF took a lot of strength from the GVAP process and vaccine and implementation research was strengthened”

Changing context in which immunizations occur

Since the beginning of the Decade of Vaccines, there have been major changes in the global context in which immunizations occur. Some of these are mentioned briefly below. The final report will provide a more detailed consideration of these changes and their implications for immunizations going forward.

Global context

- Sustainable development goals (SDGs) succeeding Millennium Development Goals (MDG). In the SDGs, immunization is less prominent than it was in the MDGs.
- WHO General Programme of Work 2019-2023. This describes three strategic priorities with associated goals: Achieving universal health coverage (1 billion more people benefitting from universal health coverage); Addressing health emergencies (1 billion more people better protected from health emergencies); Promoting healthier populations (1 billion more people enjoying better health and well-being).
- Demographic changes. Global population has increased from 7.0 billion in 2010 to 7.7 billion in 2017, with increases concentrated in the African and Eastern Mediterranean regions. The median age of the global population is currently 28.5 years and it rises each year. In 2010, 50.7% of global population lived in urban areas, by 2020, this is projected to rise to 56.2%.
- Post-Ebola focus on emerging infectious diseases and epidemic preparedness (e.g., CEPI) requires attention in addition to ongoing serious issues with immunization programs.
- Political changes. Rise in nationalism/populism with some new leaders not supporting immunization.
- Humanitarian crises and population movement. In 2017 the population of forcibly displaced persons was 68.5 million, an all-time high. This included 25.4 M refugees, 40.0 M internally displaced, and 3.1 M asylum seekers. One of every 110 people worldwide is displaced. In addition, there were an estimated 50 M “irregular” migrants (those in another country without proper documentation).

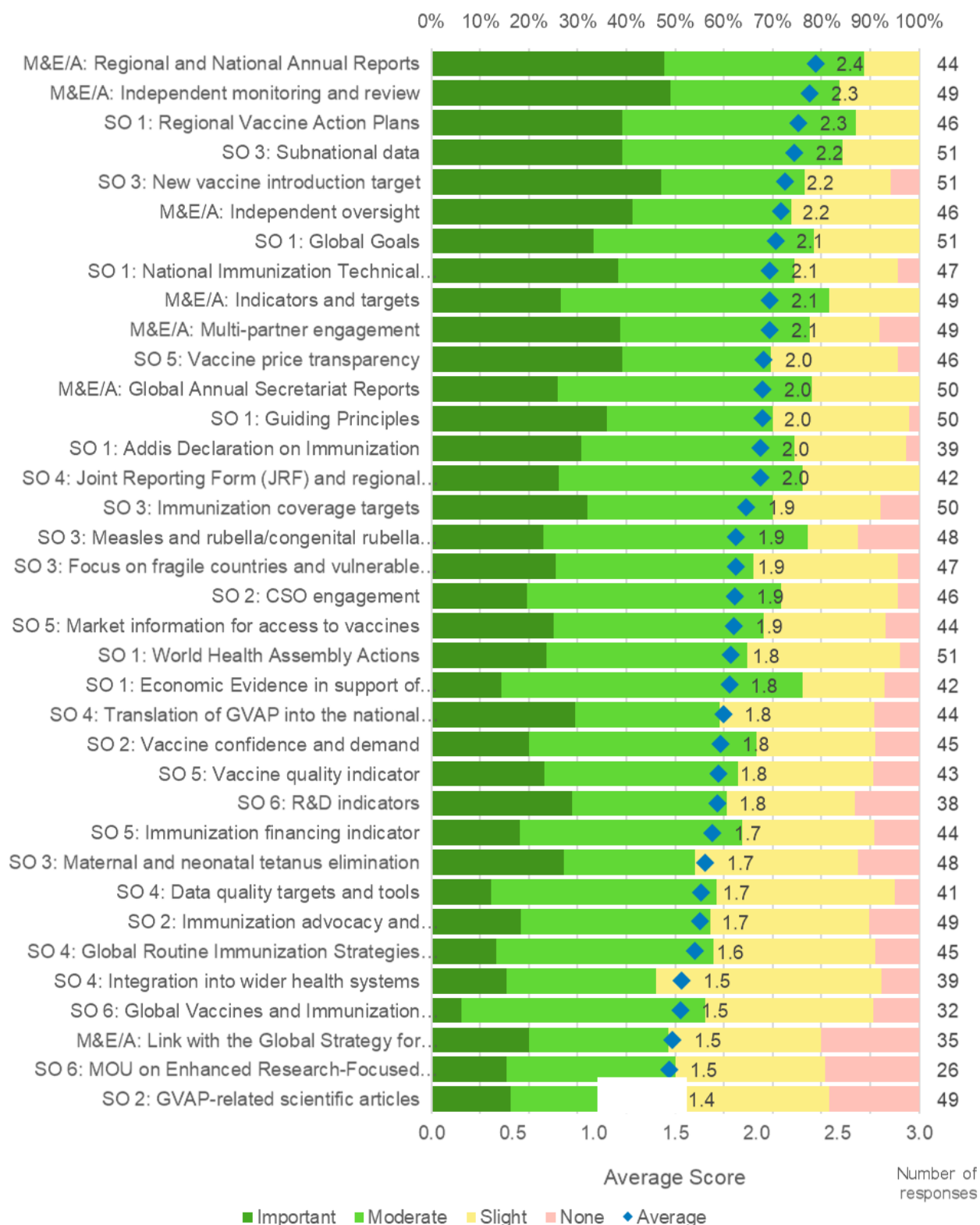
Immunization landscape

- Growth in Gavi support and transition from Gavi support. In 2010, Gavi support to country programs totaled USD 453 million, in 2018, it was USD 1.153 billion. In 2016, 16 countries were in the accelerated transition phase and five were fully self-financing.
- There has been significant strengthening of immunization systems and the quality of data has improved significantly.

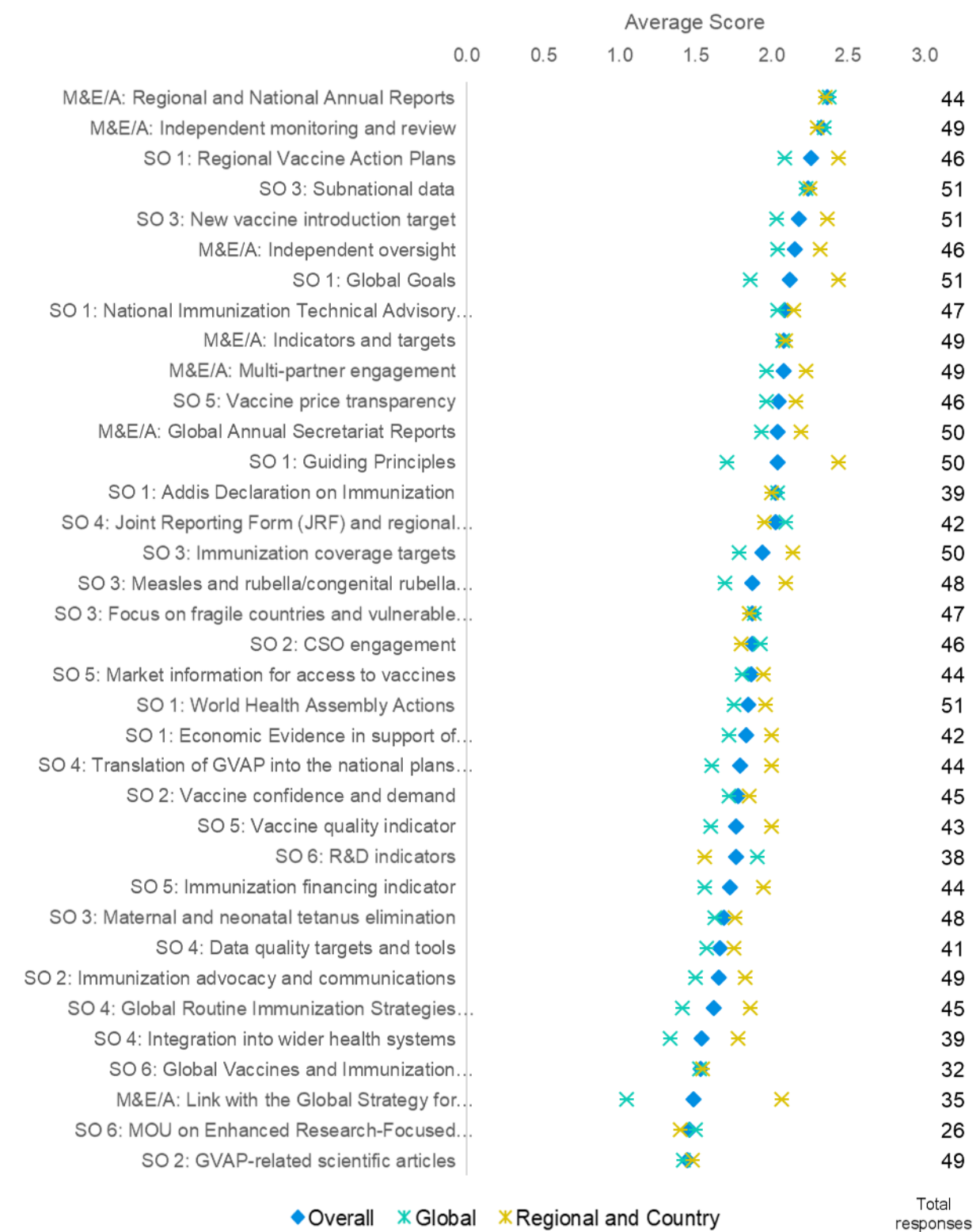
- Increase in number of NITAGs and importance of regional immunization technical advisory groups – In 2010, there were 41 functional NITAGs and in 2017, there were 98.
- Additional vaccines in program. Number of countries using given vaccine in 2010 compared to 2018: Hib 167/190, PCV 61/136, Rotavirus 29/91, IPV 60/186, HPV 40 (2012)/85.⁴
- Expanding target groups. HPV vaccine is administered to 9-12-year-olds (girls in many countries, both sexes in several). This is a different age group from the traditional EPI target group of infants.
- Global Polio Eradication Initiative (GPEI) transition. Sixteen countries are losing major support from GPEI and GPEI-supported staff have spent significant proportions of their time on activities other than polio (notably measles-rubella and routine immunization).
- Reversal of successes of programmes in different countries (e.g. Ukraine, Venezuela) due to economic, social, political crises.
- Rise in vaccine hesitancy. WHO has identified vaccine hesitancy as one of ten threats to global health.

⁴ Hib: *Haemophilus influenzae* type b, PCV: pneumococcal conjugate vaccine, IPV: inactivated poliovirus vaccine, HPV: human papillomavirus vaccine

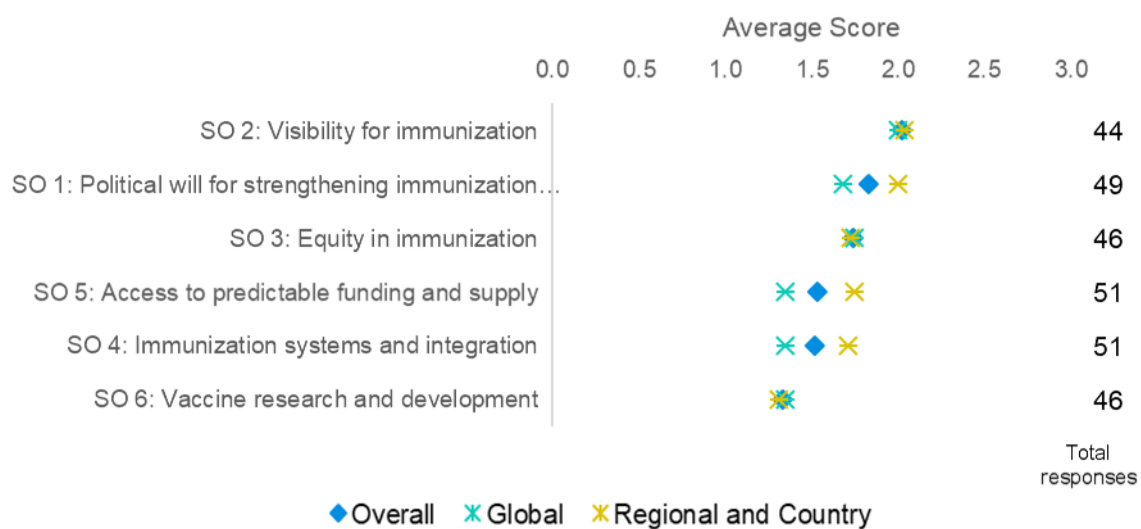
Annex 1: Perceived GVAP contribution to improving global immunization: score distribution and average score for each of the 36 survey items, all respondents combined (preliminary data as of 1 March 2019 - N=55)

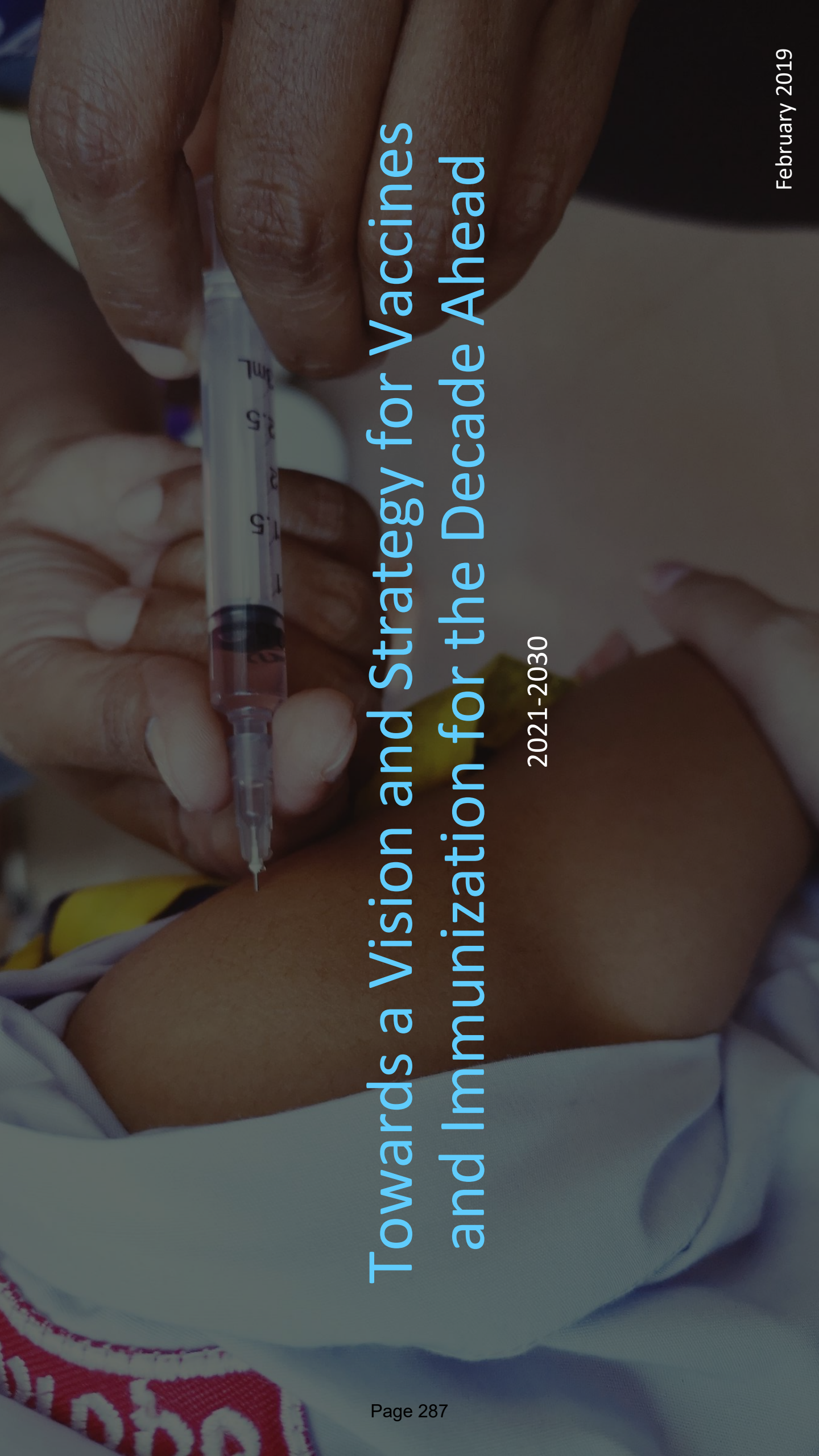


Annex 2: Perceived GVAP contribution to improving global immunization: average score for each of the 36 survey items, by type of perspective of respondent (global or regional/country) (preliminary data as of 1 March 2019 - N=55)



Annex 3: Perceived GVAP contribution to improving global immunization: average score grouped by Strategic Objective and by type of perspective of respondent (global or regional/country) (preliminary data as of 1 March 2019 - N=55)





Towards a Vision and Strategy for Vaccines and Immunization for the Decade Ahead

2021-2030

February 2019

Executive summary



Why do we need a new, post-2020 plan for vaccines and immunization?

A compelling vision and strategy for vaccines and immunization 2021-2030 is needed, so that all countries, regions and partners can define their own strategies and operational plans in a coordinated way



What will the new, post-2020 plan include?

Overall, the post-2020 plan will include four elements

- Global vision and strategy
- Local, regional and global implementation plans
- Revised M&E guidelines
- Advocacy plan and call to action

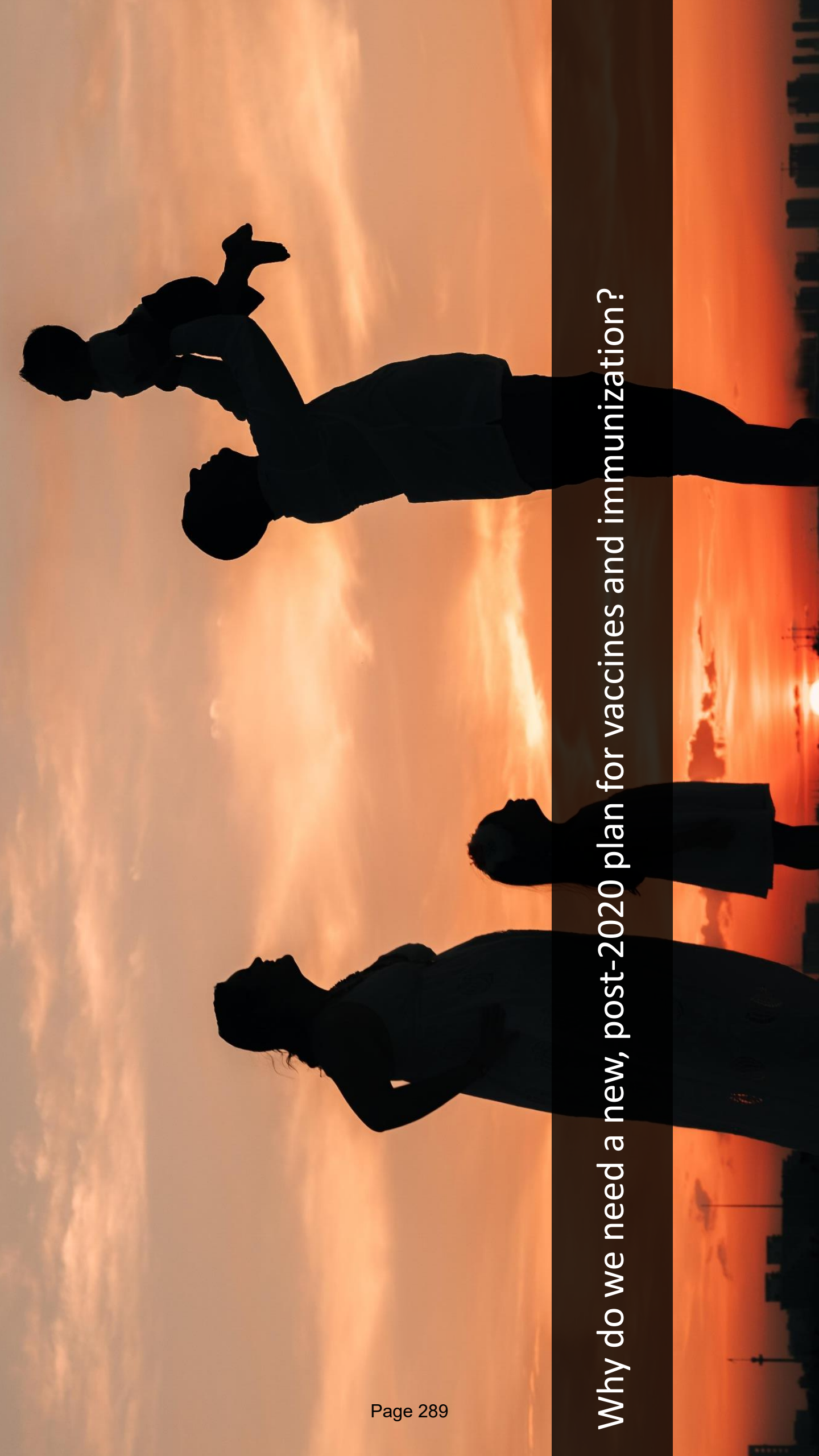
The vision and strategy is the first of the four elements. It will build from and advance existing strategies, and **enable operationalization**



How is the post-2020 plan being co-created?

The post-2020 plan is being developed through a **highly collaborative process**, which started 18+ months ago with **country consultations** that have already fed into regional business cases, and global strategies

As the journey continues, a next milestone is an **extensive stakeholder workshop** in Geneva from March 19-21, 2019



Why do we need a new, post-2020 plan for vaccines and immunization?

With the GVAP coming to an end in 2020, a new plan is needed to **set a compelling, country-centric vision and direction** for the coming decade;

Address new and emerging issues, and harness new solutions in vaccines and immunization;

And re-ignite the importance of immunization for broader health agendas



The Decade of Vaccines has achieved significant progress for immunization

- 116M** Infants received recommended DTP3 worldwide in 2017, the most ever
- 4.6M** Additional infants vaccinated in 2017 compared to 2010
- 1.8M** Fewer children went under-vaccinated in 2017 than in 2010
- 3** Additional countries achieved maternal and neonatal tetanus elimination in 2017 (Ethiopia, Haiti and the Philippines)
- 113** Countries introduced new vaccines since 2010
- +140%** Increase in the number of functional NITAGs since 2010



However most GVAP goals will not be met by 2020, with existing/emerging realities further inhibiting progress

Most GVAP goals will not be met by 2020 (select figures) ...

- 3** Polio-endemic countries remain (Afghanistan, Pakistan, Nigeria); global polio eradication by 2018 not achieved yet
- No** Region has sustained verification of measles elimination status
- Only 1** Region became rubella-free in 2018 (the Americas)
- 14** Countries yet to achieve MNT elimination
- ~85%** Coverage level stagnation level for MCV1 between 2010 and 2017 (below the 90%+ target)
- < 30%** Of countries have achieved DTP3 coverage of 90% nationally and 80% in every district
- 19.9M** Children still under-vaccinated in 2017
- 25** Low- and middle-income countries have not introduced any new/ under-utilized vaccine between 2010 and 2016

... with several current and emerging realities standing in the way of progress

Political & Economic dynamics – e.g., volatile and uncertain geopolitical dynamics generate more fragile, at-risk contexts; persisting economic and capacity inequalities in-country and between-countries are reflected in coverage disparities

Demographic dynamics—e.g., population growth, mass urbanization and migration pose major challenges for immunization systems; 'hard to reach' populations become more multi-faceted

Technological trends – e.g., social media, a potential means for spreading information and educating consumers, is also contributing to increased 'vaccine hesitancy' in some countries

Source: 2018 assessment report of the GVAP (WHO);
GVAP—Secretariat annual report 2018



The next decade will need to also address new and emerging issues, and harness new solutions in vaccines and immunization ...



Immunization will continue to evolve from a focus on infants and children to vaccinating [along the life course](#)



[Country-focus](#) will be key to ownership, political commitment and sustainability of the immunization agenda



Approaches to reach un-immunized populations will target increasingly fine and precise areas, thanks to [higher-quality data](#)



Focus will be on driving coverage and equity for existing vaccines, leveraging [innovations in delivery products and practices](#)



Thoughtful [integration](#) with Maternal, Child and Adolescent health programs and PHC, and heightened [collaboration](#) across the ecosystem will be key to deliver at-scale impact



Immunization [demand and acceptance](#) will also be essential to drive coverage



[Disease surveillance](#) will be a driving component of high functioning vaccine and immunization systems

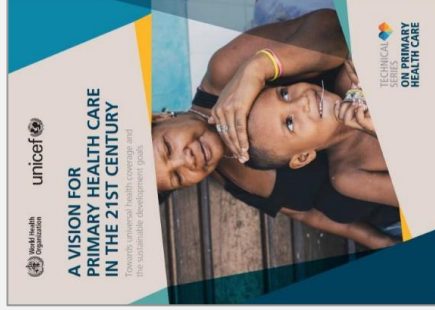


The role of vaccines in preventing or responding to [health emergencies](#), even more so in [fragile contexts](#), will become ever more important in the next decade

... while at the same time contributing to the broader global health and development agendas



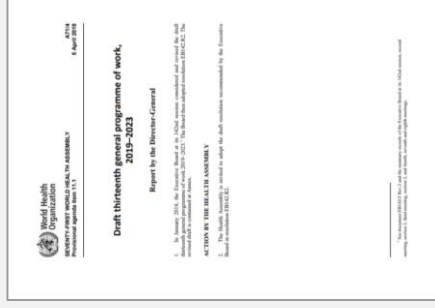
Sustainable Development Goals



Primary Health Care



Universal Health Coverage



13th General Programme of Work



What will the new, post-2020 plan include?

The post-2020 plan will include four key elements

1

A new global vision and strategy for vaccines and immunization for the entire health community up to 2030, that reflects the collective inputs of all partners and stakeholders, and provides a scaffolding for partner’ efforts

To be endorsed by Ministers of Health of all countries during WHA 73 (2020)

2

Global, regional and local implementation plans, aligned with overall strategy, tailored to context to ensure implementation

3

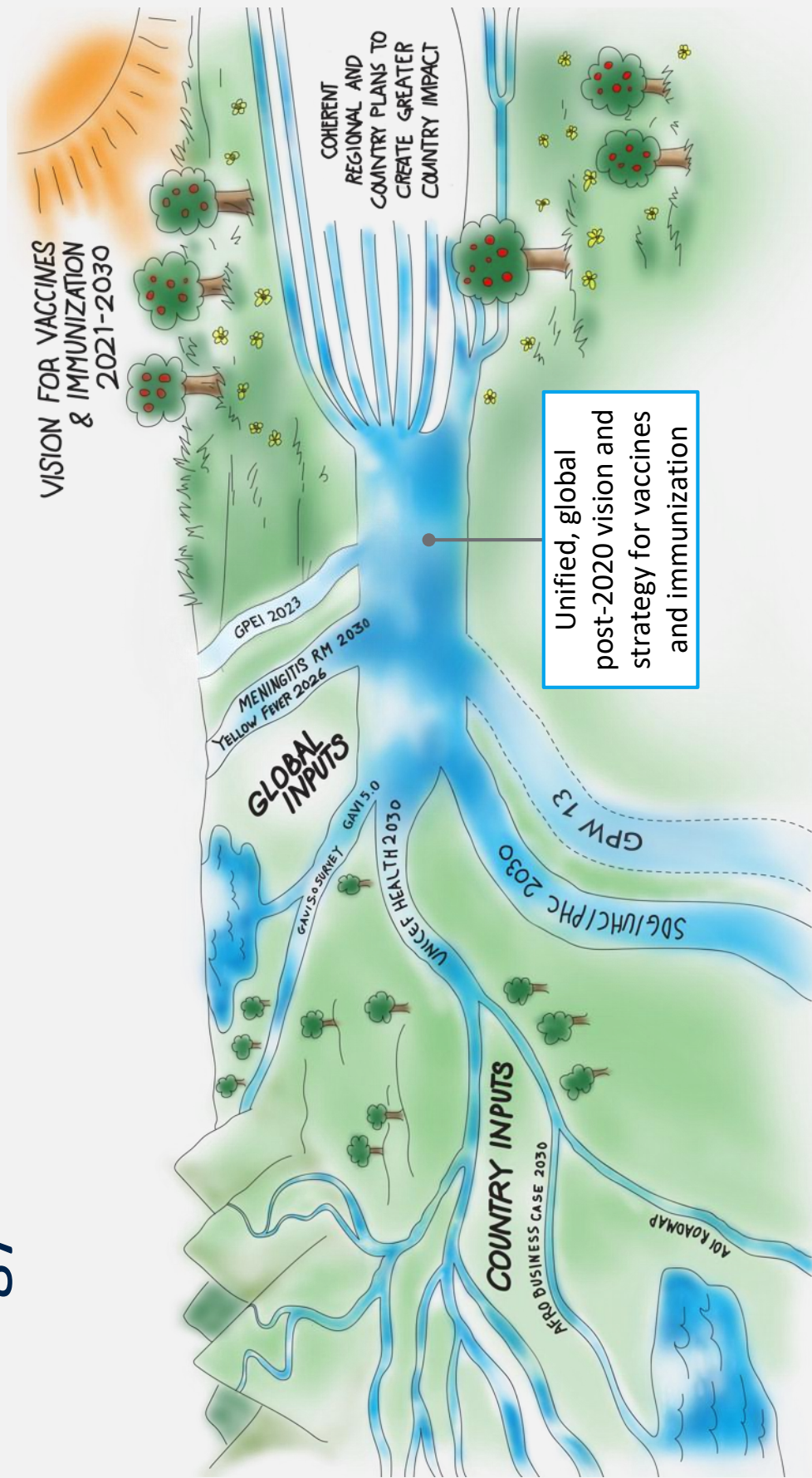
Revised M&E guidelines—streamlined, linked to other frameworks—to reduce the reporting burden and improve data quality

4

Advocacy for the post-2020 strategy to create a movement and build momentum for the new vaccines and immunization agenda

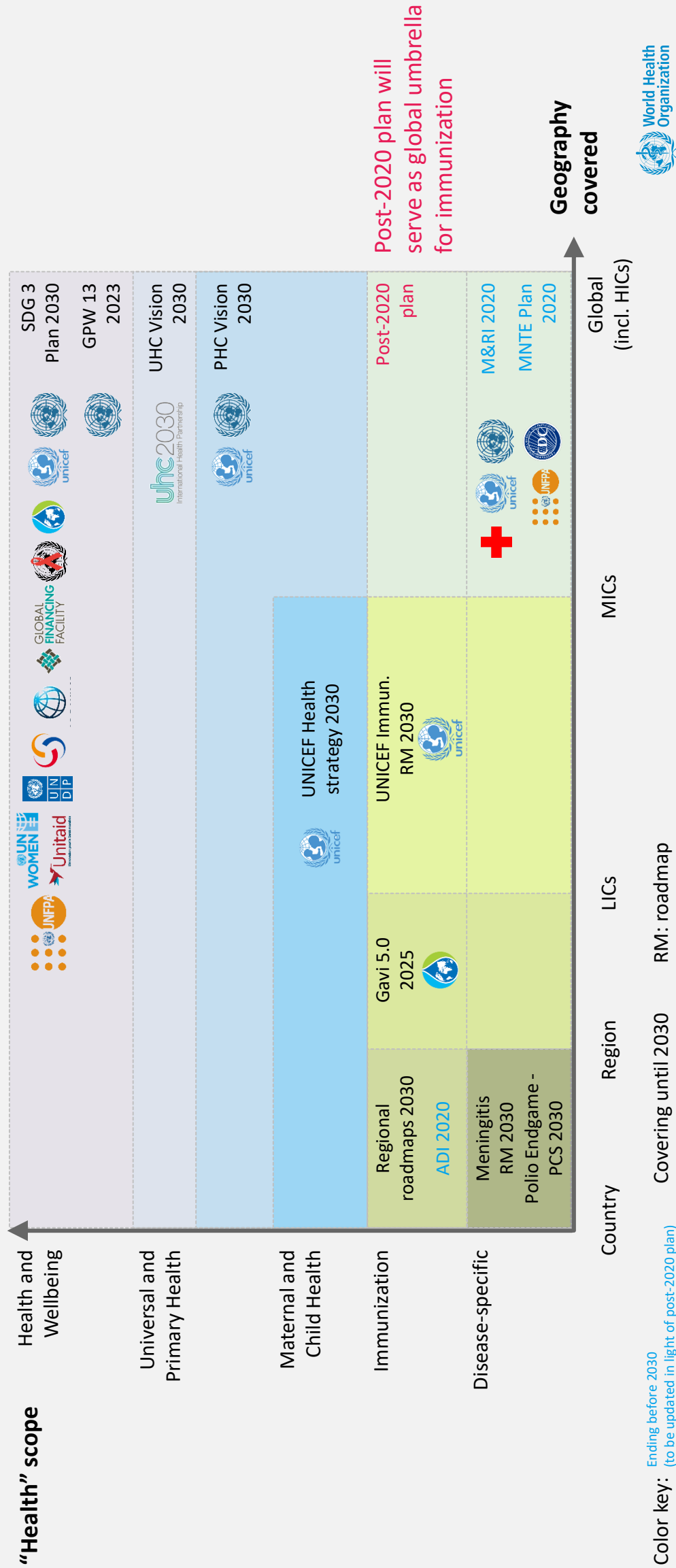
Focus between now and WHA 73

Plan being co-created bottom-up: Countries, existing strategies are the sources shaping the unified vision and strategy for 2030



Extensive country inputs have been the basis for new global and regional, health immunization and disease-specific strategies. They will constitute building blocks of the post-2020 plan


Post-2020 plan will link to fresh health agendas for 2021–2030—all of which have had substantial country consultation



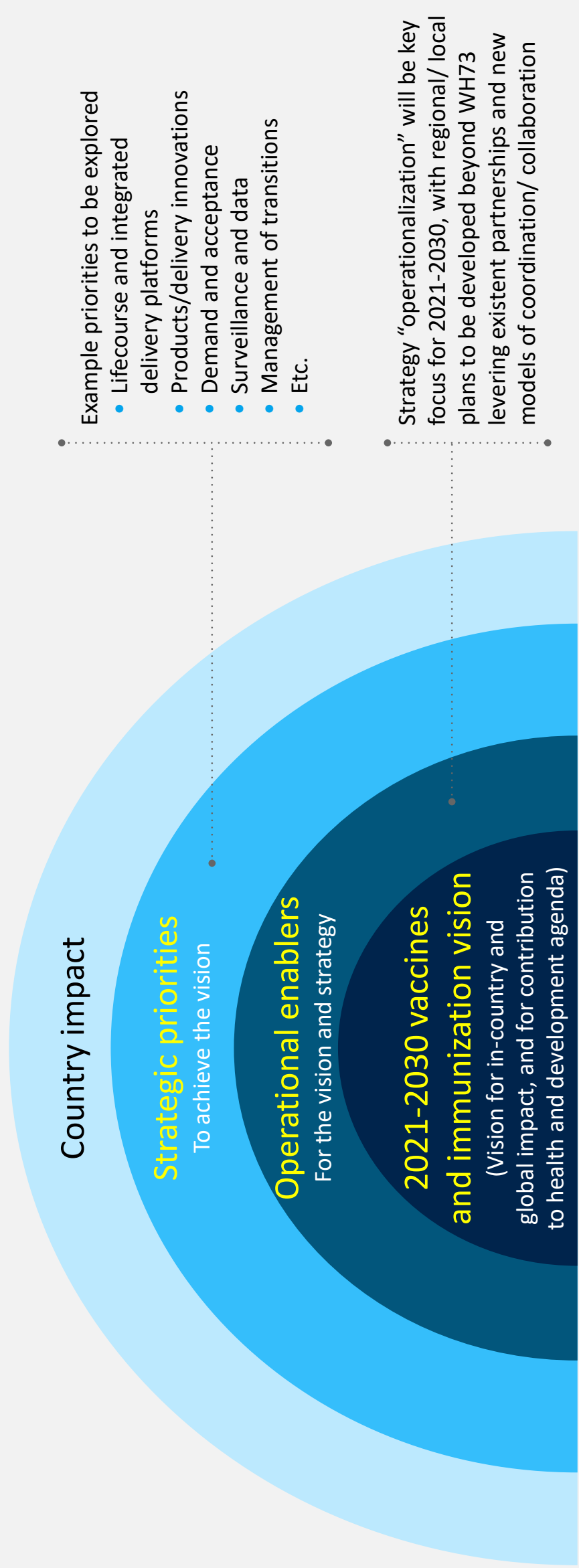
Post-2020
process will
also leverage
ongoing Gavi
5.0 process and
consultations ...

... while recognizing differences between
the two documents

Equity, Security and Prosperity

 Gavi 5.0	Post-2020
<p>Focused scope</p> <ul style="list-style-type: none"> • Priority countries • Priority vaccines • Focused interventions • Five years <p>Platforms for investments that contribute to post-2020 objectives (funding mechanism)</p> <p>Target audience is the Gavi Board</p>	<p>Broader scope</p> <ul style="list-style-type: none"> • All countries • All recommended Vaccines • Broader set of interventions • 10 years <p>Platform for aligning on a new global vision and strategy for the entire health community</p> <p>Target audience are countries and Ministers of Health/WHO</p>

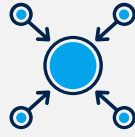
Post-2020 plan will provide unified vision and approach for vaccines and immunization, and support for country impact





How is the post-2020 plan being co-created?

Six principles are guiding development of post-2020 plan



Focus on countries

Country impact at center of plan development: focus on country ownership, implementability, and impact



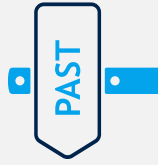
Think in novel ways; Engage broadly

Think creatively; engage more broadly: involve non-immunization partners in building plan



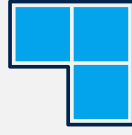
Be collaborative, while focused and practical

Collaborate with partners throughout process; generate lean, prioritized, focused, practical plan



Learn from the past

Learn lessons from GVAP 2011-20, especially on how to manage accountabilities and build effective partnerships



Build on the existing

Integrate with existing global health, partner, immunization and disease-specific strategies (UNICEF, Gavi, WHO, GPEI, M&RI, MNTE, etc.)

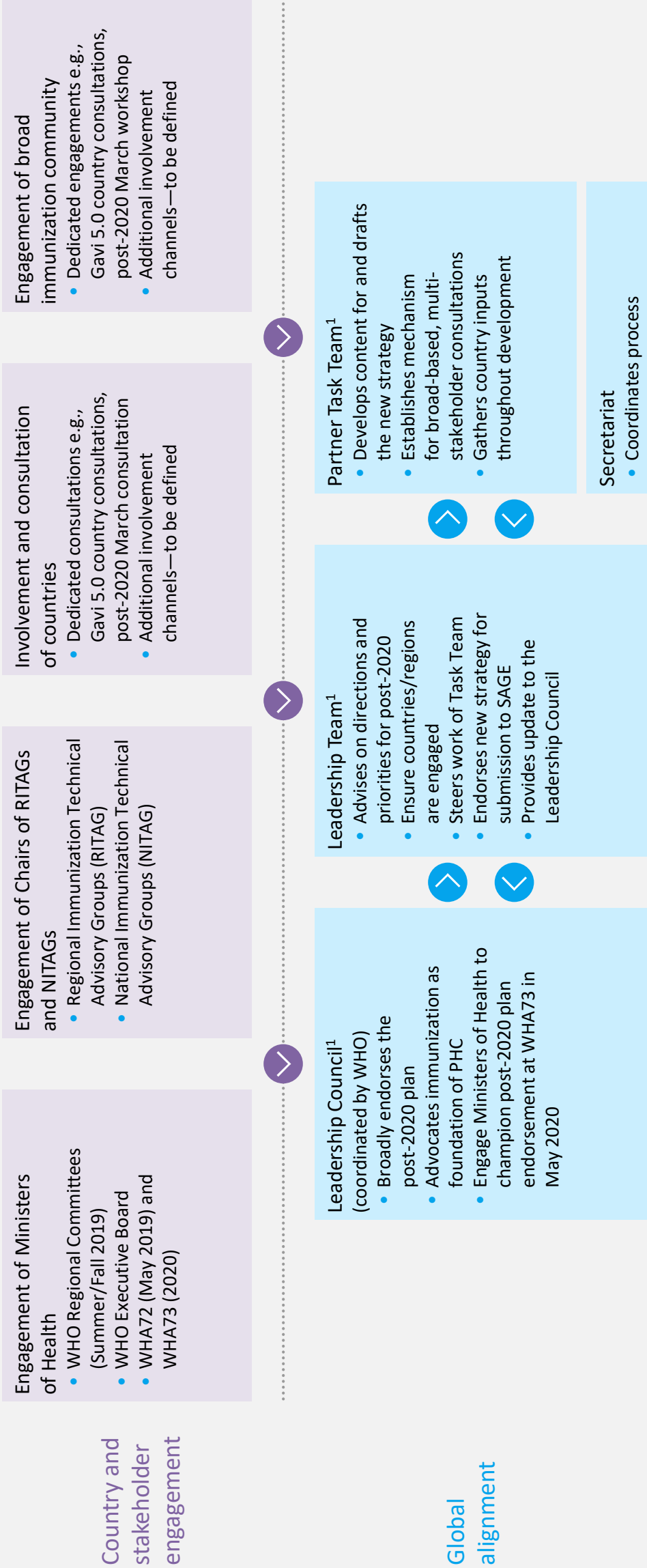


Advance broader health agendas

Lay out how next-generation immunization systems will contribute to and align with broad health agendas (SDG, UHC, PHC)

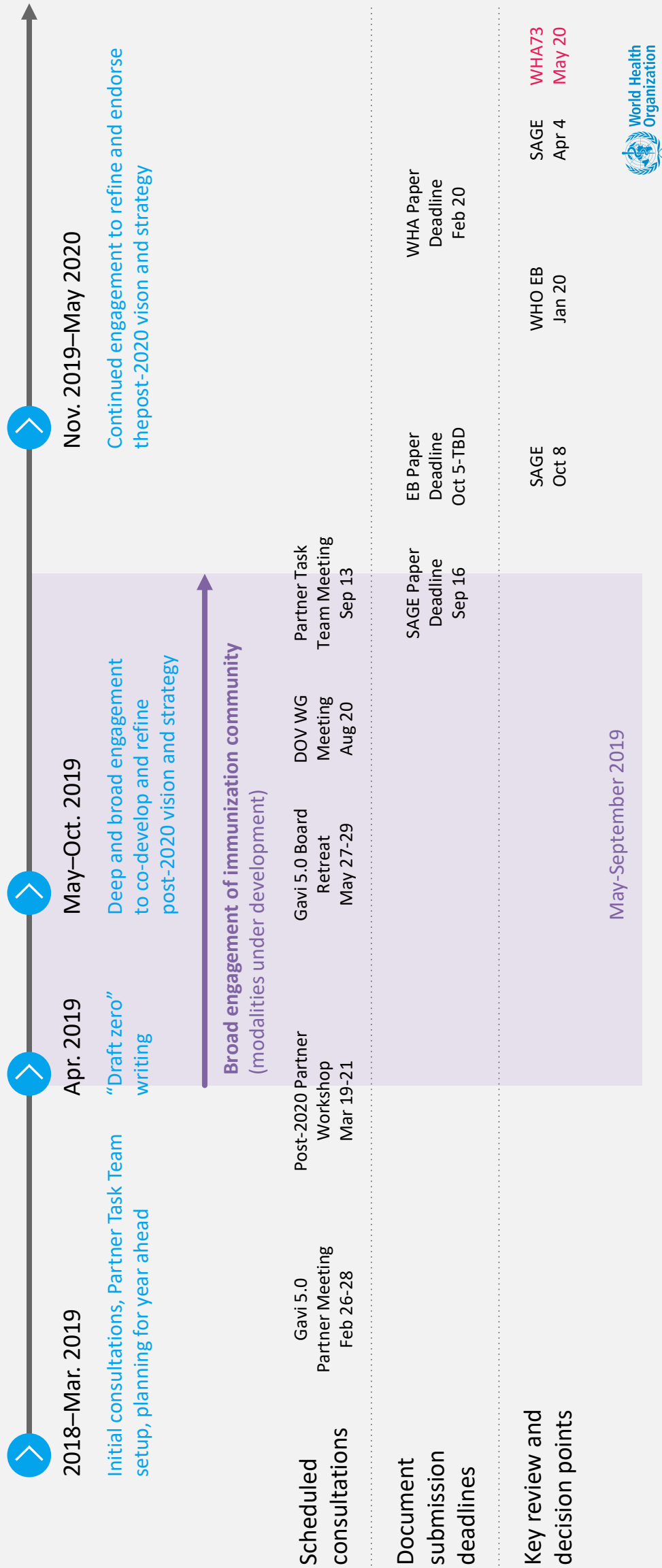
A holistic, representative and collaborative working structure propels the post-2020 plan

Country and stakeholder engagement



1. With initial representatives from CDC, CSO, BMGF, Gavi, GFF, NIH-NIAID, RITAG+, UNICEF, WHO, World Bank, others as needed

Deep and broad stakeholder engagement will enable co-creation of post-2020 vision and strategy ahead of WHA73





Creating a world in which epidemics are no longer a threat to humanity

Background

In a world characterized by increasing population density, human mobility, and ecological change, emerging infectious diseases (EIDs) pose a real and growing threat to global health security.

Epidemic diseases affect us all. They do not respect borders. If a highly contagious and lethal airborne pathogen with the characteristics of the 1918 Spanish Flu were to emerge today, it is estimated that nearly 33 million people worldwide would die in just 6 months.¹

The costs of EIDs are vast, in both human and economic terms. A report prepared by the National Academy of Science has estimated that over 10 years the global costs of epidemics could amount to \$600bn.² Even small epidemics can cause tremendous economic disruption.

The creation of CEPI

The global need for an organisation like CEPI was recognised after the devastating West African Ebola epidemic, which killed more than 11,000 people and had an economic and social burden of over \$53 billion.³

The world's response to this crisis fell tragically short. A vaccine that had been under development for more than a decade was not deployed until over a year into the epidemic. That vaccine was shown to be 100% effective, suggesting that much of the epidemic could have been prevented. It was evident that we needed a better system to speed the development of vaccines against known epidemic threats.

CEPI was launched at Davos, in 2017, by the governments of Norway and India, the Bill & Melinda Gates Foundation, the Wellcome Trust and the World Economic Forum, as the result of a consensus that a coordinated, international, and intergovernmental plan was needed to develop and deploy new vaccines to prevent future epidemics.

CEPI's mission is to stimulate and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks.

¹<http://www.idmod.org/news/node/296>

²<http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=21891>

³https://academic.oup.com/jid/article-abstract/218/suppl_5/S698/5129071

CEPI has three strategic objectives:

- **Preparedness** – Advance access to safe and effective vaccines against emerging infectious diseases
- **Response** – Accelerate the research, development and use of vaccines during outbreaks
- **Sustainability** – Create durable and equitable solutions for outbreak response capacity

Filling a critical gap in the vaccine ecosystem

Planning for EIDs is challenging: the R&D is complex, lengthy and expensive. The market potential for such vaccines is limited and testing such vaccines is difficult.

There are already many actors in the “end-to-end space” of vaccine funding and R&D implementation but a number of critical gaps have been identified, which CEPI was designed to fill (see *Figure 1.*):



Figure 1. CEPI’s role within the vaccine development pipeline.

- First, by advancing vaccines against known threats through proof of concept and safety testing in humans and establishing investigational stockpiles before epidemics begin — ‘just in case’.
- Second, by funding new and innovative platform technologies with the potential to accelerate the development and manufacture of vaccines against previously unknown pathogens (eg: 16 weeks from identification of antigen to product release for clinical trials)—‘just in time’.

- Third, by coordinating activities to improve our collective response to epidemics, strengthening capacity in countries at risk, and advancing the regulatory science that governs product development.

CEPI has moved quickly since launch

Moving from a start-up to an established global organisation

CEPI is headquartered in Oslo, Norway, and has offices in London, UK, and Washington DC in the United States.

A permanent Secretariat and CEO have been in place since 2017 and a new permanent governance structure has been implemented over the past year, establishing a more agile and independent Board, strengthening the Secretariat's executive role, adjusting the size and composition of the Scientific Advisory Committee, and focussing the activities of the Joint Coordination Group on CEPI's portfolio of vaccines.

Growing support from donors

CEPI was founded in Davos by the governments of Norway and India, the Bill & Melinda Gates Foundation, the Wellcome Trust, and the World Economic Forum.

As of March 2019, CEPI has secured over \$750 million toward its \$1 billion funding target, with financial support provided by the Bill & Melinda Gates Foundation, the Wellcome Trust, the European Commission, and the governments of Australia, Belgium, Canada, Germany, Japan, Norway and the UK (see *Table 1.*).

	Investment	Type of investment
European Commission	€ 200 m	Multi year
Japan	US\$ 125 m	Multi year
Norway	NOK 1.6 b	Multi year
Bill & Melinda Gates Foundation	US\$ 100 m	Multi year
Wellcome Trust	US\$ 100 m	Multi year
Germany	€90 m	Multi year
United Kingdom	£10 m	Single year

Canada	CA\$ 14 m	Multi year
Australia	AU\$ 6.5 m	Multi year
Belgium	€0.5 m	Single year

Table 1. CEPI's investors (as of March 2019)

CEPI offers a unique opportunity for our investors to lead on global health security and, in partnership with other governments and international organisations, invest in a solution that protects some of the most vulnerable people in the world while helping prevent the global spread of epidemics.

Calls for Proposals successfully announced

Since its launch, CEPI has announced three Calls for Proposals (CfP). The first CfP supports candidate vaccines against MERS-CoV and Nipah and Lassa viruses⁴. These were chosen from a priority list established by the WHO in its *R&D Blueprint for Action to Prevent Epidemics*.

The second CfP will advance rapid response platforms against unknown pathogens, known as Disease X⁵.

CEPI's third CfP, issued January 4, 2019, will support vaccines against Rift Valley fever and Chikungunya viruses⁶.

Partnership agreements launched

As of March 2019, CEPI has established eleven partnerships, reflecting a potential investment of up to \$350 million in 12 vaccine candidates (five against Lassa virus, four against MERS-CoV, three against Nipah virus) and three vaccine platforms to develop vaccines against Disease X. CEPI has a number of additional partnerships under negotiation (see *Table 2.* below).

⁴https://cepi.net/get_involved/cfps/

⁵https://cepi.net/get_involved/cfps/

⁶https://cepi.net/get_involved/cfps/

These partnership agreements represent just the start of CEPI's product development portfolio.

Themis Bioscience	Lassa & MERS vaccines	Up to \$37.5m
Inovio Pharmaceuticals	Lassa & MERS vaccines	Up to \$56.0m
International AIDS Vaccine Initiative	Lassa vaccines	Up to \$54.9m
Profectus Biosciences, Emergent Biosolutions & PATH	Nipah vaccine	Up to \$25.0m
Profectus Biosciences, Emergent Biosolutions & PATH	Lassa vaccine	Up to \$36.0m
IDT Biologika	MERS vaccine	Up to \$36.0m
Janssen Vaccines & University of Oxford	MERS, Lassa and Nipah vaccines	Up to \$19.0m
University of Tokyo	Nipah vaccine	Up to \$31.0m
Imperial College London	saRNA platform (Rabies, Marburg, 'Flu)	Up to \$8.4m
University of Queensland	Molecular clamp platform (MERS, RSV, 'Flu)	Up to \$10.6m
CureVac	mRNA platform (Rabies, Yellow Fever, Lassa Fever)	Up to \$34.0m

Table 2. CEPI's portfolio (As of March 2019).

CEPI's focus on Ebola

In addition to our priority diseases (Lassa fever, MERS, Nipah, Disease X, Chikungunya and Rift Valley fever), CEPI is also working on Ebola. Our work on Ebola is guided by the following principles:

- Aim to achieve the overall goal of attaining licensure for two or more vaccines.
- Facilitate licensure through data collection and analysis needed by advancing scientific understanding of immune response and supporting novel or flexible approaches to authorization and licensure.
- Support clinical trials in affected countries including in an outbreak situation when they aim for licensure in certain risk groups and subpopulations, and advance or simplify delivery of vaccine in the field through vaccine-related innovation.
- Support a generalizable approach to sustainable manufacturing that includes Ebola vaccines.
- Not to exclusively fund the deployment or delivery of vaccine.

Vaccine Sciences

To address the critical knowledge gaps and tools needed for rational and accelerated vaccine development, and future access to a licensed product, CEPI has set up an enabling sciences programme. Epidemiological knowledge gaps critical for vaccine development and assessment of disease burden are addressed through projects in affected countries, and through collaboration with external partners CEPI ensures diagnostics validation, training and capacity strengthening is addressed.

To facilitate comparison of vaccine candidates and appropriate assays serving future licensing, CEPI has also established partnerships to develop biological standards and assays.

CEPI is dependent on the scientific community and product developers to reach its goals, and engagement of these groups are hence core to success.

Background

The polio eradication program in 2018/2019 has continued to strive for eradication of Wild Poliovirus Type 1 (WPV1) in endemic areas and control of outbreaks caused by circulating vaccine derived polioviruses (cVDPVs).

In 2018, 33 WPV1 cases were reported worldwide (21 in Afghanistan, 12 in Pakistan), compared to 22 in 2017 (14 in Afghanistan, 8 in Pakistan). As of 12 February 2019, 3 WPV1 cases have been reported this year (1 in Afghanistan, 2 in Pakistan). In addition to paralytic cases, there is continued detection of WPV1 through environmental surveillance (ES) in the Northern, Central and Southern corridors of transmission in Afghanistan and Pakistan. Genetic analysis of the isolates indicates that there are several independent chains of transmission persisting: there have been detections of 6 different genetic clusters since January 2018. In Nigeria, there have been no cases or environmental samples of WPV1 since September 2016. However, approximately 100,000 children remain inaccessible for vaccinations in Borno.

cVDPV outbreaks continued in several countries: 104 cases of cVDPV were reported in 2018. Of these, 20 cVDPV2 in the Democratic Republic of Congo (DRC), 34 cVDPV2 in Nigeria, 26 cVDPV1 in Papua New Guinea (PNG), 12 cVDPV in Somalia (5 cVDPV2, 6 cVDPV3 and 1 co-infection), 10 cVDPV2 in Niger, 1 cVDPV2 in Mozambique and 1 cVDPV1 in Indonesia. As of 12 February 2019, there have been no cases of cVDPV in 2019.

The remaining challenges to final eradication and cVDPV2 control are:

- In Pakistan, the program is struggling to implement key National Emergency Action Plan (NEAP) priorities and TAG recommendations, related to regular oversight functions (regular meetings of provincial task forces and PM Focus Group) and creating an enabling environment for the program (national and international staff do not have visa/clearance to enter the country or access certain high-risk areas).
- In Afghanistan, the main challenge is accessibility in Kandahar and part of Gazni, where for over a year there has been a ban on house-to-house campaigns in Taliban controlled areas.
- In Nigeria, there is hesitance to using mOPV2 in outbreak response, due to the risk of seeding VDPV2. However, this may be leading to poor quality response and campaign coverage.
- In DRC, there are concomitant outbreaks of cholera and Ebola. This has resulted in reduced government commitment to responding to VDPV2 outbreaks and presents a risk of poliovirus spread to neighbouring countries.

Polio Eradication, Integration and Certification: The Endgame Strategy 2019-2023 was finalized and will provide high-level guidance for the global program in the next five years. This new strategy comprises three themes:

1. Eradication: Stopping transmission of the wild poliovirus and preventing, detecting, and responding to outbreaks.
2. Integration: Collaborating with immunization and emergency partners to eradicate polio and to protect populations.
3. Certification: Certify eradication and containment of all WPVs and ensure long-term polio security.

Purpose of the session and summary

This session will consist of three presentations: (1) global epidemiological overview including presentation of the main areas from the new polio endgame strategy, (2) brief introduction to the guidelines for surveillance of vaccine derived poliovirus among persons with primary immune deficiencies; and (3) report from deliberations of SAGE Polio Working Group.

For this SAGE meeting, there is one item for endorsement: Guidelines for Implementing Poliovirus Surveillance among Patients with Primary Immunodeficiency Disorders (PIDs). These guidelines were designed to initiate more systematic surveillance especially for non-paralyzed long-term poliovirus excretors among PID persons. These guidelines are based on SAGE's recommendation from October 2016: "SAGE agreed with the Polio Working Group's assessment that immunodeficiency-related vaccine-derived polioviruses (iVDPV) could constitute a risk of seeding communities and triggering outbreaks. SAGE endorsed the proposed approach to expand AFP surveillance to detect more iVDPVs by screening suspected primary immunodeficiency patients for poliovirus excretion."

In addition, 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.

Background documents in the yellow book

- Report from meeting of SAGE WG on polio (held on February 12-13, 2019)
 - This report provides summary of the deliberations of the SAGE Working Group
- Draft "Guidelines for Implementing Poliovirus Surveillance among Patients with Primary Immunodeficiency Disorders (PIDs)" for endorsement
 - The guidelines are designed to supplement the current AFP and environmental poliovirus surveillance systems to help identify all poliovirus excretors and thus achieve and maintain eradication of all polioviruses. They are provided for country teams, mid-level managers, and surveillance staff at all levels.

Background documents on the web

- None

12-13 February
Geneva

2019

17th Meeting of the SAGE Polio Working Group

Conclusions and recommendations

Note for the Record



World Health
Organization

Background

The 17th face-to-face meeting of the SAGE Polio Working Group (WG) was held on 12-13 February, 2019 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.

Context and topics

Expected outcomes of the meeting:

1. To review the GPEI programme update, including the WPV and VDPV epidemiology and overview of the Polio Eradication, Certification, and Integration: The Endgame Strategy 2019-2023
2. To take note of the new scheme for certification of polio eradication proposed by the Global Certification Commission in October 2018
3. To further discuss “readiness criteria” for bOPV withdrawal including whether the withdrawal of poliovirus type 3 from bOPV should be considered and, if so, the timing and pre-conditions for such withdrawal
4. To review and endorse guidelines for surveillance of VDPVs among persons with primary immunodeficiency (iVDPV surveillance)
5. To note the current version of the previously reviewed Containment Breach Protocol currently put out for public comment

Minutes of the meeting

Programme update

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

In 2018, 33 WPV1 cases were reported worldwide (21 in Afghanistan, 12 in Pakistan), compared to 22 in 2017 (14 in Afghanistan, 8 in Pakistan). As of 12 February 2019, 3 WPV1 cases have been reported this year (1 in Afghanistan, 2 in Pakistan).

In addition to paralytic cases, there is continued detection of WPV1 through environmental surveillance (ES) in the Northern, Central and Southern corridors of transmission in Afghanistan and Pakistan. Genetic analysis of the isolates indicates that there are several independent chains of transmission persisting: there have been detections of 6 different genetic clusters since January 2018. In Nigeria, there have been no cases or environmental

samples of WPV1 since September 2016. However, approximately 100,000 children remain inaccessible for vaccinations in Borno.

Regarding cVDPV, 104 cases of cVDPV were reported in 2018: 20 cVDPV2 in the Democratic Republic of Congo (DRC), 34 cVDPV2 in Nigeria, 26 cVDPV1 in Papua New Guinea (PNG), 12 cVDPV in Somalia (5 cVDPV2, 6 cVDPV3 and 1 co-infection), 10 cVDPV2 in Niger, 1 cVDPV2 in Mozambique and 1 cVDPV1 in Indonesia. As of 12 February 2019, there have been no cases of cVDPV in 2019.

The WG was updated regarding ongoing challenges to achieving interruption of transmission in endemic and outbreak countries, specifically:

- In Pakistan, the program is struggling to implement key National Emergency Action Plan (NEAP) priorities and TAG recommendations, related to regular oversight functions (regular meetings of provincial task forces and PM Focus Group) and creating an enabling environment for the program (national and international staff do not have visa/clearance to enter the country or access certain high-risk areas).
- In Afghanistan, the main challenge is accessibility in Kandahar and part of Gazni, where for over a year there has been a ban on house-to-house campaigns in Taliban controlled areas.
- In Nigeria, there is hesitance to using mOPV2 in outbreak response, due to the risk of seeding VDPV2. However, this may be leading to poor quality response and campaign coverage.
- In DRC, there are concomitant outbreaks of cholera and Ebola. This has resulted in reduced government commitment to responding to VDPV2 outbreaks and presents a risk of poliovirus spread to neighbouring countries.

Lastly, an update was provided on the development of Polio Eradication, Integration and Certification: The Endgame Strategy 2019-2023. This new strategy comprises three themes:

1. Eradication: Stopping transmission of the wild poliovirus and preventing, detecting, and responding to outbreaks.
2. Integration: Collaborating with immunization and emergency partners to eradicate polio and to protect populations.
3. Certification: Certify eradication and containment of all WPVs and ensure long-term polio security.

WG decisions/recommendations

- The SAGE WG emphasised that country ownership and achieving high routine immunisation coverage is essential to stopping poliovirus transmission and sustaining interruption. This will require collaboration with Gavi, the Vaccine Alliance and the Expanded Programme on Immunization (EPI) for all high-risk countries.

- The WG acknowledged the continued efforts of GPEI staff in Afghanistan and Pakistan. However, concern was expressed over the lack of progress to interrupt WPV1 in the active corridors of transmission, illustrated by continued detection of several independent genetic lineages of WPV1. The WG highlighted that the circulation of several lineages indicates that for each lineage there is a sufficient pool of susceptible individuals to sustain transmission, and a reduction in number of lineages is usually seen prior to interruption.
- The WG recommended that WHO leadership at the highest-level supports country staff in Afghanistan and Pakistan to operate on an emergency basis. This includes work to overcome operational barriers such as the access of staff to security high risk areas.
- The SAGE WG acknowledged that the development of a proactive GPEI hub in the EMRO region in Amman, Jordan could relieve pressure on the staff operating in these areas.
- The WG expressed concern over the persistence of cVDPV2 outbreaks, with emphasis on the situation in Nigeria and DRC. The WG highlighted the importance of country commitment to conduct a rapid outbreak response and emphasised that mOPV2 is the only tool currently available to prevent spread of cVDPV2.
- The SAGE WG recommends a rapid and high-quality outbreak response with mOPV2 to all cVDPV2 outbreaks.
- The WG recommended WHO to support the recommendations of the independent monitoring board (IMB) and external reviews and that these are incorporated into the GPEI strategy.

IPV Supply and mOPV stockpile updates

The SAGE WG was presented with an update on the IPV, bOPV and mOPV2 supply and stockpile outlook. Due to the IPV supply shortage, 33 countries procuring IPV vaccines through UNICEF were unable to access IPV supply following the switch from tOPV to bOPV in April 2016. As of February 2019, 31 out of 33 countries have reintroduced at least one dose of IPV into their routine immunization, with Mongolia and Zimbabwe planning for introduction later in 2019.

Available IPV doses in 2019, projected around 78 million doses (Mds), have been allocated based on programmatic prioritisation: 61 Mds allocated to routine immunization requirements; 6Mds allocated to endemic countries for accelerating interruption of transmission of WPV1 (Afghanistan, Pakistan and Nigeria); 5.2Mds allocated to catch up campaigns (in Angola, Sudan and Liberia); and 6Mds yet to be allocated. Future projections indicate there will be sufficient IPV supply for the introduction of 2 doses in all countries

procuring through UNICEF countries by 2022 and to catch-up children that had been missed due to the supply shortage in 2020/2021 (requiring 43Mds).

Countries that are self-procuring IPV, such as China and India, and countries procuring through the PAHO Revolving Fund continue to have access to at least one dose of IPV.

As of February 2019, the current mOPV2 stockpile is at 31Mds, with a pending request from Nigeria for 3Mds. Over 2019, the current forecast projects a utilization of 62Mds and incoming supplies of 100Mds, which would in theory result in ~70Mds in the stockpile at the end of 2019. However, this prediction is highly sensitive to additional needs for mOPV2 to respond to cVDPV2 outbreaks. The stockpile is under close and ongoing review by GPEI.

WG decisions/recommendations

- The SAGE WG welcomed the update that every country, except Zimbabwe and Mongolia, which are planning to introduce IPV in April 2019, have now introduced at least one dose of IPV into routine immunization.
- The SAGE WG emphasised the importance of all countries achieving high routine immunization coverage with IPV.
- The SAGE WG further highlighted the need for timely organization of catch-up campaigns of the 43 million missed children that accumulated due to IPV supply shortage in lower risk countries.
 - However, the SAGE WG took note that current vaccine supply projections indicate that it is very unlikely that there will be sufficient vaccine to complete the vaccination of missed cohorts before 2020.
 - The SAGE WG emphasized that independently of when vaccine supplies are available for vaccination of missed cohorts, countries must conduct these catch-ups. Not vaccinating these children will represent a long-term risk for countries that should be avoided. It was acknowledged that in 2019 IPV has already been allocated for 3 countries to conduct catch-up campaigns.
- The SAGE WG recommends the gradual introduction of a 2nd IPV dose (either full IM or fractional ID) into routine immunization of all countries currently using only one dose as soon as supply becomes available.
- The SAGE WG re-iterated earlier statements on the adoption of fractional IPV. The clinical trial results of intramuscular administration of fIPV from Cuba were discussed and SAGE WG encouraged additional data to be generated from another setting.
- The SAGE WG was concerned about the limited availability of mOPV2 in finished form during the 2019 calendar year.

Presentation of sequential certification for polio eradication

An update from the Global Certification Committee (GCC) meeting in October 2018 was provided to SAGE. The GCC recommended to the Director General of WHO that a sequential approach to global certification be adopted, with WPV3 certification to take place as soon as appropriate in 2019 or 2020, and independently of WPV1 certification. Between WPV3 and WPV1 global certification, the absence of cVDPV3 could be verified. The GCC also advised that the eradication programme should conduct a comprehensive review of the programmatic implications of sequential certification.

The SAGE WG was presented with the epidemiology of WPV3, which has not been detected globally since November 2012. The Americas, European, South-East Asian and Western-Pacific regional certification committees (RCC) have certified elimination of WPV3. The last reported case of WPV3 was in the African region, isolated from an infant aged 11 months in Yobe, Nigeria, who had onset of paralysis on November 10, 2012 and the last environmental WPV3 isolate was from a sample collected in Lagos, Nigeria, on November 11, 2012. The SAGE WG were notified that the African region is planning to certify elimination of all WPV by late 2019 or early 2020.

The GPEI director, Michel Zaffran, requested members of the SAGE WG to discuss the implications of the timing of the certification of WPV3 eradication. Concerns have been expressed from the Eastern Mediterranean and African regions that the certification of eradication of WPV3 may send confusing messages to the countries and the public and be detrimental to intensified activities that are on-going in these regions. In the African region, the programme is putting pressure on countries to strengthen surveillance, moving towards regional certification of all WPV. In Pakistan and Afghanistan, the programme is trying to intensify efforts to interrupt transmission of WPV1 in the middle of the low season.

WG decisions/recommendations

- The SAGE WG agreed that WPV3 certification should proceed in a timely manner and be celebrated as a global achievement.
- It was suggested that WPV3 certification should only proceed once AFRO and EMRO regions can communicate this milestone without negatively impacting the performance of country programme. This requires a clear, effective communication plan to be developed.
- The SAGE WG emphasised that WPV3 certification should not necessarily be dependent upon - or combined with - certification of all WPV in the African region.

Update of public comments on Containment Breach Protocol

The SAGE WG were provided with the revised guidance document “Public Health Management of Facility-Based Exposure to Live Polioviruses - Guidance in managing exposed persons for countries hosting facilities that maintain live polioviruses”. The original draft protocol was reviewed by the SAGE WG in September 2018, the GCC in October 2018 and the WHO public health ethics committee. The revised document will be uploaded to GPLN containment page as interim guidance for a period of public comments and the final version will be presented to full SAGE in October 2019.

WG decisions/recommendations

- The SAGE WG acknowledged the progress made with the Containment Breach Protocol and were comfortable with the revised protocol.

Proposed criteria for OPV2 restart

Since the tOPV to bOPV switch in April 2016, VDPV2 incidence and emergencies have been higher than expected. Persistent transmission of cVDPV2 has resulted in multiple mOPV2 campaigns to control outbreaks, which has likely seeded the emergence of new VDPV2 events and outbreaks. In the context of declining mucosal immunity against poliovirus serotype 2, it was proposed that the GPEI programme evaluate what criteria would need to be met to request restart of OPV2 containing vaccine in routine immunization and campaigns.

There are several possibilities for vaccination schedule, such as re-introduction of tOPV or mOPV2 into routine immunization or supplementary immunization campaigns (SIAs), which could be on a sub-regional, regional or global scale. Example criteria were suggested, including: disease criteria, such as a higher incidence of VDPV2 after tOPV withdrawal, relative to before; epidemiologic criteria, such as endemic cVDPV2, expansive geographic spread or new cVDPV2(s) seeded outside of a response zone; and vaccine / stockpile criteria, such as depletion of (finished) stockpile or failure of nOPV2 development.

The UNICEF Supply Division provided input on the timeline that would be required for tOPV restart from a vaccine manufacturing perspective. Initially, the vaccine bulk would need to be prepared, which would take around 8 months and necessitate containment requirements to be waived. As there would be a sole bulk producer globally, this would put a limit on production. After the bulk vaccine is available, there would be need for vaccine fill/finish, testing and application for licensure. Therefore, advance notification and preparation would be critical with the entire process likely to take about three years, under the assumption that OPV is still in production.

WG decisions/recommendations

- The SAGE WG agreed that discussions on restart criteria are important and should be on the agenda for the next SAGE WG meetings.
- The SAGE WG acknowledged the points made by the UNICEF Supply Division that the re-introduction of OPV2 would require advance preparation of several years to produce the vaccine and achieve testing.
- Members of the SAGE WG emphasized that due to the shortage of IPV supplies, IPV-only vaccination with high coverage has not yet been fully examined as a strategy for eliminating transmission.

Guidelines for Implementing Poliovirus Surveillance among Patients with Primary Immunodeficiency Disorders (PIDs)

SAGE in its meeting in October 2016 recommended that GPEI establishes surveillance capable of detecting iVDPV excretors among PID patients, especially those PID patients that do not present with paralysis. To that end, a working group on iVDPV surveillance has been established and its first task was to develop guidelines to provide clear, concrete instructions to introduce and conduct surveillance for poliovirus among patients diagnosed with primary immune deficiency.

The epidemiology of iVDPV patients was presented to the WG followed by an overview of the proposed guidelines. The SAGE WG was asked to review the guidelines in advance of the meeting and provide comments with the objective to submit the draft to the full SAGE for review and endorsement.

WG decisions/recommendations:

- The SAGE WG acknowledged that iVDPV cases will continue to present a challenge after WPV eradication and therefore it is important to continue understanding the burden of iVDPV excretion and having the ability to identify these cases.
- The SAGE WG provided feedback on the guidelines and suggested revisions:
 - The guidelines should clearly emphasize that PID children and their close contacts should never receive OPV;
 - The guidelines should expand and provide more details regarding how to conduct community investigations around iVDPV cases;
 - The potential of survival of PID individuals in low-income countries should not be ignored, due to availability of private healthcare in some areas.
- The SAGE WG recommended that after the suggested revisions are made, the guidelines will go to full SAGE for review and endorsement.

Readiness criteria for bOPV withdrawal

The presentation discussed the readiness criteria for bOPV withdrawal that were outlined by SAGE in September 2018 and how the criteria could be defined as successfully met. The readiness criteria recommended by SAGE in September 2018 were:

1. Adequate population immunity, especially in high-risk communities
2. No persistent cVDPV1 or cVDPV3 circulation (circulation beyond the 6 months after first notification)
3. Availability of sufficient IPV supplies for all countries to adopt a two IPV dose schedule (either IM or ID)
4. Established Primary Immunodeficiency Disorder (PID) surveillance
5. Therapeutic options for clearing infections among iVDPV excretors are available

A potential additional criterion was suggested as:

6. Progress toward nOPV1 and/or nOPV3 vaccine development.

WG decisions/recommendations:

- The SAGE WG agreed that the current criteria need refining to provide specific and objectively measurable definitions. It was highlighted that measuring and defining adequate population immunity would need the most substantial analysis.
- The SAGE WG agreed that refining criteria should be on the agenda of upcoming SAGE Polio WG meetings, with a presentation and discussion for each of the criteria.
- Some members of the SAGE WG suggested criteria could be classified into two groups: essential criteria and preferable criteria, with the latter being desirable not absolutely critical to achieve before bOPV withdrawal can proceed.
- The SAGE WG did not agree that progress towards nOPV1 and/or nOPV3 vaccine development should be an essential criterion for bOPV withdrawal; however, it could be a preferable criterion.
- The SAGE WG agreed that the criteria for removal of OPV3 and OPV1 may differ, and this would need to be defined if the programme decided to withdraw sequentially.

Weighing PROs and CONs of a withdrawal of poliovirus type 3 from bOPV

An evaluation of the epidemiology of vaccine-associated paralytic poliomyelitis (VAPP) and VDPV caused by type 3 was provided to SAGE WG. AFP data from India demonstrates the proportion of VAPP cases associated with PV3 (either as mixture with PV1 or exclusively) was 42% between July and December 2015 and 49% between July and December 2016. As the global pre-switch burden in OPV using countries was estimated at 400 cases/year, approximately 130 VAPP cases are likely associated with PV3 worldwide every year and could be averted through removal of OPV3. However other measures, such as introduction

of IPV into the immunization schedule at an early age, may provide protection against VAPP including type 3 associated VAPP.

The WHO Expanded Programme on Immunization (EPI) provided the logistical and programmatic dimensions of a bOPV to mOPV1 switch. The gargantuan efforts from all levels of GPEI partners, regional offices, in-country partners and Ministries of Health to conduct the tOPV to bOPV switch in 2016 was described together with the lessons learnt from this effort. Concerns were expressed over the political leverage it would require to motivate and mobilise countries to conduct the removal of type 3 OPV as an interim step prior to full withdrawal, as this added step may divert resources and attention at a critical time for GPEI and may negatively impact the final quality of OPV cessation.

The implications on vaccine supply and licensing were outlined by the UNICEF Supply Division. Currently, there are supply commitments for bOPV of 4 billion doses on contract; therefore, a switch would ideally take place during 2022 to allow full utilization of this supply. A switch to mOPV1 before 2022 would require negotiations and cancellations of existing contracts and potential financial compensation. A budget will be necessary to secure bOPV production in the final stages, including residual stocks at the time of the switch and a budget for an mOPV3 stockpile.

WG decisions/recommendations:

- The SAGE WG agreed that there is an imperative to avert unnecessary cases of paralytic disease due to vaccine poliovirus. However, the SAGE WG also acknowledged the “gargantuan” task to implement a switch from bOPV to mOPV1, especially considering a possible final switch looming on the horizon. SAGE WG agreed that the missed opportunity to secure wild virus eradication may in the end result in more children being paralyzed because of the resources being diverted for type 3 withdrawal.
- The SAGE WG agreed that the current priorities for GPEI are to stop transmission of WPV1 in endemic countries and to stop persistent cVDPV2 outbreaks. Therefore, SAGE WG concluded that the removal of OPV3 in the current landscape should not be considered due to the substantial time and resources it would require that would disrupt focus on the above priorities and a resulting lost opportunity to concentrate on WPV eradication in the first place.
- The SAGE WG also discussed with no firm conclusion that there are several options for implementing a change from bOPV to mOPV1, should this be considered, including a gradual product replacement of bOPV to mOPV1 into routine immunization over a pre-defined time-period, on a sub-regional or regional level, rather than globally synchronised however the potential risk of this approach regarding emergences of cVDPV3 would need to be understood

- The SAGE WG suggested that an in-depth review of the epidemiological data, and the logistical and political considerations involved are conducted to guide future decision-making and communications strategy.
- The SAGE WG agreed to revisit this topic on a regular basis as the programmatic situation evolves.

Assessing the risk of poliovirus circulation and the role of OPV preventive SIAs pre-cessation

This presentation was to provide the SAGE WG with an updated analysis of the impact of preventative SIAs and did not require decision or recommendations from SAGE WG. Current risk assessments have largely identified the same countries at high and medium-high risk over time. The risk-assessment task team (RATT) focus is on a national scale, while the true risk and SIAs are subnational. Future preventive SIAs have been planned as per SAGE recommendation, with the emphasis on cVDPV prevention. The scope of GPEI-funded preventive SIAs will not increase in the pre-cessation period, but the risk remains of potential outbreaks in countries without preventive SIAs.

ANNEX 1: Agenda

ANNEX 2: List of Participants



World Health Organization

17th Meeting of the SAGE Polio Working Group (WG)

M205, WHO, Geneva

February 12-13, 2019

AGENDA

Expected outcomes of the meeting:

1. To review the GPEI programme update, including the WPV and VDPV epidemiology and overview of the Polio Eradication, Certification, and Integration: The Endgame Strategy 2019-2023
2. To take note of the new scheme for certification of polio eradication proposed by the Global Certification Commission in October 2018
3. To further discuss “readiness criteria” for bOPV withdrawal including whether the withdrawal of poliovirus type 3 from bOPV should be considered as a first step and, if so, the timing and pre-conditions for such withdrawal
4. To review and endorse guidelines for surveillance of VDPVs among persons with primary immunodeficiency (iVDPV surveillance)
5. To note the current version of the previously reviewed Containment Breach Protocol currently put out for public comment

Day 1 (Feb 12)

09:00 - 09:15	Welcome and opening remarks	WG Chair
09:15 - 10:30	Programme update <ul style="list-style-type: none">• Progress toward interruption of WPV and cVDPV2• Progress with the other objectives of the Polio Eradication and Endgame strategic plan• Overview of the Polio Eradication, Certification, and Integration: The Endgame Strategy 2019-2023	M. Zaffran, WHO
10:30 – 11:00	IPV Supply update and update on mOPV stockpile	A. Ottosen , I. Lewis
11:00 – 11:30	Coffee break	
11:30 – 12:00	Presentation of sequential certification for polio eradication (update from GCC meeting)	G. Tallis

12:00 – 12:30	Update of public comments on Containment Breach Protocol	G. Tallis
12:30 – 13:30	Lunch	
13:30 – 14:30	Proposed criteria for tOPV restart (and discussion)	J. Modlin
14:30 – 15:30	iVDPV Surveillance:	
	<i>Presentation of draft guidelines for iVDPV surveillance</i>	O. Mach
	<i>Update on Antiviral development</i>	J. Modlin
15:30 – 16:00	Coffee break	
16:00 – 17:00	Discussions and wrap up of the day <i>(Working Dinner Restaurant: Cafe du Soleil, topic: “TBD”)</i>	

Day 2 (Feb 13)

9:00 – 10:30	“Readiness criteria” for bOPV withdrawal AND weighing PROs and CONs of a withdrawal of poliovirus type 3 from bOPV INCLUDING DISCUSSION	R. Sutter O. Mach, D. Chang-Blanc A. Ottosen
10:30 – 11:00	Coffee break	
11:00 – 11:30	Assessing the risk of poliovirus circulation and the role of OPV preventive SIAs pre-cessation	S. Wassilak
12:30 - 13:30	Lunch break	
13:30 - 16:00	Closed session: Finalizing WG recommendations (Coffee break at 15:30)	WG members & Secretariat

Background materials that will be shared with WG members at least 2 weeks prior to the meeting:

- Updated draft of the Containment Breach Protocol
- Draft iVDPV surveillance guidelines



World Health Organization

List of Participants
17th Meeting of the SAGE Polio Working Group
12 – 13 February 2018
WHO-HQ, Salle M205

Polio SAGE Working Group Members

Dr Ilesh Vinodrai Jani, co-chair National Institute of Health Mozambique	ilesh.jani@gmail.com
Prof J. Peter Figueroa, co-chair Professor, Public Health, Epidemiology & AIDS Department of Community Health & Psychiatry University of the West Indies Mona Kingston 7, Jamaica	peter.figueroa10@gmail.com
Dr Jean-Marc Olivé Chair of the Technical Advisory Group (TAG) Pakistan, Afghanistan, Horn of Africa & Lake Chad Basin	jmjolive@gmail.com
Dr Yagob Al-Mazrou, Secretary General Saudi Health Council Riyadh 12628 Saudi Arabia	yalmazrou@chs.gov.sa
Dr Jacob John Thekkekara Advisor, Christian Medical College Hospital 439 Civil Supplies Godown Lane Kamalakshipuram TN 632 002 Vellore India	tjacobjohn@yahoo.co.in
Dr Guillaume Chabot-Couture Director of research, global development Institute for Disease Modeling Seattle, WA USA	gcouture@idmod.org



<p>Dr Shelley Deeks Chief, Communicable Diseases, Emergency Preparedness and Response Public Health Ontario Toronto Canada</p>	<p>Shelley.deeks@oahpp.ca</p>
<p>Professor Jeffrey Mphahlele Vice President for Research South African Medical Research Council Pretoria South Africa</p>	<p>jeffrey.mphahlele@mrc.ac.za</p>
<p>Dr Khalequ Zaman Scientist and Epidemiologist International Centre for Diarrhoeal Disease Research, Bangladesh Dhaka Bangladesh</p>	<p>kzaman@icddr.org</p>
<p>Dr Nick Grassly Imperial College London St Mary's Campus, Norfolk Place London W2 1PG UK</p>	<p>n.grassly@imperial.ac.uk</p>
<p>Dr Walter Orenstein Associate Director Emory Vaccine Center Room 446, Dental School Building Mailstop 1370/004/1AD 1462 Clifton Road, NE Atlanta, USA</p>	<p>worenst@emory.edu</p>
<p>Dr Youngmee Jee – ON THE PHONE Director, Center for Infectious Disease Research NIH, Korea CDC Seoul Republic of Korea</p>	<p>jeey62@gmail.com</p>



External participants	
Stephen Sosler Technical Advisor GAVI Alliance Geneva, Switzerland	ssosler@gavi.org
Dr Steven Wassilak Global Immunization Division Centers for Disease Control and Prevention Atlanta, Georgia USA	sgw1@cdc.gov
John Modlin Deputy Director for Research, Polio Global Development Bill & Melinda Gates Foundation 500 Fifth Avenue, North Seattle, WA 98119 USA	john.modlin@gatesfoundation.org
UNICEF Secretariat	
Mr Ian Lewis Contracts Manager, Polio Unit Vaccine Center, UNICEF Supply Division 10-12 Oceanvej Copenhagen, Denmark	ilewis@unicef.org
Ms Ann Ottosen Contracts Manager Vaccine Center, UNICEF Supply Division Copenhagen, Denmark	aottosen@unicef.org
Dr Jalaa Abdelwahab Deputy Director, Polio Unit UNICEF New York, USA	jabdelwahab@unicef.org



WHO-HQ	
Mr Michel Zaffran Director, POL	zaffranm@who.int
Dr Roland Sutter Special Adviser to Director POL	sutterr@who.int
Dr Ondrej Mach Team Lead, POL/RPC/CTR	macho@who.int
Dr Daphne Moffett Technical Adviser, POL/RPC/CNT	moffettd@who.int
Dr Harish Verma Medical Officer, POL/RPC/CTR	vermah@who.int
Dr Carolyn Sein Technical Officer, POL/RPC/PAI	seinc@who.int
Dr Visalakshi Jeyaseelan Technical Officer, POL/RPC/CTR	jeyaseelanv@who.int
Dr Martin Eisenhower Technical Officer, POL/RPC/PAI	eisenhawerm@who.int
Dr Arshad Quddus Coordinator, POL/DAI	quddusa@who.int
Dr Vachagan Harutyunyan Team Lead, POL/DAI	harutyunyanv@who.int



Dr Graham Tallis Senior Scientific Advisor, POL/DAI	tallisg@who.int
Ms Tracey Goodman Manager FWC/IVB/EPI	goodmant@who.int
Mr Alejandro Ramirez Gonzalez Technical Officer, FWC/IVB/EPI	ramirezgonzaleza@who.int
Ms Diana Chang Blanc Manager FWC/IVB/EPI	changblancd@who.int
Ms Grace Macklin Rapporteur	grmacklin1gmail.com



GUIDELINES

for Implementing
Poliovirus Surveillance
among Patients with
**Primary
Immunodeficiency
Disorders (PIDs)**



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Acronyms and abbreviations

AFP	Acute flaccid paralysis
cVDPV	Circulating vaccine-derived poliovirus
CVID	Common variable immunodeficiency
EPI	Expanded Programme on Immunization
ES	Environmental surveillance
FUP	Follow-up
GPEI	Global Polio Eradication Initiative
GPLN	Global Polio Laboratory Network
HIV	Human immunodeficiency disease
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IHR	International Health Regulations
IPV	Inactivated poliovirus vaccine
iVDPV	Immunodeficiency-associated vaccine-derived poliovirus
L20B	Mouse transgenic cell line
MoH	Ministry of Health
NPEV	Non-polio enterovirus
OPV	Oral poliovirus vaccine
PID	Primary immunodeficiency disorder
RD	Rhabdomyosarcoma continuous cell line
RT-PCR	Reverse transcription polymerase chain reaction
SIA	Supplementary immunization activity
SL	Sabin-like
SL1	Sabin-like type 1
SL2	Sabin-like type 2
SL3	Sabin-like type 3
VAPP	Vaccine-associated paralytic poliomyelitis
VDPV	Vaccine-derived poliovirus
VDPV1	Vaccine-derived poliovirus type 1
VDPV2	Vaccine-derived poliovirus type 2
VDPV3	Vaccine-derived poliovirus type 3
VP1	Viral protein 1
WHO	World Health Organization
WPV	Wild poliovirus
WPV1	Wild poliovirus type 1
WPV2	Wild poliovirus type 2
WPV3	Wild poliovirus type 3

1 Introduction

The Global Polio Eradication Initiative (GPEI) owes its success to the effective use of the oral poliovirus vaccine (OPV) in routine immunization and supplemental immunization activities (SIAs). Unfortunately, in rare circumstances, the attenuated Sabin strains in OPV cause vaccine-associated paralytic poliomyelitis (VAPP) in the vaccine recipient or a close contact.¹ In addition, through prolonged replication in a single immunodeficient host or serial transmission in an under-vaccinated community, these attenuated polioviruses can regain the neurovirulence and transmission characteristics of wild poliovirus.² When this occurs, these polioviruses are referred to as vaccine-derived polioviruses (VDPVs).

VDPVs that have been established through community circulation in under-vaccinated populations are referred to as circulating vaccine-derived polioviruses (cVDPVs). These have become a fundamental concern for the programme, as they have been responsible for more than 900 poliomyelitis cases since their first description in 2001.³ Strengthening routine immunization systems is necessary to avoid an emergence of cVDPV. After community transmission has become established, interrupting cVDPV requires an implementation of outbreak response, including high-quality SIAs that reach every child in affected communities.

A far smaller but potentially serious problem is represented by VDPVs that evolve in patients with inherited primary immunodeficiency disorders (PIDs) following exposure to OPV viruses, referred to as immunodeficiency-related vaccine-derived polioviruses (iVDPVs).^{2,4} To mitigate the individual and community risks posed by iVDPVs during the polio endgame and the post-eradication era, it is important to identify those PID patients excreting polioviruses and provide the strategies and treatments available to rid both the individual and the community of the risk posed by iVDPVs.^{4,5} However, the current poliovirus surveillance systems are not well designed to identify non-paralyzed iVDPV-infected PID patients who may shed iVDPV for months or years before they become paralyzed or initiate community circulation. Acute flaccid paralysis (AFP) surveillance can only detect transmission through cases of paralysis, and although environmental surveillance can detect iVDPV shed by asymptomatic carriers, it is unable to identify the individual shedder.

The surveillance system proposed in these guidelines is designed to supplement the current AFP and environmental surveillance systems to help identify all poliovirus excretors and thus achieve and maintain eradication of all polioviruses. They are provided for country teams, mid-level managers, and surveillance staff at all levels.

2 Background and current epidemiology of iVDPVs

Primary immunodeficiency disorders (PIDs) represent a spectrum of genetically acquired disorders of the immune system.^{5,6} Individuals with PIDs affecting the B-cell system are at higher risk for developing VAPP upon receiving OPV or in close contact with someone recently vaccinated.⁷ In addition, because of their inability to mount an adequate humoral immune response, poliovirus intestinal replication and shedding may persist longer than the usual four to six weeks observed in healthy individuals.⁸ This prolonged intestinal replication can lead to the development of iVDPVs.⁹⁻¹² Although most individuals with PID clear poliovirus infection within six months, fewer than 5% excrete polioviruses for six months to five years (defined as prolonged infections), and a few may excrete vaccine strains for more than five years (chronic infections).

Between 1961 (the year OPV was introduced) and 2000, only 19 PID patients with prolonged/chronic excretion of poliovirus were reported and recorded in the WHO registry, most of whom lived in high-income countries. Between 2001 and 2018, 122 additional cases were reported, with a shift in prevalence to middle-income countries in the Middle East and Asia.^{2,6} The shift from high- to middle-income countries may be partly explained by the adoption of IPV in high-income countries and improvement in the survival of PID patients in OPV-using middle-income countries and in low income countries the possibility of increased survival of PIDs may be due to availability of private health facilities in some areas. Higher incidence of PID patients in countries with high prevalence of consanguineous marriages may also explain higher reports in certain Middle Eastern countries. Among the 141 PID patients excreting poliovirus identified between 1961 and 2018, 62.4% excreted type 2 poliovirus – and the most common PID associated with poliovirus excretion was severe combined immune deficiency. Only 22.2% of PID patients were prolonged excretors, and 1.6% were chronic excretors.

Multicountry studies searching for asymptomatic poliovirus excretors among ≈1200 individuals with PIDs found poliovirus excretion in ≈3%, with ≈1% excreting iVDPV.^{7,8} These and other studies also confirmed that prolonged poliovirus excretion is associated with severe B-cell or combined PIDs, such as common variable immunodeficiency (CVID) or severe combined immune deficiency. Individuals with partial immunoglobulin deficiencies or individuals with primary or secondary T-cell deficiencies, such as chronic HIV infection, clear poliovirus as efficiently as healthy individuals.⁹

In addition to the risk of developing paralytic poliomyelitis, individuals infected with iVDPV present the potential risk of initiating VDPV outbreaks. Community and household contact spread of iVDPV or Sabin strains shed by a PID patient has been rare to date with only two documented reports in 2005, among an Amish community with low immunization coverage in the U.S. and in Spain.^{10,11} However, the risk of community spread of iVDPVs may change with the reduction of population immunity expected after wild poliovirus (WPV) eradication and the improvement in healthcare enabling PID patients to survive longer in lower resource settings. Modeling analysis suggests that five to ten years following cessation of OPV use, asymptomatic long-term iVDPV excretors living in countries with poor sanitation (which raises the potential for intense fecal-oral transmission of poliovirus) pose a significant risk for the re-emergence of poliovirus circulation.⁴

3 Implementing polio surveillance among PID patients

3.1 - Objectives and types of surveillance

Objectives: To detect excretors of poliovirus among PID patients, to outline effective case management protocols, and to propose a public health response that reduces both the individual's risk of developing poliomyelitis and the community's risk of poliovirus transmission.

Type of surveillance: Both passive and active surveillance will need to be implemented due to the expected low incidence and prevalence of PID cases in each facility.

- *Passive surveillance:* Data and reports will be sent by designated health facilities. Such reporting will include immediate notification of confirmed PID cases, as well as ongoing periodic follow-up. A monthly report of zero cases will be submitted by the facility focal person.
- *Active surveillance:* A designated surveillance official, usually external to the health facility, will conduct visits at least quarterly. These visits will include interviews with physicians and support staff and reviews of registers, log books, or medical records to ensure that no reports/data are incomplete or missing. These visits to sentinel facilities are also used for sensitization and refresher training of facility staff.

3.2 - Steps to set up poliovirus surveillance among PID patients

The following steps are recommended for the initial implementation of polio surveillance for PIDs.

Initial steps for establishing poliovirus surveillance among PID patients

- Sensitize public health officials on the importance of poliovirus surveillance among PID patients, using results of the global risk assessment model and data from national registries from PID centers and referral systems for PID patients.
- Identify sentinel reporting sites using the criteria of being a referral health facility for diagnosis and treatment of patients with immunodeficiency disorders. Identify a focal point in each sentinel site, preferably a specialized physician.
- Adapt the general polio surveillance guidelines to country requirements.
 - Integrate PID surveillance with the other polio surveillance systems in the country: AFP, environmental, enterovirus, etc. To facilitate operations, define clear leadership for poliovirus surveillance among PIDs within the polio surveillance structure by designating a dedicated national focal person/team and facility focal points.
 - Develop country-specific guides for the management of PID patients with poliovirus excretion including access to immunoglobulin therapy and compassionate use of antiviral drugs.

Assigning roles and responsibilities for poliovirus surveillance among PID patients

At the sentinel reporting site

- Focal point (physician) at the sentinel site is the liaison with the surveillance staff and is responsible for case detection and immediate notification, coordination of investigation and follow-up at facility level, treatment of cases, and preparation and submission of monthly/zero reports.
- Physician(s) at the sentinel facilities to detect confirmed PID patients and initiate testing for poliovirus in coordination with the focal point.
- Administrative and health staff to support the submission of monthly zero reports, collection and shipment of specimens, and recording information into electronic database.

Surveillance officers (could be AFP surveillance officers at district and provincial levels)	<ol style="list-style-type: none"> 1) Conduct active surveillance visits to sentinel sites (every quarter) 2) Conduct notifications, investigations, and follow-ups of PIDs with specimens positive for Sabin or VDPV
National PID surveillance focal point/coordinator	<ul style="list-style-type: none"> • Coordinate surveillance activities, technical support, training, and supportive supervision • Maintain the national database, submitting case-based and aggregated reports to country surveillance authorities and the World Health Organization (WHO). • Be the liaison with AFP surveillance, laboratory, and environmental surveillance. • Coordinate response activities • With support of the regional level adapt the generic training material • Conduct training of surveillance staff and focal points of reporting sites as, well as orientation to physicians and support staff in identified sentinel sites. • Facilitate access to antiviral therapy
WHO Surveillance focal point/polio team at the regional level	<ul style="list-style-type: none"> • Conduct risk assessment and country prioritization for implementing poliovirus surveillance among PID patients • Provide technical support to country programmers regarding guidelines, planning, training, and evaluation activities • Provide data management support and maintain regional database • Coordinate laboratory services, response activities and facilitate access to therapy • Conduct fundraising activities to address financial gaps where required
WHO polio team at Global level	<ul style="list-style-type: none"> • Overall technical guidance and support • Conduct research and evaluation activities • Coordinate global laboratory activities • Maintain the global database • Liaise with Jeffrey Modell Foundation and immunologists network • Facilitate process of continued antiviral research and availability of and access to therapy • Avail funds to cover identified gaps
Staff in Global Polio Laboratory Network (GPLN)	<ul style="list-style-type: none"> • Test the specimens according to the GPLN protocols • Report results to the facility focal person and surveillance officer • Enter results in the polio laboratory database (Polio information system) • Report and send isolates that need further analysis to referral laboratories

3.3 - Role of the laboratory

The role of the laboratory is critical to the polio endgame generally and to PID surveillance specifically, as it is the laboratory that confirms the presence or absence of the virus in humans and the environment.

Patients who meet the case definition of PIDs at risk of excreting poliovirus will have their stool samples tested in one of the 164 WHO-accredited poliovirus laboratories in the Global Polio Laboratory Network (GPLN). Similar to AFP surveillance:

- Laboratory confirmation is based on isolation of poliovirus on monolayers of tissue culture cells (RD and L20B). Isolation of non-polio enterovirus (NPEV) is also possible and should be reported as a separate result.
- Intratypic differentiation is conducted by reverse transcriptase polymerase chain reaction (RT-PCR) to identify the virus as WPV, VDPV, or Sabin, as well as the virus serotype (1, 2, 3).

- Genetic sequencing helps monitor evolution of strains within the same patient (i.e., Sabin to VDPV, development of resistance to antivirals) and detects potential spread in the community by comparing the nucleotide sequence of the VP1-coding region of poliovirus isolates with poliovirus isolated in samples from healthy contacts or environmental surveillance. This information will guide the type and intensity of the public health response required.

4 Case detection

4.1 – PID patients at risk of poliovirus excretion

The purpose of the surveillance is to identify PID patients with poliovirus excretion before the virus paralyzes them and before they may initiate community transmission. The focal person and other physicians at the sentinel site will be responsible for identifying patients with a PID that is eligible for testing because of the associated risk for poliovirus excretion (as per case definition in Section 5).

The programme will identify two types of cases:

- Individuals previously diagnosed with a PID, who will be identified through retroactive search of national and facility registries.
- Individuals newly diagnosed with a PID known to be associated with prolonged poliovirus excretion, who will be screened for poliovirus excretion shortly after confirming the PID diagnosis.

The physician will notify the surveillance officer and complete and submit a notification form for “PID patient at risk of poliovirus excretion.”

What to do with identified PID patients?

- 1 Fill in a notification form and send to the surveillance officer.
- 2 Collect two (2) stool samples, 24 hours apart, fill out appropriate form, and ship to WHO-accredited laboratory.
- 3 Upon receipt of laboratory result, inform patients and any interested parties.
- 4 If results are positive, follow the protocol for detailed investigation and case management (section 6).
- 5 If results are negative, plan follow-up stool testing on an annual basis (or following exposure to OPV polioviruses).

The information reported in the notification form should include:

- Basic demographics (age, sex, area of residence, detailed contact information including address and phone number)
- PID diagnosis, if available (including results of quantitative immunoglobulin measurement)
- Presence or absence of symptoms that could be related to poliovirus infection (paresis, paralysis, meningitis, other)
- Type and dates of polio vaccination (OPV, IPV) and history of recent (<3 months) exposure to OPV from close contact (family member) or community (OPV campaign in the area)

The opportunity will be used to emphasize to the family that PID patients and their close contacts should never receive OPV

4.2 - Specimen collection from PID patients at risk of poliovirus excretion

The physician will initiate collection of stool specimens, ideally two stool specimens at least 24 hours apart; however, in some circumstances, it may not be feasible to collect more than one specimen. Support staff at the sentinel facility will ensure that collection of stool specimens and shipment to the poliovirus laboratory adhere to the established country requirements.

Specimen collection guidelines

Volume of stool	8–10 g, about the size of two adult thumbnails. This amount permits duplicate testing, if required.
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Storage and handling	Specimens should be placed in appropriate containers with a tight seal to ensure there is no leakage or possibility of desiccation. Specimen containers must be placed immediately in a designated cold box at 4–8°C between frozen ice packs. Specimens should arrive at a WHO-accredited laboratory within 72 hours of collection. If this is not possible, the specimens must be frozen at -20°C and then shipped frozen, preferably with dry ice or with cold packs that have also been frozen at -20°C.
Documentation	All specimens should reach the laboratory accompanied by a specimen collection form completed accurately and legibly. Laboratory forms must include variables pertinent for the laboratory staff to identify the patient; apprehend the reason for testing and type of testing required (i.e., first test in a PID patient or a follow up of a poliovirus shedder or previously tested PID patient with negative results); and communicate results to the required parties (focal point/physician in sentinel facility, surveillance officer, referral laboratory, and WHO).

5 Case definitions and case classification

5.1 – Case definition for PID patient at risk of excretion

The PID case at risk of poliovirus infection is an individual of any age who has a primary antibody disorder, humoral (B-cell) or combined humoral (B-cell) and cellular (T-cell) immunodeficiency disorder, confirmed for levels of immunoglobulin below standards for age.

Specific PIDs with known risk of prolonged poliovirus excretion are highlighted (see panel at right).

Because of the very low likelihood of prolonged poliovirus excretion,^{12,13} individuals with the following immunodeficiency disorders are not to be included and are not eligible for poliovirus testing in the absence of paralysis:

1. Isolated deficiencies of IgA or IgM, or IgE abnormality
2. Transitory or secondary immunodeficiency (i.e. related to infections including HIV, chronic illness, treatment with immunosuppressive therapy, etc.).

PIDs with known risk of prolonged poliovirus excretion

- Antibody disorder, including hypogammaglobulinemia, agammaglobulinemia, X-linked agammaglobulinemia, and other antibody deficiencies.
- Severe combined immunodeficiency disorder and other combined humoral and T-cell deficiencies.
- Common variable immunodeficiency disorder (CVID).
- Others, including major histocompatibility complex deficiencies or immunodeficiency-centromeric facial anomalies syndrome (ICF).

If paralysis is present at the time of PID diagnosis, the case should be reported as an AFP case to the polio surveillance officer and investigated according to AFP surveillance guidelines.⁶ At the same time, the case will also be included in the PID surveillance database for coordinated treatment, contact sampling and follow up.

5.2 - Case definition for PID patient with confirmed poliovirus excretion

For poliovirus surveillance among PID patients, a 'confirmed' case is a PID case at risk of prolonged poliovirus shedding – as per the definition above – whose stool specimen tested positive for poliovirus, including VDPV, WPV, or Sabin viruses.

5.3 - Classification based on laboratory results

Based upon the results of the testing, the final classification will be:

PID specimen classification	
PID with VDPV (i.e. iVDPV)	Refers to a PID patient with isolation of VDPV in stool specimen(s). Depending on the serotype, it will be iVDPV1, iVDPV2, or iVDPV3.
PID with WPV	Refers to PID patient with isolation of WPV in the stool specimen. Depending on the serotype, it will be WPV1, WPV2, or WPV3. (Note: Although this situation is possible, it is extremely unlikely).
PID with Sabin virus	Refers to a PID patient with isolation of Sabin-like poliovirus in stool specimen(s). Depending on the serotype, it will be SL1, SL2, or SL3.
PID negative for poliovirus	No poliovirus detected in the stool. It refers to a PID patient with no laboratory evidence of Sabin, VDPV, or WPV in an adequate stool specimen (see Section 4 for adequate specimen guidelines).

It should be noted that PID patients with poliovirus infection may progress from one classification to another. 'PID with Sabin' may progress to 'PID with VDPV,' and paralysis may also appear in any individual with asymptomatic infection by Sabin or VDPV strains.

PID Patients with AFP

PID patients who develop paralysis during follow-up will have stools tested for poliovirus as soon as possible after paralysis onset, with their case classification determined per AFP guidelines.^{15,16}

The PID surveillance system will record those patients for follow up and treatment.

- **Vaccine-Associated Paralytic Poliomyelitis (VAPP) case** – PID patient with AFP and isolation of Sabin-like poliovirus in a stool specimen with residual paralysis at 60 days and beyond, for whom the Expert Review Committee excluded other causes of AFP based on additional neurological examinations.
- **iVDPV “paralytic” case** - PID patient with AFP and isolation of VDPV in a stool specimen.
- **Compatible case** - PID patient with AFP but inadequate specimens and no poliovirus isolation, who is classified by the Expert Review Committee as polio compatible. These individuals should go through a thorough evaluation to rule out other causes of AFP (including non-polio enterovirus [NPEV] infection).¹⁴

6 Case investigation & management

6.1 - Follow up and repeat sampling of PID patients at risk of poliovirus excretion

The following schedule of specimen collection for poliovirus testing is recommended:

- Initial poliovirus testing is recommended for every individual diagnosed with a PID associated with a risk of prolonged poliovirus excretion. This includes previously diagnosed and known (registered) PID patients, as well as newly diagnosed PID patients.
- Repeat testing for follow-up
 - Monthly: For PID patients with a specimen positive for SL, VDPV, or WPV as explained next under case investigation.
 - Annually: For PID patients with negative specimens.

6.2 - Detailed investigation for PID patients with confirmed poliovirus excretion

The surveillance officer, in coordination with staff from the sentinel facility, will conduct a case investigation for those PID patients with specimens positive for poliovirus, within 48 hours of receiving the laboratory results. The objectives of the investigation will be to assess the risk of poliovirus circulation in the surrounding community and to initiate case management and public health response.

The investigation should involve the collection of additional information from the patient, close family contacts, and surrounding community.

Investigation guidelines	
Patient	<ul style="list-style-type: none">○ Source of exposure of the PID patient to OPV, such as travel, visitors, routine immunization and immunization campaigns, based upon the estimated time of viral intestinal replication inferred from molecular analysis.○ Assess potential for patient initiating transmission into the community, such as attendance to daycare or school, admission into health facility or institution, and availability of sanitation infrastructure.
Close contacts	<ul style="list-style-type: none">○ Determine polio vaccination status.○ Assess medical history suggestive of immunodeficiency.○ Stool samples may be collected among close (family) contacts or community contacts of a PID patient with shedding of WPV, Sabin, or VDPV. The surveillance officer(s) conducting the case investigation will oversee organizing stool collection. The number of contacts and the type of contacts to be sampled will follow the guidelines for response to polio virus event/outbreak.^{8,9} Procedures for collection and transport of specimens are as explained above.
Community	<ul style="list-style-type: none">○ Assess polio vaccination status (IPV, OPV) especially among children younger than five years through community surveys and desk review of coverage data.○ Assess risk factors for fecal-oral transmission (high population density, inadequate sanitation and sewage infrastructure, etc.).○ Active search for AFP cases in health facilities and community.

6.3 - Case management and public health response

The case management and scope of public health response will depend on the type of poliovirus isolated, the sequencing data, and the presence of risk factors for community transmission.

Public health response guidelines	
PID patient positive for Sabin-like poliovirus	
If Sabin types 1 or 3 are isolated	Repeat specimen testing monthly to monitor clearance of infection or progression to iVDPV. Confirm clearance of poliovirus infection by obtaining two negative specimens separated at least by one month. In addition, initiate discussions with surveillance and public health officials to plan potential treatment with antivirals.
If Sabin type 2 is isolated	Notify country public health authorities and WHO according to the International Health Regulations (IHR) Annex 2 (2005), initiate event investigation within 48 hours of laboratory confirmation of the results and plan specific public health response as explained in the guidelines. ⁸
PID patient positive for WPV, VDPV, or Sabin strains progressing to VDPV in serial samples	
<ul style="list-style-type: none"> Once the laboratory identifies WPV or VDPV in any stool sample, the Ministry of Health (MoH) should notify country public health authorities and WHO according to the IHR Annex 2 (2005). Local surveillance staff should initiate event investigation that includes enhanced polio surveillance activities and assessment of population immunity as explained above. 	
<ul style="list-style-type: none"> The public health response will depend on the detection of community circulation. 	
Any WPV isolation	Conduct outbreak response
VDPV	If there is evidence of circulation of this polio strain in the community (healthy community contacts or environmental samples), it will be considered an outbreak (cVDPV) and will require vaccination campaigns appropriately scaled depending on the community risk. (Please refer to guideline.)
	If there is no evidence of circulation of this poliovirus strain in the community, the response may consist of administration of IPV to household members and close community contacts. (Please refer to guideline.)

6.4 - Treatment

Treatment with antiviral drug therapy may be encouraged for PID patients in the following circumstances:

- Individual has VDPV isolated in any stool specimen
- Individual excreting Sabin strains for more than two months
- Individual excreting WPV

PID patients with prolonged NPEV infections may also benefit from antiviral treatment. At present, polio antivirals are not indicated for contacts potentially exposed to infection.

The immunologist or specialist physician attending the PID patient will coordinate with the surveillance officers and the appropriate regulatory and public health authorities for the decision-making process, follow-up with manufacturer, and implementation of procedures for treatment and follow-up.

Because polio antivirals are currently in development, access to the drug is under 'limited compassionate use.' Each sentinel facility conducting surveillance for PID patients with poliovirus excretion should coordinate with the central level (MoH) for preparation of necessary documentation and importation of antiviral drug(s) upon diagnosis of a new patient candidate to the treatment. Health staff will also follow a standardized protocol regarding drug dosage, schedule of administration and

follow-up poliovirus testing to both ensure the safety of the patient and assess the effectiveness of the treatment. Country-specific regulatory agencies, manufacturers, and public health officials should endorse the drug procurement plan and the administration protocol.

6.5 - Other management measures

All PID patients shedding poliovirus are expected to receive the following case management measures:

- Treatment for the PID and its complications, such as administration of intravenous immune globulin or bone marrow transplant, according to the type of PID and the country standard level of care.
- Counseling and education of the patient and family to avoid future receipt of live vaccines and ensure appropriate hand and toilet hygiene to prevent transmission of poliovirus to contacts.
- Polio vaccination of health staff using IPV and adherence to standard precautions for infection control in healthcare facilities or institutions where the PID patient may receive clinical care.
- Vaccinations of close contacts with IPV, if required (similar to the PID patient, close contacts should never receive OPV).

7 Data analysis and monitoring and evaluation

An important aspect of a successful polio eradication programme is a well-developed information system that provides programme managers and health workers with the necessary information to take appropriate actions.

Analysis of PID surveillance data is required for measuring the sensitivity and consistency of the surveillance system to ensure it is functioning at the desired level. Surveillance data is useful in the decision-making process in the following ways:

- Detecting and monitoring PID patients with prolonged excretion of poliovirus
- Treating infection and preventing the future development of patient paralysis and other adverse neurological outcomes
- Preventing the introduction and circulation of poliovirus excreted by the patient into the community
- Including the number and geographical location of excretors of Sabin/iVDPV in periodic country risk assessments of polio outbreaks

PID surveillance data should be reviewed quarterly at the national level to detect and quantify occurrence, assess changing patterns over time, determine risks for excretion, monitor progress, and evaluate the performance of the surveillance system itself.

7.1 - Information management

- The PID database will be a case-based data system included in the overall polio information system (POLIS). It will function as a registry with a unique identifier assigned to the patient upon diagnosis of PID (PID patient at risk of excreting PV) and allow for repeated specimen collection and changes in case status over time.
- The PID database will link with other polio data management systems such as:
 - *AFP case-based data*: A link between these two databases is essential. A case with confirmed poliovirus excretion and paralysis will need to be reported through the AFP surveillance system as well. Conversely, a PID cases detected through the AFP system will also be included in the PID database for management and follow-up.
 - *Environmental surveillance (ES) data system*: This system compares genetic sequences of VDPV from human and environmental sources to confirm or rule out community circulation of iVDPVs.
 - *Laboratory and polio nucleotide sequencing (PONS) databases*: All laboratory results are entered in those databases regardless of the source of the virus. Laboratory results from PID patients and sequencing data from isolated poliovirus will be recorded in these databases.

Main sources of the data:

- Case Investigation Form of “PID patients at risk of excreting poliovirus”
- Detailed Case Investigation Form of “PID patients with confirmed poliovirus excretion”
- Follow-up forms
- PID patient registry/ line list
- Completeness and timeliness of reporting units
- Active surveillance visit forms

7.2 - Suggested epidemiologic analysis

- Number of PID patients at risk of poliovirus excretion reported (and tested) by year, by sentinel facility, and by country
- Number of PID patients with negative poliovirus excretion, prolonged Sabin excretion (more than six months), asymptomatic iVDPV excretion, VAPP or iVDPV by sentinel facility, country, and year
- Spot maps of PID patients with poliovirus excretion by geographic area, country, and year
- Age and sex distribution of PID patients with prolonged Sabin excretion or iVDPV excretion
- Distribution of PID patients diagnosed with prolonged Sabin excretion or iVDPV excretion according to duration of shedding (prolonged versus chronic)
- Distribution of PID patients diagnosed with prolonged Sabin excretion or iVDPV excretion by PID diagnosis
- Percentage of PID individuals diagnosed with prolonged Sabin excretion or iVDPV excretion for whom a detailed investigation (contacts and community) was conducted
- Results of contact and/or environmental sampling conducted to investigate a PID patient with iVDPV excretion
- Percentage of PID patients with prolonged Sabin excretion or iVDPV excretion who received antiviral treatment
- Percentage of PID patients who cleared poliovirus excretion after antiviral treatment
- Percentage of PID patients with NPEV infection
- Outcome of cases (shedding, stop shedding, death, lost to follow-up)

7.3 - Performance indicators

Surveillance for poliovirus excretion among PID patients should be reviewed quarterly at polio eradication data review meetings, together with data from other polio surveillance systems (AFP, ES). The indicators in the table below should be reviewed at all levels at least every six months. Data should also be analyzed in conjunction with information provided by AFP and environmental surveillance in Annual Country Risk Assessments and reports of the National Committee for the Certification of Poliomyelitis.

Indicator	Target
Percentage of registered (previously diagnosed) PID patients who are tested for poliovirus excretion per sentinel facility/country. (Denominator should be national registry or facility registry of PID patients).	≥ 90%
Percentage of PID patients newly diagnosed (in the same year) tested for poliovirus excretion per sentinel facility/country. (Denominator should be national registry or facility registry of PID patients).	≥ 90%
Percentage of PID patients with poliovirus excretion for whom a detailed case investigation (with contact tracing and community assessment) is conducted within 48 hrs of laboratory results.	≥ 80%
Percentage of specimens arriving at a WHO-accredited laboratory in good condition	≥ 80%
Percentage of specimens arriving at a WHO-accredited laboratory within 3 days of collection	≥ 80%
Percentage of stool specimens for which laboratory results are sent to sentinel facility/submitting agencies within a defined period: - within 14 days of specimen receipt for poliovirus isolation - within 7 days of isolate receipt for intratypic differentiation - within 7 days of intratypic differentiation for sequencing results	≥ 80%
Percentage of follow-up specimens collected out of expected	≥ 80%
Number of active surveillance visits implemented out of planned	≥ 90%

Annex 1 - Recommended data elements

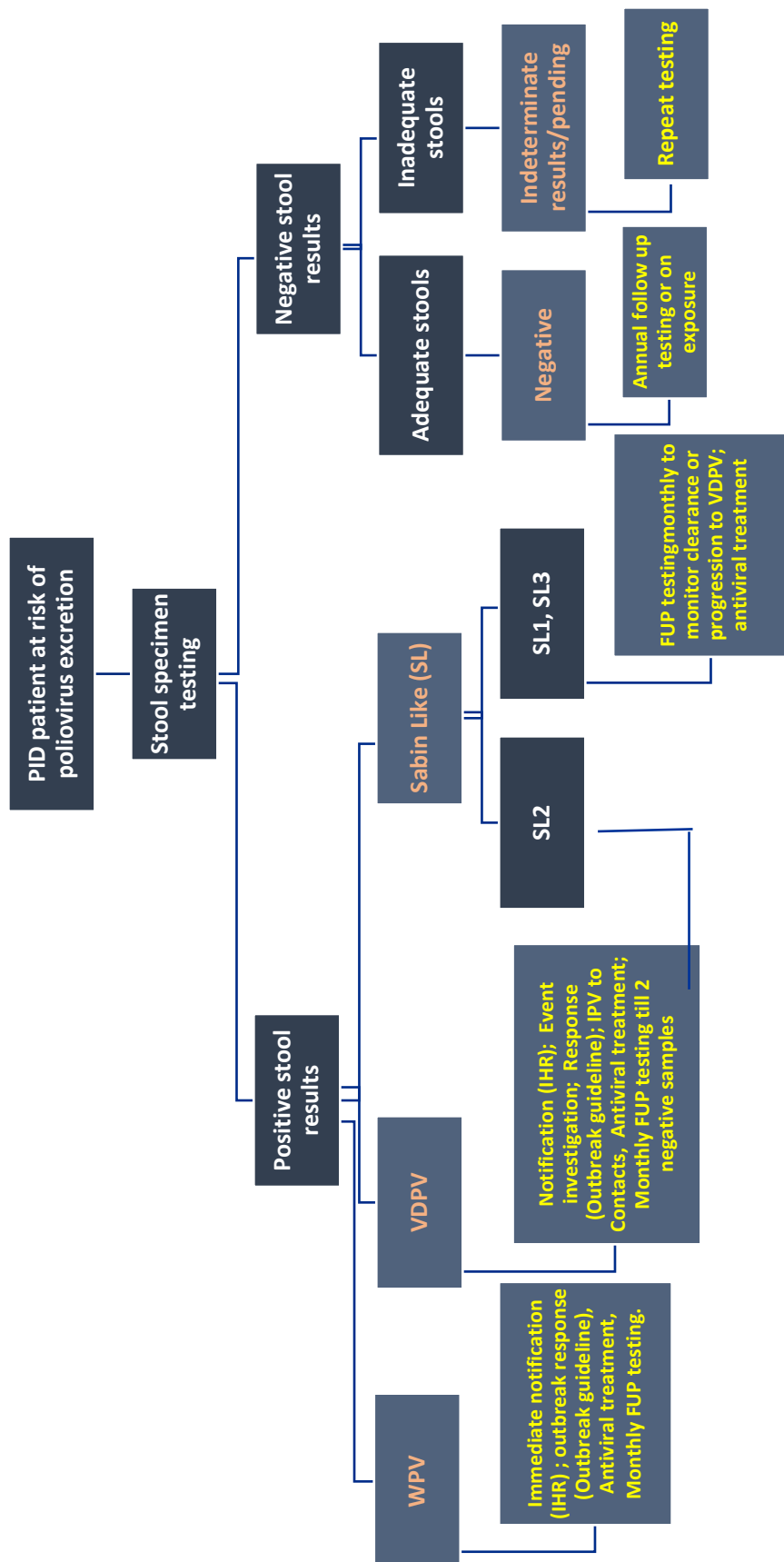
PID Case Investigation Form (Variables)

- Case identification
 - Unique Case Identifier PPD - Country Code - Province Code - District Code – Year – Case Number (PPD-XXX-XX-XX-XX-XXX)
 - First name (Patient)
 - Last name (Patient)
 - Parent or legal guardian's name
 - Physician name
 - Physician's phone number (Number)
 - Country
 - Province
 - District
 - Health facility name
 - Health facility address
- Demographics
 - Date of birth* (DD/MM/YYYY)
 - Age group at the time of investigation (number)
 - Sex (1=male; 2=female; 9=unknown)
 - Residence address (province, district, town/village, street, etc.)
 - Phone number
- Medical History
 - Date of first consultation with immunology centre (suspect PID) (DD/MM/YYYY)
 - Date of confirmation of PID diagnosis (DD/MM/YYYY)
 - PID diagnosis (1 – Severe Combined Immunodeficiency; 2 – Common Variable Immunodeficiency; 3 – Hypogammaglobulinemia; 4 – Agammaglobulinemia; 5 – Other; 6 – Pending)
 - If 5 – Other, please specify
 - Age (in years and months) at diagnosis of PID
 - Is the patient receiving IVIG (1 – yes; 2 – no)
 - Polio Vaccination Number of IPV doses received in routine immunization (Number; 99 if unknown)
 - Number of OPV doses received in routine immunization (Number; 99 if unknown)
 - Number of IPV doses received during campaigns (Number; 99 if unknown)
 - Number of OPV doses received during campaigns (Number; 99 if unknown)
 - Date of last OPV dose received*
 - Close family members have received OPV doses in last 6 months? (1=Yes, 2=No)
 - Date when family member received OPV
 - Date of last OPV campaign in community
 - Polio Investigation (Polio Surveillance Team) Notification date (of confirmed PID to Polio Surveillance Team; DD/MM/YYYY)
 - Investigation Date (by polio surveillance; DD/MM/YYYY)
 - Paralysis present at the time of first notification (1=Yes, 2=No). If 1=Yes, please notify through the AFP surveillance system – insert AFP EPID number
 - Initial Stool Collection Stool 1 Collection Date (DD/MM/YYYY) Stool 2 Collection Date (DD/MM/YYYY)
 - Stool date sent to lab (DD/MM/YYYY)
 - Date stool specimen arrived at the laboratory* (DD/MM/YYYY)
 - Condition of stool on arrival to the laboratory (1=Good, 2=poor, 99=unknown) *

- Laboratory results
 - Date final culture results sent from laboratory to PID physician/EPI*
 - Date intratypic differentiation (ITD) results sent from laboratory to PID physician/EPI*
 - Date genomic sequencing results sent from laboratory to PID physician/EPI*
 - Polio type 1 isolated? (1=yes, 2=no, 3=specimen not processed) *
 - If yes, specify the type and fill in PID positive for Polio Form (WPV, VDPV, Sabin-like, mixture,
 - If VDPV, number of nucleotide change
 - Polio type 2 isolated? (1=yes, 2=no, 3=specimen not processed) **
 - If yes, specify the type and fill in positive for Polio Form (WPV, VDPV, Sabin-like, mixture,
 - If VDPV, number of nucleotide change
 - Polio type 3 isolated? (1=yes, 2=no, 3=specimen not processed) **
 - If yes, specify the type and fill in positive for Polio Form (WPV, VDPV, Sabin-like, mixture,
 - If VDPV, number of nucleotide change
 - Non-polio enterovirus (NPEV) isolated? (1=yes, 2=no, 3=specimen not processed) *
- Classification
 - Current Diagnosis & Classification (1-PID with WPV; 2-PID with VDPV; 3-PID with Sabin; 4-PID negative for polio; 5-PID pending polio lab result)
 - Is the child eligible for antiviral polio treatment? (1-Yes; 2-No)
 - Is the antiviral polio treatment requested? (1-Yes; 2-No)
 - Date start of treatment (DD/MM/YYYY)
 - Date end of treatment (DD/MM/YYYY)
 - Comments (e.g. type of antiviral, compliance, etc.)
 - Are contact collected (1-Yes; 2-No; 99-Not applicable/unknown)
 - If 1-Yes, fill in PID contact form
 - Is the child registered for follow up stool testing? (1-Yes; 2-No; 99-Not applicable/unknown)
 - If 1-Yes, when is the date for follow up? (DD/MM/YYYY)

* Data elements with asterisks should be included on the case notification, follow-up, and case investigation forms.

Annex 2 - Classification and decision-making chart



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Session Executive Summary: Malaria Vaccine

Session 7 (Wednesday 3 April, 13:10 – 15:10) - 2h

SAGE focal point: Fred Were

WHO technical focal point: Mary Hamel

1. Background

RTS,S/AS01 is the first and, to date, only vaccine to show a protective effect against malaria among young children in a Phase 3 trial. In October 2015, SAGE and the Malaria Policy Advisory Committee (MPAC) recommended pilot implementation of RTS,S/AS01 to address outstanding questions related to the public health use of the vaccine. WHO adopted the SAGE/MPAC recommendations and published its first Malaria Vaccine Position Paper in January 2016.

The Malaria Vaccine Implementation Programme (MVIP) has been developed in line with these recommendations to answer the identified outstanding questions. Coordinated by WHO, the Programme supports introduction of the malaria vaccine into the routine immunization programme in selected areas of 3 countries (Ghana, Kenya and Malawi) and rigorous evaluation of the programmatic feasibility of administering the 4 vaccine doses required for optimal impact, the vaccine's impact on mortality, and its safety in the context of routine use. The countries are expected to launch vaccination in Q1/Q2 2019.

A Framework for Policy Decision (FPD) on RTS,S/AS01 has been developed to describe how and when data collected through the MVIP will be used to inform a WHO policy recommendation on the use of the vaccine beyond the pilots. Through review of the proposed Framework, SAGE and MPAC members will have an opportunity to discuss and align on the relative contribution of the collected data to a future policy recommendation. As suggested by SAGE and MPAC, a working group with representation by both advisory groups and other experts has been established to provide recommendations on the Framework.

2. Session Objective

The main objective of this session is to present SAGE with the recommendations by the SAGE/MPAC Working Group on the Framework for Policy Decision on RTS,S/AS01 and request SAGE's consideration and endorsement of the proposed Framework.

3. Session Summary

The session will consist of three presentations, followed by ample time for discussion:

1. A short introduction and reminder of the rationale for developing the Framework for Policy Decision on RTS,S/AS01,
2. A brief update on the status of the Malaria Vaccine Implementation Programme and recap of data informing the Framework (the latter will be a short repetition of information covered in the preparatory teleconference call on 5 March 2019), and
3. Presentation of the Working Group recommendations.

SAGE members will be requested to review and consider the proposed Framework for endorsement. The value of the Framework as future reference relies on a shared understanding and alignment

among SAGE and MPAC members on the expectations and requirements for a potential policy recommendation for RTS,S/AS01. MPAC members are therefore invited to join the session either in person or by phone. MPAC will be requested to formally endorse the Framework when they meet in person the following week (10-12 April 2019).

4. Background Reading (Yellow Book)

- **Proposed Framework for Policy Decision on the RTS,S/AS01 Malaria Vaccine**, prepared by Working Group and WHO Secretariat, including the following sections and annexes:
 - Executive Summary
 - Introduction
 - Working Group Recommendations
 - Background on the RTS,S/AS01 malaria vaccine: Phase 3 trial to pilot implementations
 - Data and Information used by the WG to inform recommendations
 - Annex 1: Framework for Policy Decision Working Group Terms of Reference
 - Annex 2: Working Group membership, convenings, and DOIs
 - Annex 3: Questions presented to Working Group – 3 Dec 2018
 - Annex 4: Expected timing of availability of pilot implementation evidence
 - Annex 5: Prior vaccine and malaria intervention policy decisions and considerations

MALARIA VACCINE IMPLEMENTATION PROGRAMME (MVIP)

PROPOSED FRAMEWORK FOR POLICY DECISION ON RTS,S/AS01 MALARIA VACCINE

**FOR THE STRATEGIC ADVISORY GROUP OF EXPERTS (SAGE)
ON IMMUNIZATION AND THE MALARIA POLICY ADVISORY
COMMITTEE (MPAC)**

PREPARED BY THE FRAMEWORK FOR POLICY DECISION ON
RTS,S/AS01 WORKING GROUP AND THE WHO SECRETARIAT

11 March 2019

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I. EXECUTIVE SUMMARY

The intention of this proposed Framework for Policy Decision (FPD) document is to provide relevant background and information and to present the Working Group recommendations to the World Health Organization (WHO)'s Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) on how the data generated by the Malaria Vaccine Implementation Programme (MVIP) can be used, as they become available, to inform policy decisions. The Framework will provide an opportunity for discussion and alignment of views prior to key time points for recommendations by the SAGE and MPAC to WHO regarding the broader use of the RTS,S/AS01 malaria vaccine.

To develop the Framework, a Working Group was established of representatives from WHO advisory bodies involved in malaria vaccine policy decision making. They reviewed data and information that led to the 2016 WHO malaria vaccine position paper, and data and information that has emerged since then. Background was provided on the MVIP, along with a summary of policy precedents on malaria interventions and prior SAGE policy decisions on vaccines, to facilitate Working Group discussions around a series of FPD key questions.

Existing data and information – leading up to and incorporated in the 2016 WHO malaria vaccine position

Phase 3 trial: RTS,S/AS01 has been developed over more than three decades by GlaxoSmithKline (GSK), including through a collaboration, begun in 2001, with PATH's Malaria Vaccine Initiative. RTS,S/AS01 is the first and, to date, only vaccine to show a protective effect against malaria among young children in a Phase 3 trial (MAL-055). This multisite trial was conducted at 11 sites in seven African countries and showed a vaccine efficacy, when given in four doses to children aged 5–17 months at first vaccination, of 39% (95% CI, 34–43) against clinical malaria and 29% (95% CI, 6–46) against severe malaria during a median of 48 months follow-up [1]. The vaccine reduced severe malaria anaemia, the most common manifestation of severe malaria in moderate to high transmission areas, by 61% (95%CI 27–81) and the need for blood transfusions by 29% (95% CI 4–47)[4]. The Phase 3 data indicated that a fourth RTS,S/AS01 dose given 18 months after the third dose provided sustained vaccine efficacy against clinical and severe malaria in children aged 5–17 months. This result suggested that three doses alone had no effect on the overall incidence of severe malaria, the apparent protective effect in the first 18 months being balanced by a relative increase in cases in the period from 18 months to the end of the trial [1].

Because of the high frequency of malaria in endemic countries, with children suffering many bouts of malaria each year, the absolute impact was considerable despite the modest vaccine efficacy. Among participants aged 5–17 months at first vaccination who received a 3-dose or a 4-dose schedule, the estimated numbers of cases of clinical malaria averted by study end (M2.5-SE) were 1363 (95% CI, 995–1797) and 1774 (95% CI, 1387–2186) per 1000 vaccinees, respectively. The largest numbers of cases averted per 1000 vaccinees were at sites with the greatest disease burden, reaching more than 6500 cases averted per 1000 children vaccinated with 4 doses [1].

During the Phase 3 trial, the vaccine was associated with an increased risk of febrile seizures within seven days of vaccination; overall, the risk of seizures was similar among children who received RTS,S/AS01 and those who received the comparator vaccine (possibly due to a reduction in malaria-

related seizures). Two safety signals were identified during the trial for which causality has not been established: meningitis (any cause) and cerebral malaria. Among 5 to 17 month olds in the 20 months following the first RTS,S/AS01 dose, meningitis was reported in 16 of the 5948 participants in the RTS,S/AS01 group, and in 1 of the 2974 participants in the control group, a relative risk of 8.0 (95%CI, 1.1–60.3). From study month 21 until trial end, 2 cases of meningitis were reported in the RTS,S/AS01 4-dose group (n=2681), 3 cases in the 3-dose group (n=2719), and 0 cases in the control group (n=2702). In the same age group, from study months 0 to 20, 13 cases of possible cerebral malaria (by expert review) occurred in the combined 3- and 4-dose RTS,S/AS01 group compared to 7 in the control group. From study month 21 until trial end, there were 7 cerebral malaria cases in the 4-dose RTS,S/AS01 group, 8 cases in the 3-dose RTS,S/AS01 group, and 2 cases in the control group[1].¹ A *post hoc* analysis showed an imbalance in mortality among girls (all ages), with about 2-fold higher death rate among girls who received RTS,S/AS01 than among girls who received comparator vaccines ($p=0.001$); the ratio of deaths among boys was slightly lower in the RTS,S/AS01 arms versus the control arm [2]. The Phase 3 trial was conducted in settings with improved access to quality care and there was very low mortality among children enrolled in the trial. The WHO advisory groups and the European Medicines Agency (EMA) concluded that all of these described safety signals may have arisen by chance [2].

Regulatory: The EMA, under a process known as Article 58, reviewed data on the quality, safety and efficacy of RTS,S/AS01 and issued a positive scientific opinion in July 2015. The positive scientific opinion means that the quality of the vaccine and its risk/benefit profile is favourable from a regulatory perspective. In its assessment, the EMA applied the same rigorous standards as for medicines to be marketed within the European Union [3]. The EMA's assessment is being updated as new data become available and has remained valid since the original issuance.

Policy: In January 2016, following a joint review of evidence by WHO's SAGE and MPAC following review by the Joint Technical Expert Group on Malaria Vaccines (JTEG), WHO published its position for RTS,S/AS01. WHO recommended pilot implementation of the RTS,S/AS01 vaccine in distinct settings in sub-Saharan Africa in order to generate critical evidence to enable decision-making about potential wider scale use.

The 2016 WHO position paper called for pilot implementation of the malaria vaccine through phased designs and in the context of ongoing high coverage of other proven malaria control measures. The pilot implementations would demonstrate the extent to which the protection demonstrated in children aged 5–17 months in the Phase 3 trial can be replicated in the context of routine health systems, particularly in view of the need for a 4-dose schedule that requires new immunization contacts. Other questions identified by WHO to be addressed as part of pilot implementations include the extent to which RTS,S/AS01 vaccination impacts all-cause mortality, which could not be adequately assessed in the Phase 3 trial owing to the very low overall mortality in the trial; whether there is a differential impact in boys and girls; and whether there are excess cases of meningitis and cerebral malaria, as identified during the Phase 3 trial, which would suggest that these effects are causally related to RTS,S/AS01 vaccination [2].

¹ Safety profile of the RTS,S/AS01 malaria vaccine in infants and children: additional data from a phase III randomized controlled trial in sub-Saharan Africa' (Human Vaccines & Immunotherapeutics; in press)

As part of its recommendation from the 2015 review process, the JTEG advised WHO to monitor emerging data from the pilot implementations and noted that it would be appropriate for WHO to recommend country-wide introduction if concerns about safety have been resolved, and if favourable implementation data become available, including high coverage of the fourth dose [4].

New data and information – since the January 2016 position paper

Pilot implementation: Following a call for expressions of interest, Ghana, Kenya and Malawi were selected, using standardized criteria, to participate in the pilot implementations [5]. The Programme is being implemented over multiple years with activities begun in 2017 and evaluations expected to be completed by 2023. RTS,S/AS01 vaccine introduction is anticipated to start in the first half of 2019 in all countries, upon confirmation of readiness of all relevant components. The Programme consists of three components:

- 1) Vaccine introduction through national immunization programmes in selected areas of each country with moderate to high malaria transmission. The vaccine has received special authorization for use in context of the pilot implementations by each country's national regulatory authority following a joint convening by the African Vaccine Regulatory Forum (AVAREF). The aim is to reach approximately 360,000 children per year in the selected areas.
- 2) A WHO-sponsored pilot evaluation master protocol has been developed for ongoing implementation by country-based research partners to conduct studies to:
 - Assess the programmatic feasibility of delivering a four-dose schedule, including new immunization contacts, in the context of routine health service delivery;²
 - Evaluate the vaccine's impact on severe malaria and all-cause mortality;³ and
 - Further characterize vaccine safety in the context of a routine immunization programme, with special attention to the safety signals observed in the Phase 3 trial.⁴
- 3) GSK-sponsored Phase 4 studies form part of the RTS,S/AS01 Risk Management Plan agreed between GSK and the EMA to further assess vaccine safety, effectiveness and impact in routine use [6]. In addition to enhanced hospitalization surveillance, the Phase 4 study will include active surveillance through home visits and continuous monitoring of outpatient visits and hospitalisations at health care facilities in a subset of areas in which the vaccine is and is not being administer. The WHO-sponsored pilot evaluations complement the GSK-sponsored Phase 4 study.

Evidence and experience from the pilot implementations will inform recommendations on the vaccine's potential use on a wider scale in Africa. The FPD Working Group reviewed expected pilot data availability and power calculations of key safety and impact end points. The calculations were based on current assumptions included in the statistical analysis plan under development (see Annex

² Routine coverage data from the health information systems will be available as the programme unfolds and household surveys in 2020/2021 and 2021/2022 will document coverage of doses 1-3 and 4, respectively.

³ The evaluation of impact on survival will be through community mortality surveillance and is powered to detect a 10% reduction in all-cause mortality in each country. This is expected to be complete in 2023.

⁴ The potential safety signals identified through the Phase 3 trial will be monitored at a number of sentinel hospitals. Adverse events following immunization will also be assessed through routine pharmacovigilance at all health facilities in the pilot areas.

4) related to expected rate of accrual of relevant disease events and vaccine introduction timelines across the three MVIP countries.

Long-term follow-up of children from 3 of the 11 sites included in the Phase 3 trials (MAL-076): The soon-to-be published results of GSK's MAL-076 study were shared with the FPD Working Group. Continued open label monitoring of children who were enrolled in the Phase 3 clinical trial at 3 of the 11 trial sites⁵ showed that there was protection against clinical and severe malaria over the total of 7 years of follow-up and in the 3 additional years of follow-up there was no further imbalance observed in meningitis, cerebral malaria, nor sex-specific mortality. Notably, there were very few cases of severe malaria observed after the 4 years of follow-up during the Phase 3 trial, presumably due to the development of acquired immunity, regardless of whether children received RTS,S/AS01 or comparator vaccine. These long-term follow-up results showed no evidence of an overall excess of severe malaria in RTS,S/AS01 recipients [7] who received three RTS,S/AS01 doses and no rebound of disease after the fourth vaccine dose. The MAL-076 results indicate that the previously observed excess in severe malaria among children who received only three doses of RTS,S/AS01, from the time that the fourth dose would have been given to the end of the Phase 3 trial, was time limited (see Section V for more on MAL-076).⁶

Background information on malaria reviewed by the FPD Working Group and on policy precedents for introduction of vaccines against other diseases (see Annex 5)

Immunization: Vaccines are among the most successful public health interventions. Millions of lives have been saved and substantial disability averted due to the implementation and scale-up of vaccines against other diseases. The FPD Working Group reviewed prior SAGE policy decisions on other vaccines to inform questions pertinent to RTS,S/AS01 with attention to the type and quality of data available at the time of a recommendation. Rotavirus vaccines, pneumococcal conjugate vaccines (PCVs), and dengue vaccine case studies were the most relevant examples for this exercise.

Malaria: The FPD Working Group reviewed the current status of malaria transmission as well as policy precedent for malaria interventions. The 2018 World Malaria Report estimates that over 400,000 people, mainly young African children, died from malaria in 2017. This is despite considerable progress in malaria control since 2000 with the implementation and scale-up of interventions to combat the disease. Currently recommended malaria prevention tools—long lasting insecticidal nets (LLINs), Intermittent Preventive Treatment in infants (IPTi), Intermittent Preventive Treatment in pregnancy (IPTp), indoor residual spraying (IRS), and in areas with highly seasonal malaria, seasonal malaria chemoprevention (SMC)—provide substantial protection against malaria morbidity and mortality but are at risk due to emerging biological resistance in the malaria parasites and anopheline vectors. The last two years have seen a plateau in progress in malaria control and an increased urgency to develop and implement new strategies to get malaria control back on track [8]. In contrast to the process for SAGE vaccine policy decisions published in position papers, malaria intervention policy decisions have not followed a consistent procedure or format for publication.

⁵ 3 of the 11 Phase 3 trial sites (Korogwe (Tanzania); Kombewa (Kenya); Nanoro (Burkina Faso)) had an additional 3 years of follow up.

⁶ MAL-076 study results submitted for publication (GSK)

The RTS,S/AS01 vaccine may be an important new intervention to add to the current package of malaria control interventions - one that is neither drug nor insecticide based, and that can be delivered through the existing immunization delivery system. A malaria vaccine provided through the routine childhood vaccination programme could reach children not otherwise reached with malaria control interventions, including those in the lowest socio-economic strata.

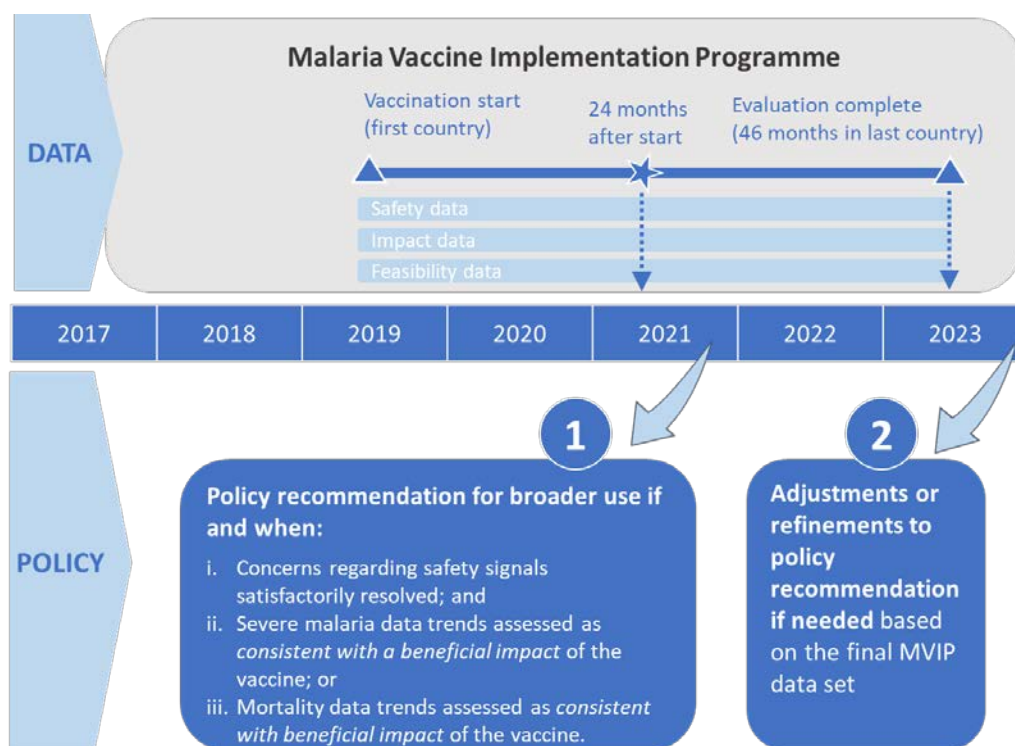
Below is a summary of the FPD Working Group recommendations; all are further discussed in Section III:

- 1) The SAGE and MPAC should consider recommending a step-wise approach for review and policy decision on broader use of RTS,S/AS01 based on emerging pilot data (see Figure 1).
 - Step 1: A WHO policy recommendation on the use of RTS,S/AS01 beyond the pilot countries could be made if and when:
 - i. concerns regarding the safety signals observed in the Phase 3 trial (related to meningitis, cerebral malaria and sex-specific mortality) are satisfactorily resolved, by demonstrating either the absence of a risk of an important size during RTS,S/AS01 pilot implementation or an assessment of a positive risk-benefit profile despite adverse event(s); and
 - ii. severe malaria data trends are assessed as *consistent with a beneficial impact* of the vaccine; or
 - iii. mortality data trends are assessed as *consistent with beneficial impact* of the vaccine.

Based on current assumptions across the three MVIP countries' related to the expected rate of accumulating events and vaccine introduction timings, such data on safety and impact trends could be available approximately 24 months after RTS,S/AS01 vaccine introduction in the Programme. Updated estimates will be confirmed within a statistical analysis plan when there are preliminary data on event rates (see Annex 4).
 - Step 2: Adjustments or refinements to the policy recommendation for broader use of RTS,S/AS01 can be made based on the final MVIP data set, with particular focus on the value of the fourth dose, expected to be available approximately 50 months after start of vaccination in the third MVIP country.
- 2) There is a need to resolve safety concerns on meningitis, cerebral malaria, and sex-specific mortality to establish the risk-benefit profile of the vaccine, as reassuring safety data are required for a policy recommendation.
- 3) The policy recommendation for broader use could be made in the absence of data showing vaccine impact on mortality. Impact on severe malaria is an acceptable surrogate indicator for impact on mortality, and could support a policy recommendation if assessed as consistent with a beneficial impact.
- 4) A policy recommendation for broader use of RTS,S/AS01 need not be predicated on attaining high coverage (including coverage of the fourth dose). High coverage for a newly introduced vaccine is frequently not attained until several years after the start of implementation.
- 5) Barring substantial adverse impact on the coverage of other vaccines or malaria control interventions, the impact of RTS,S/AS01 introduction on the coverage of these interventions should not influence the policy recommendation. Rather these indicators should inform strategies for implementation, including areas to call attention to or to provide opportunities for improvement.

- 6) Cost effectiveness estimates should be regularly refined, as data become available for increasingly precise calculations, and presented at appropriate time points.
- 7) Expansion within MVIP countries should be synchronized with recommendation for broader use across sub-Saharan Africa.
- 8) In the context of the step-wise approach to policy recommendations, the pilots should continue on to complete data collection to establish the public health value of the fourth dose, including assessment of the vaccine's impact on mortality.
- 9) Conflicting data among the MVIP countries would require careful investigation into the reasons for differences. The pilots should continue with plans for analysis even if data are delayed or not available in all countries.
- 10) Criteria that could result in WHO not recommending RTS,S/AS01 vaccine for use or that may lead to a decision to defer a policy recommendation to a later time point were recommended by the Working Group.

Figure 1: Proposed step-wise approach to policy recommendation



II. INTRODUCTION

In January 2016, WHO published its first malaria vaccine position paper, adopting the joint recommendations by the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC) [2]. Recognizing the importance of malaria as a major cause of morbidity and mortality, particularly in sub-Saharan Africa, the need for new malaria control tools, and the potential significant contribution of the RTS,S/AS01 malaria vaccine to further reduce malaria burden, WHO recommended pilot implementation of the vaccine in sub-Saharan Africa.

The Malaria Vaccine Implementation Programme (MVIP) has been developed in line with these recommendations to address the identified outstanding questions related to the public health use of the vaccine. The Programme supports introduction of the malaria vaccine in selected areas of Ghana, Kenya and Malawi accompanied by rigorous evaluation of the vaccine's feasibility, safety and impact in routine use. The primary aim of the Programme is to generate additional data to enable a WHO policy decision on the broader use of the RTS,S/AS01 malaria vaccine in sub-Saharan Africa.

A. Purpose of the Framework for Policy Decision

The Framework for Policy Decision (FPD) on RTS,S/AS01 aims to describe how and when data collected through the MVIP will be used to inform a WHO policy recommendation on vaccine use beyond the pilots.

The Framework considers the relative contribution of the collected data on feasibility, safety, and impact to a future policy recommendation. It also provides clarity on the expected use of the data in anticipation of potential changes in SAGE and MPAC membership between the time the SAGE/MPAC recommendations were made (2015) and availability of data from the pilot implementations. It is anticipated that funders, potential funders, and manufacturers can refer to the Framework for planning purposes. Finally, the Framework is non-binding as other factors might impact a policy decision (such as a new highly efficacious intervention). Both SAGE and MPAC supported the development of such a Framework during their 2018 meetings.⁷

B. FPD Working Group

The FPD on RTS,S/AS01 Working Group includes representatives from the SAGE, MPAC, IVIR-AC, modelling groups, and the MVIP Programme Advisory Group (PAG). The Working Group Terms of Reference (see Annex 1) define its operations and specific responsibilities.

Working group members have reviewed relevant background information and other considerations for the RTS,S/AS01 policy decisions. Discussion were structured around key questions for the working group to consider in the context of RTS,S/AS01 (see Annex 3).

The subsequent sections present the Working Group's recommendations and summarize the background information that informed the Framework.

⁷ SAGE and MPAC meeting reports, October 2018

III. WORKING GROUP RECOMMENDATIONS

The Working Group is comprised of representatives from advisory bodies involved in malaria vaccine policy decision making (See Annex 1 and 2). The following background and information were provided during their meetings (see Annex 2) to facilitate their deliberations:

- *Existing data and information that led to the current policy position (Section IV)*
- *Data and information that have emerged since then (Section V)*
- *Questions posed to the FPD Working Group (Annex 3)*
- *Expected availability of evidence from the pilot implementations (Annex 4)*
- *Considerations based on precedent from malaria interventions policies, prior SAGE policy decisions on other vaccines, and immunization coverage trajectories following new vaccine introductions (Section V and Annex 5)*

Recommendation 1: The SAGE and MPAC should consider recommending a step-wise approach for review and policy decision on broader use of RTS,S/AS01 based on emerging pilot data.

Step 1: A WHO policy recommendation on the use of RTS,S/AS01 beyond the pilot countries could be made if and when:

- i. concerns regarding the safety signals observed in the Phase 3 trial (related to meningitis, cerebral malaria and sex-specific mortality) are satisfactorily resolved, by demonstrating either the absence of a risk of an important size during RTS,S/AS01 pilot implementation or an assessment of a positive risk-benefit profile despite adverse event(s); and
- ii. severe malaria data trends are assessed as *consistent with a beneficial impact* of the vaccine; or
- iii. mortality data trends are assessed as *consistent with beneficial impact* of the vaccine.

Based on current assumptions across the three MVIP countries' related to the expected rate of accumulating events and vaccine introduction timings, such data on safety and impact trends could be available approximately 24 months after RTS,S/AS01 vaccine introduction in the Programme. Updated estimates will be confirmed within a statistical analysis plan when there are preliminary data on event rates (see Annex 4).

Step 2: Adjustments or refinements to the policy recommendation for broader use of RTS,S/AS01 can be made based on the final MVIP data set, with particular focus on the value of the fourth dose, expected to be available approximately 50 months after start of vaccination in the third MVIP country.

Table 1 includes the potential timing of review and key available data from the MVIP based on the step-wise approach to policy recommendation.

Table 1. Step-wise approach to policy recommendation

	Step 1	Step 2
Policy decision	Initial policy decision on broader use of RTS,S/AS01 if safety signals satisfactorily resolved and severe malaria impact data trends are assessed as consistent with findings from the Phase 3 trial, and mortality data are compatible with a beneficial effect of the vaccine	Update or refinement of the policy recommendation, if needed, with particular focus on value of fourth dose
Potential timing of review*	In late 2021, approximately 30 months after vaccine introduction in the first country, based on approximately 24 months of data across MVIP.	In late 2023, at the end of the pilots, based on approximately 50 months of data after vaccine introduction in 3 rd MVIP country.
Key available data from MVIP	<ul style="list-style-type: none"> – Data on potential safety signals identified through the Phase 3 trial (meningitis, cerebral malaria, sex-specific mortality) – Impact on severe malaria and trends in impact on mortality – Coverage of first 3 doses from representative sample household survey and from administrative data – Approximately 6 months of administrative coverage data for dose 4 – Contextual and behavioural factors related to RTS,S/AS01 uptake through first 3 doses – Costs of delivering first 3 doses – AEFI^[1] and pre-specified AESI^[2] reported through MoH routine pharmacovigilance systems – AEFI and AESI data collected through active surveillance as part of GSK-sponsored Phase 4 study 	<ul style="list-style-type: none"> – Information on fourth dose coverage – Added value of the fourth dose with respect to impact on severe malaria and mortality – GSK-sponsored Phase 4 study interim analysis
Not yet available	<ul style="list-style-type: none"> – Impact on mortality – Dose 4 coverage from representative sample household survey & administrative data 	

**based on current assumptions across the 3 MVIP countries related to expected rate of accrual of relevant disease events and vaccine introduction timelines. Updated estimates will be made when there are preliminary data on event rates.*

The FPD Working Group based its recommendation for a step-wise approach on the principle that a decision on broader use of the RTS,S/AS01 malaria vaccine beyond the pilot countries be made at the earliest possible timepoint when robust evidence is available to ascertain a positive risk-benefit profile of the vaccine. In developing these recommendations, the FPD Working Group established a hierarchy of data requirements:

^[1] Adverse events following immunization (AEFI)

^[2] Adverse events of special interest (AESI)

1. Reassuring safety data are considered of primary importance and a pre-condition for a positive policy recommendation; it is critical to understand whether there are causal associations between RTS,S/AS01 and any of the safety signals observed in the Phase 3 trial.
2. Impact is an important consideration, with impact on severe malaria considered an acceptable surrogate indicator for impact on mortality; trends should be assessed as *consistent with beneficial impact* of the vaccine. There should be recognition that the impact of the vaccine on severe malaria may not necessarily be the same because of what can be achieved during clinical trials as compared to pilot implementation.
3. The policy recommendation for broader use of RTS,S/AS01 need not be predicated on attaining high coverage (including coverage of the fourth dose). High coverage for a newly introduced vaccine is frequently not attained until several years after the start of implementation.

Providing a policy recommendation as soon as there is sufficiently robust evidence is important not only in view of the vaccine's potential public health impact, but also to provide the advanced signal to the manufacturer that may be needed to maintain vaccine production, increase likelihood of uninterrupted supply, and trigger financing mechanisms should there be a recommendation for broader use of RTS,S/AS01. The FPD seeks to reduce some of the uncertainty around the timing of a policy recommendation by indicating a potential policy roadmap as reference for the manufacturer and funders' advanced decision making. The likely dependencies of the policy recommendation need to be considered and anticipated, specifically:

- Manufacturer's considerations for supply:

Unlike other vaccines, there is no dual market for RTS,S/AS01. Continued vaccine production by GSK after the 10 million doses committed for the Programme are dependent on the outcome and timing of: a) policy recommendation for broader use of RTS,S/AS01; b) MVIP countries' decisions on continuous vaccination and expansion to comparison areas; and c) purchase order or funding commitment to maintain manufacturing production capacity beyond 2020. GSK will not be in the position to maintain on-going manufacturing activities until there is formal commitment to procure the vaccine beyond the MVIP. Without continued manufacturing, there will be a gap in supply between end of the pilot and start of broader use of the vaccine due to the time required to re-start the facility, along with uncertainty around the increased costs. Though endorsement of a FPD does not guarantee positive results, a step-wise policy recommendation approach may further enable discussions and risk-sharing options among public health partners to ensure continuous supply of RTS,S/AS01. Transparency and advance notice are required between GSK and key stakeholders on the timing of forthcoming manufacturing decision points.

- Financing decisions

Endorsement of a FPD provides guidance on the potential timing of a WHO policy recommendation, enables advanced planning on financing decisions and windows for broader roll-out, and also support for MVIP countries continuing to vaccinate.

Furthermore, the endorsement of a FPD could serve as a positive signal while fundraising in 2019 for the resources required to complete the Programme. Currently, the MVIP is funded between 2017 and 2020, but due to the timing of funding cycles there were few commitments made beyond this point to complete the Programme from 2021 to 2023.

Recommendation 2: There is a need to resolve safety concerns on meningitis, cerebral malaria, and sex-specific mortality to establish the risk-benefit profile of the vaccine, as reassuring safety data are required for a policy recommendation.

Under the Article 58 procedure, the EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of the vaccine outweigh its risks and issued a positive scientific opinion [3] in July 2015. The CHMP noted it had not established that the safety signals identified in the Phase 3 trial were causally linked to the vaccine, and they could be due to chance. They recommended that further data on the signals be obtained through the Manufacturer's post-marketing Risk Management Plan. The January 2016 WHO position paper identified key questions to be addressed as part of pilot implementations, including "whether excess cases of meningitis and cerebral malaria identified in the Phase 3 trial are causally related to the vaccine" and to determine impact of the vaccine on mortality by sex [2]. The WHO-led pilot evaluations⁸ and the GSK-sponsored Phase 4 study⁹ have been designed to address the safety signals identified in the Phase 3 trial. Additionally, reports of AEFI and pre-specified AESI captured through the Ministry of Health routine pharmacovigilance systems or the GSK-sponsored phase 4 study will be reviewed and assessed by the ministries of health and/or national regulatory authorities. The MVIP Data Safety and Monitoring Board (DSMB) will review data from all of these sources on an ongoing basis and, should safety concerns arise in the pilot implementations, could recommend stopping vaccinations to the Programme Advisory Group and WHO leadership.

The FPD Working Group agreed that resolution of the safety signals is of key importance for a recommendation on broader use of the vaccine. Based on current assumptions related to the expected rate of accrual of disease events and vaccine introduction timings in the three MVIP countries, it is estimated that, if there is no true excess of meningitis, cerebral malaria, and mortality in girls, it would be possible to rule out relative risks of these respective events of an acceptable magnitude approximately 24 months after vaccine introduction, based on the upper 95% confidence level on the relative rate estimates (see Annex 4).

If an excess of one or more of these adverse events were to be found during the Programme, discussions would be required around whether any observed benefits of the vaccine (i.e. reductions in severe malaria, anaemia, blood transfusions) would still justify a recommendation for broader use. Benchmarking against other vaccines with known risks (e.g. rotavirus vaccine risk of intussusception) would be useful.

Recommendation 3: The policy recommendation for broader use could be made in the absence of data showing vaccine impact on mortality. Impact on severe malaria is an acceptable surrogate indicator for impact on mortality, and could support a policy recommendation if assessed as consistent with a beneficial impact.

⁸ WHO-sponsored pilot evaluations: there will be 4 to 8 sentinel hospitals per country conducting active in-patient surveillance with focus on monitoring of meningitis and cerebral malaria. To ensure quality, an external monitor will report standards on adherence to clinical algorithms for diagnosis. Community-based mortality surveillance will engage village reporters to document all deaths in children (included the sex of the deceased). Verbal autopsy teams, village reporting supervisors, and reference laboratories will also provide quality assurance.

⁹ In the GSK-sponsored Phase 4 programme, a cohort will be enrolled into a prospective study with 10 home visits over a two-year time period and active in-patient surveillance in sentinel hospitals to measure AESI, AEFI, and association of meningitis and cerebral malaria.

It is unlikely that a significant country-specific impact on mortality will be demonstrable before the end of the pilot evaluations (46 months in each country), if the mortality reduction is of the size the Programme is powered to detect (10% reduction in all-cause child mortality).¹⁰ Data trends on the impact on severe malaria may be available earlier (approximately 24 months after vaccine introduction). The measured benefit in terms of severe malaria at this time could possibly be reduced by apparent later rebound effects in children who receive only three vaccine doses. Overall benefit against severe malaria will be available after 46 months of evaluation in each MVIP country. It is anticipated that sufficient data on the safety signals may have accrued by 24 months after the first vaccination to rule out adverse effects, as described above, if there is no true increased risk.

The FPD Working Group considered impact on severe malaria to be an acceptable surrogate indicator for likely impact on mortality. Impact trends in data on severe malaria and mortality, with associated levels of uncertainty, could be presented to inform policy decisions. The recommendations on impact on severe malaria and mortality align with MPAC recommendations made in Oct 2018 [7].

There are several reasons for not waiting until all evaluations are completed in 2023 before WHO recommends policy on broader use of the RTS,S/AS01 vaccine:

- 1) For no other vaccine has the SAGE required and WHO stipulated demonstration of mortality impact prior to making an initial recommendation for vaccine use. Rather, data on mortality impact has resulted in modifications of recommendations as those data became available.
- 2) The previous concern, expressed in the SAGE/MPAC recommendations from October 2015, around a potential excess risk of severe malaria in long-term follow-up of children who miss the fourth dose has been reduced by the findings from the MAL-076 seven year follow-up study. MAL-076 data showed that the previously observed apparent rebound in severe malaria among those children who received three doses of RTS,S/AS01 was time limited with no overall excess in severe malaria, very few severe malaria cases after four years of follow up, and no additional imbalance observed in safety signals or deaths. Overall, children benefited from three or four doses of the vaccine, with more benefit in terms of protection against clinical or severe malaria observed among children who received four doses.¹¹ This is new information that was not available at the time of the October 2015 SAGE/MPAC recommendations and provides reassurance that children who receive only three doses benefit overall, with respect to clinical malaria, and are not at higher risk of severe malaria than children who received no vaccine doses [4].

The FPD Working Group recognised that the impact of the vaccine on severe malaria would not necessarily be the same as that measured during the Phase 3 clinical trials because of what can be achieved during clinical trials as compared to programme implementation. If less than expected impact is due to low vaccine coverage, programmatic improvements to increase RTS,S/AS01 vaccine coverage will be required.

¹⁰ This endpoint will be evaluated through community-based surveillance systems relying on village reporters. Verbal autopsies on reported deaths will confirm age, RTS,S/AS01 vaccination status, and attempt to ascertain the cause of death. Mortality data are powered for country-specific estimates, and will also be aggregated across countries.

¹¹ MAL-076 study results submitted for publication (GSK)

Recommendation 4: A policy recommendation for broader use of RTS,S/AS01 need not be predicated on attaining high coverage (including coverage of the fourth dose).

A FPD Working Group review of the SAGE policy recommendations on other vaccines showed that feasibility data are rarely available at time of initial policy recommendation. Instead, revisions to prior recommendations have incorporated findings from post-marketing studies on feasibility as they become available. Furthermore, at least several years of implementation are typically required to achieve high vaccine coverage and in some settings this may not be achieved for many years. Challenges can be expected in particular for new vaccine introduction outside the Expanded Programme on Immunization (EPI)'s current schedules, however there was agreement among the FPD Working Group that feasibility can be improved with time. Implementation challenges have been met and addressed with other vaccine introductions as well as malaria control interventions. Data on vaccine coverage and lessons learned on implementation will be collected during the pilot and used for programmatic improvement going forward.

Data reviewed by the SAGE and MPAC in 2015 indicate that children who did not receive the fourth dose of RTS,S/AS01 would experience benefit against clinical malaria but not significant benefit against severe malaria from vaccination [4]. Data available from the MAL-076 long term follow up study¹² indicate that the previously observed apparent rebound in severe malaria among children who received only three doses of RTS,S/AS01 was time limited, with very few severe malaria cases after four years of follow up, and no further imbalance observed in safety signals or deaths.¹³ MPAC reviewed these data in October 2018 and concluded that they provide further reassurance on the absence of a rebound effect after the fourth dose, or a persistent rebound effect after only three doses, and give further reinforcement of the safety profile of the vaccine, and its apparent benefit in children who receive three or four doses [7].

For these reasons, in the context of the FPD, the Working Group concluded that it is not desirable or feasible to define a target threshold for vaccine coverage, including fourth dose coverage, to predict impact or to inform a policy decision. Rather, anticipated coverage levels should be factored into the projected data availability of the safety and impact endpoints. Vaccine coverage attained, and methods used to increase coverage, serve as lessons learned to improve vaccine implementation, rather than to determine the policy decision.

Recommendation 5: Barring substantial adverse impact on the coverage of other vaccines or malaria control interventions, the impact of RTS,S/AS01 introduction on the coverage of these interventions should not influence the policy recommendation. Rather these indicators should inform strategies for implementation, including areas to call attention to or to provide opportunities for improvement.

The RTS,S/AS01 vaccine is proposed as a potential additional tool to complement the existing package of WHO-recommended preventive, diagnostic and treatment measures for malaria in children. The Phase 3 trial occurred in the context of high bed net coverage and good access to quality health care [2].

¹² 3 of the 11 Phase 3 trial sites (Korogwe (Tanzania); Kombewa (Kenya); Nanoro (Burkina Faso)) had an additional 3 years of follow up.

¹³ MAL-076 study results submitted for publication (GSK)

Delivery of RTS,S/AS01 through the ministries of health, led by the EPI and in coordination with the National Malaria Control Programme (NMCP), could serve as a unique opportunity to reach children who have not been reached with other malaria interventions. The RTS,S/AS01 immunization regimen provides new contacts for children in their second year of life, enhancing opportunities to increase coverage of other childhood vaccines and other health interventions. The Programme will utilize cross-sectional household surveys to measure RTS,S/AS01 uptake and coverage, impact on coverage of other vaccines, insecticide-treated nets (ITN) use, and health care seeking behaviour, as well as a qualitative assessment through interviews of parents and health workers to understand the obstacles and opportunities for vaccine delivery. A measured reduction in health intervention uptake, coverage or use associated with RTS,S/AS01 introduction could be addressed with targeted interventions and/or messaging.

Therefore, barring any substantial adverse impact to the use of malaria control interventions and coverage of other childhood vaccines, pilot data should be used to inform programmatic improvements and vaccine implementation, rather than to inform policy decision.

Recommendation 6: Cost effectiveness estimates should be regularly refined, as data become available for increasingly precise calculations, and presented at appropriate time points.

Based on currently available data, RTS,S/AS01 compares favourably in relation to global cost effectiveness estimates of several other vaccines. While RTS,S/AS01 was found to be less cost-effective overall than some other malaria interventions, RTS,S/AS01 is expected to be highly cost-effective in moderate to high transmission settings and may play an important and cost-effective role alongside other interventions [9]. Gavi, the Vaccine Alliance, has included RTS,S/AS01 in their analyses of potential vaccine investment strategies and has continued to examine both the potential impact and cost effectiveness of the vaccine.

A review of policy precedents show that cost-effectiveness is rarely incorporated into an initial policy recommendation for broader use. Rather there should be refinement of the cost effectiveness estimates for RTS,S/AS01, including risk of adverse events, as more pilot data become available. These refined cost effectiveness estimates should be presented at appropriate time points to the SAGE and MPAC. During the pilot implementation, economic analyses will be conducted on the delivery costs and budget impact of the malaria vaccine on routine health systems to inform ministries of health. These data, with evidence from the evaluations (i.e. impact on severe malaria and/or mortality end point, dose regimen, etc.) will be used to validate and/or update existing modelled estimates on public health impact and cost-effectiveness of the malaria vaccine.

Data and economic analyses for cost effectiveness will be completed regardless of the timing of a policy recommendation for broader use. They will likely be used to inform decisions by stakeholders, such as countries and financing agencies. WHO and PATH are continuing to work with relevant agencies to explore future funding mechanisms for the vaccine (the major cost driver), should WHO recommend the vaccine for broader use.

Recommendation 7: Expansion within MVP countries should be synchronized with recommendation for broader use across sub-Saharan Africa.

As stipulated in the pilot evaluation master protocol, to meet the evaluation objectives, the vaccine

will be made available through routine immunization services in vaccination areas¹⁴ of the Programme for a minimum of 30 months following the start of vaccination. In line with the January 2016 WHO position paper calling for a “phased design,” ministries of health in the MVIP countries view pilot implementation as a phased vaccine introduction. The EPI Programmes have voiced their preference to continue vaccinations (provided there are no safety signals and there are positive trends of impact) as any start/stop is detrimental to programme operations and community mobilization. MVIP countries could therefore decide to continue vaccinations in these areas beyond the minimum 30 months of routine immunization.

Expansion of vaccinations to the comparison areas was advised by the WHO Research Ethics Review Committee, should the vaccine be found to have a positive risk/benefit profile. The FPD Working Group suggested that expansion to comparison areas could occur at the time when broader use of RTS,S/AS01 beyond the pilot countries is recommended because the same criteria would need to be met. Countries will likely rely on the SAGE and MPAC recommendations for broader use before making decisions on introduction in the comparison areas.

There should be regular briefings with the SAGE and MPAC on the Programme’s plans for comparison area expansion as, ideally, this expansion would be synchronized with recommendation for broader use. Provided there is sufficient supply available, the national regulatory authorities are in agreement, and a positive risk/benefit profile is maintained, it would not make sense to withhold vaccinations from the pilot comparison areas until after the end of the Programme.

The vaccine donation offered by GSK for the pilot implementations would be sufficient to allow for continuous vaccination within implementation areas and vaccination of comparison areas through the end of the Programme, if desired by MVIP countries. It is important to address the risk of vaccination start/stop in advance due to time required for decision making, financing, vaccine availability, and implementation planning (see Recommendation 1). Creative mechanisms should be considered to ensure supply and funding are available for expanded vaccination, as well as continued vaccination, within the MVIP countries until recommendations and financing are in place for broader use.

Recommendation 8: In the context of the step-wise approach to policy recommendations, the pilots should continue through to completion of data collection to establish the public health value of the fourth dose, including assessment of the vaccine’s impact on mortality.

The MVIP should continue to generate data throughout the entire implementation and evaluation periods (expected to be 46 months in each country) regardless of whether an earlier policy recommendation is provided (barring a safety concern resulting in earlier pilot end). Impact on all-cause mortality along with updated cost effectiveness estimates can be incorporated into the final dataset for review by advisory bodies. These real-life data will also be of interest to countries and funding agencies.

Completion of the MVIP beyond an initial recommendation will also provide important information on the role of the fourth dose. Contrary to the findings in the Phase 3 trial, mathematical models predict a relatively small incremental impact of the fourth dose on severe malaria, with over 90% of

¹⁴ The pilot area in each country is comprised of areas (districts or sub-counties) that introduce the vaccine at the beginning of the programme and areas initially without the vaccine acting as comparison.

the modelled impact achieved through administration of the first three doses. These results are consistent with the 2015 modelling analysis presented to the SAGE and MPAC. Modelling indicates that the largest difference in impact between the four-dose and three-dose group in the Phase 3 trial would have been expected at study end in the Phase 3 trial, with impact decaying in both groups following this time, as age incidence curves are also decreasing. This is consistent with observed trends in the MAL-076 study that little difference is seen between the three-dose and four-dose groups in the longer follow-up. Further analysis of the Phase 3 MAL-055 data indicated a difference between the three-dose and four-dose group in regard to impact against severe disease (but not clinical disease) before the fourth dose was given. However, this difference is most likely due to chance.

If it is found upon completion of the Programme that the fourth dose provides little incremental benefit in real life settings, the recommendation could be modified (e.g. to a three-dose regimen).

Recommendation 9: Conflicting data among the MVP countries would require careful investigation into the reasons for differences. Continue forward with plans for analysis even if data are delayed or not available in all countries.

Recommendation 10: Criteria that could result in WHO not recommending RTS,S/AS01 vaccine for use or that may lead to a decision to defer a policy recommendation to a later time point were recommended by the Working Group.

To issue a recommendation not to implement the RTS,S/AS01 vaccine:

- When there is a clear safety risk (e.g. meningitis) assessed to be unfavourable in context of risk-benefit profile
- If there is something in the risk-benefit profile that could critically undermine the confidence and trust in the national immunization programme

To defer a decision on RTS,S/AS01 to the end or near the end of the pilot evaluations:

- If there is significant uncertainty about safety issues (meningitis, cerebral malaria, sex-specific mortality)
- If impact is not assessed as consistent with a beneficial effect

IV. BACKGROUND ON THE RTS,S/AS01 MALARIA VACCINE: PHASE 3 TRIAL TO PILOT IMPLEMENTATIONS

A. Phase 3 RTS,S/AS01 Trial

RTS,S/AS01 is the first and, to date, only vaccine to show a protective effect against malaria among young children in a Phase 3 trial [1]. This multisite trial was conducted over 5 years at 11 sites in seven sub-Saharan African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and the United Republic of Tanzania). The trial was conducted in settings with improved access to quality care, high coverage and use of LLINs, and there was very low mortality among children enrolled in the trial.

Vaccine efficacy: When four doses of RTS,S/AS01 were given to children aged 5–17 months at first vaccination the vaccine efficacy was 39% (95% CI, 34–43) against clinical malaria and 29% (95% CI, 6–46) against severe malaria during a median of 48 months follow-up [1]. The data presented in the position paper indicate that a fourth RTS,S/AS01 dose given 18 months after the third dose provided sustained vaccine efficacy against clinical and severe malaria in children aged 5–17 months. The vaccine reduced severe malaria anaemia, the most common manifestation of severe malaria in moderate to high transmission areas, by 61% (95%CI 27–81) and the need for blood transfusions by 29% (95% CI 4–47). The Phase 3 data indicated that a fourth RTS,S/AS01 dose given 18 months after the third dose provided sustained vaccine efficacy against clinical and severe malaria in children aged 5–17 months. This result suggested that three doses alone had no effect on the overall incidence of severe malaria, the apparent protective effect in the first 18 months being balanced by a relative increase in cases in the period from 18 months to the end of the trial [1].

Impact: Among participants in the 5–17 month age category who received a 3-dose schedule or a 4-dose schedule, the estimated numbers of cases of clinical malaria averted by study end (M2.5-SE) were 1363 (95% CI, 995–1797) and 1774 (95% CI, 1387–2186) per 1000 vaccinees, respectively.^{15 16} The largest numbers of cases averted per 1000 vaccinees were at sites with the greatest disease burden, reaching more than 6500 cases averted per 1000 children vaccinated with 4 doses. Because of the high frequency of malaria in endemic countries, with children suffering many bouts of malaria each year, the absolute impact was considerable despite the modest vaccine efficacy.

Modelled public health impact and cost-effectiveness: A comparison of four mathematical models enabled the assessment of RTS,S/AS01's potential public health impact and cost-effectiveness [9]. This was carried out using Phase 3 clinical trial clinical malaria outcome data for the 5–17 month age group with follow-up time of 32 months or longer to generate estimates of cases, deaths, and disability-adjusted life-years (DALYs) averted over a 15 year period.¹⁴ The models assumed that vaccine implementation was added to existing levels of malaria control interventions and treatment. With an assumed coverage of 90% for the first 3 doses, with 80% of these individuals receiving the fourth dose (72% coverage overall), all models predict a substantial additional public health impact of RTS,S/AS01 in settings with PfPR_{2–10} between 10% and 65%.¹⁷ In these settings, median modelled estimates range

¹⁶ The impact of RTS,S/AS01 vaccination has been assessed by an estimation of cases averted in the Phase 3 clinical trial, and by use of mathematical models to predict the impact of RTS,S/AS01 when administered through the routine EPI programme. The estimated number of cases averted by RTS,S/AS01 in the trial was the sum of differences in the number of cases between the control and the RTS,S/AS01 groups, expressed per 1000 participants vaccinated.

¹⁷ Prevalence of infection as measured by cross-sectional surveys in those aged 2–10 years. Prevalence of infection in children is a commonly used measure of malaria parasite transmission.

from 200 to 700 deaths averted per 100 000 children vaccinated with a four-dose schedule, and 10% to 28% of all malaria deaths averted in vaccinated children aged <5 years. Public health impact and cost-effectiveness tended to be greater at higher levels of transmission.

At an assumed vaccine price of \$5 per dose and a PfPR_{2–10} of 10–65%, the models predicted a median incremental cost-effectiveness ratio compared with no vaccine of \$30 (range 18–211) per clinical case averted and \$80 (44–279) per DALY averted for the three-dose schedule, and of \$25 (16–222) and \$87 (48–244), respectively, for the four-dose schedule. Higher incremental cost-effectiveness ratio (ICERs) were estimated at low PfPR_{2–10} levels. These predictions of RTS,S/AS01 cost-effectiveness per DALY averted are positive and comparable with other new vaccines based on mathematical models.

Safety: No fatal adverse events were assessed as causally related to RTS,S/AS01 vaccination. In the 5–17 month age category, from the first dose to the trial end, serious adverse events (SAEs) were slightly less frequent in the RTS,S/AS01 groups than in the control group. In this age group, febrile convulsions were an identified risk in RTS,S/AS01 recipients in the 7 days following vaccination, but overall seizures were balanced among children who received RTS,S/AS01 and those who received the comparator vaccine (possibly due to a reduction in malaria-related seizures). Febrile seizures resolved without long-term consequence and are not unique to this vaccine [4].

Two safety signals were identified during the trial for which causality has not been established: meningitis (any cause) and cerebral malaria. Among 5–17 month olds in the 20 months following the first RTS,S/AS01 dose, meningitis was reported in 16 of the 5948 participants in the RTS,S/AS01 group, and in 1 of the 2974 participants in the control group, a relative risk of 8.0 (95%CI, 1.1–60.3). From study month 21 until trial end, 2 cases of meningitis were reported in the RTS,S/AS01 4-dose group (n=2681), 3 cases in the 3-dose group (n=2719), and 0 cases in the control group (n=2702). In the same age group, from study months 0 to 20, 13 cases of possible cerebral malaria (by expert review) occurred in the combined 3- and 4-dose RTS,S/AS01 group compared to 7 in the control group. From study month 21 until trial end, there were 7 cerebral malaria cases in the 4-dose RTS,S/AS01 group, 8 cases in the 3-dose RTS,S/AS01 group, and 2 cases in the control group[1].¹⁸

A *post hoc* analysis showed an imbalance in mortality among girls, with about 2-fold higher deaths among girls who received RTS,S/AS01 than among girls who received comparator vaccines (p=0.001); the ratio of deaths among boys was slightly lower in the RTS,S/AS01 arms versus the control arm. A relationship between the RTS,S/AS01 vaccine and these findings has not been established.

The WHO advisory bodies and EMA concluded that all of these described safety signals may have arisen by chance. The signals were not seen in a pooled analysis of 2981 children who received RTS,S/AS01 during phase 2 trials [10] nor has the potential meningitis signal been seen in the more than 4000 children who have received RTS,S/AS01 in ongoing trials to evaluate alternative dosing regimens or to measure efficacy with annual boosters in highly seasonal areas.¹⁹ The pilot evaluations and a Phase 4 study (further explained below) have been designed to provide further information.

¹⁸ Safety profile of the RTS,S/AS01 malaria vaccine in infants and children: additional data from a phase III randomized controlled trial in sub-Saharan Africa' (Human Vaccines & Immunotherapeutics; in press)

¹⁹ Personal communication on 27 Feb 2019 with Sir Brian Greenwood

B. SAGE/MPAC recommendations leading up to 2016 WHO position paper

In accordance with the WHO's mandate to provide guidance to Member States on health policy matters, WHO is tasked with developing evidence-based immunization policy recommendations. The SAGE is an independent advisory group 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. The subsequent recommendations are then reflected in WHO vaccine position papers. The MPAC was established in 2011 to provide independent advice to WHO on developing policy recommendations to control and eliminate malaria. MPAC has deliberated and provided advice on the usefulness of important potential malaria control tools, including seasonal malaria chemoprevention (SMC) and mass drug administration (MDA), and has guided the development or revision of guidelines for current malaria control tools. The Joint Technical Expert Group on malaria vaccines (JTEG) was jointly established by the Initiative for Vaccine Research (IVR) and the Global Malaria Programme (GMP) to provide advice to WHO on activities related to the development of malaria vaccines at or nearing the pivotal Phase 3 trial stage.

In October 2015, the MPAC and the SAGE recommended that data be collected through the pilot implementations of RTS,S/AS01 to answer remaining questions on feasibility, safety, and impact of the vaccine to inform a policy recommendation on wider use of RTS,S/AS01. WHO adopted the MPAC/SAGE recommendations in its first Malaria Vaccine Position Paper in January 2016 [2]. WHO recommended pilot implementation of the RTS,S/AS01 vaccine in 3–5 distinct epidemiological settings in sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings, in order to generate critical evidence to enable decision-making about potential wider scale use.

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

The Joint Technical Expert Group on Malaria Vaccines (JTEG) advised WHO to monitor emerging findings and indicated that, if appropriate, the SAGE and MPAC may broaden recommendations on the basis of these emerging findings. As part of its recommendation from the 2015 review process, the JTEG advised WHO to monitor emerging data from the pilot implementations and noted that it would be appropriate for WHO to recommend country-wide introduction if concerns about safety have been resolved, and if favourable implementation data become available, including high coverage of the fourth dose [4]. However, no specific thresholds or guidance were provided to ascertain the meaning of the terms 'resolved safety concerns', 'favourable implementation data' or 'high coverage of the fourth dose'.

Based on the efficacy data from the Phase 3 trial, WHO did not recommend the use of the RTS,S/AS01 vaccine in the younger (6–12 weeks) age category, as the vaccine efficacy was found to be low in this age category.

C. Malaria Vaccine Implementation Programme (MVIP)

The Programme has been developed to execute the 2016 WHO recommendation for pilot implementation of the RTS,S/AS01 malaria vaccine to address several outstanding questions related to the public health use of the vaccine.

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

The selection of Ghana, Kenya and Malawi to participate in the pilot implementations was made public on 24 April 2017, just ahead of World Malaria Day and during African Vaccination Week [5].

The Programme consists of three components: 1) Ministry of Health-led vaccine introduction; 2) WHO-sponsored pilot evaluations; and 3) GSK-sponsored Phase 4 study.

1) Vaccine introduction

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

Close collaboration with the NMCP will ensure that existing WHO-recommended prevention tools, such as LLINs and artemisinin-based combination therapies (ACTs), continue to be deployed on a wide scale.

The vaccine has received special authorization for use in context of the pilot implementations by each country's national regulatory authority following a joint convening by AVAREF. The aim is to reach approximately 360 000 children per year in the selected areas.

2) Pilot evaluations

While it is critical that the MVIP represents routine vaccine implementation through the national immunization programmes, the evaluation components must be conducted in a scientifically rigorous manner to generate answers to the remaining questions. For this reason, RTS,S/AS01 will be introduced in some areas at the beginning of the programme with other areas, initially without RTS,S/AS01 introduction, acting as comparison. The division into vaccine implementation or comparison areas has been completed through randomization to generate the strongest possible evidence on the impact and safety of the vaccine. Identical and established monitoring systems in

both implementation and comparison areas will record impact and safety outcomes through observational and cross-sectional studies. Surveillance over the course of 46 months will allow evaluation of key variables more than 1 year following the administration of the fourth vaccine dose in a sufficiently large number of children to meet sample size needs.

A master protocol for the pilot evaluations was developed by WHO and received approval by the WHO Research Ethics Review Committee in February 2018. Country-based research partners have been contracted to implement country-specific protocols. The subsequent sections provide further information about the three evaluation components: a) feasibility; b) impact; and c) safety.

a) Assess the programmatic feasibility of delivering a four-dose schedule, including new immunization contacts, in the context of routine health service delivery

The operational feasibility of providing RTS,S/AS01 at the recommended 4-dose schedule will be evaluated in the context of routine health service delivery. The primary objective of the feasibility evaluation is to estimate the coverage of RTS,S/AS01 in the implementation areas, defined as the proportion of children aged 12-23 months who had received 3 doses of RTS,S/AS01 by 12 months of age, and the proportion of children aged 27-38 months who had received their fourth dose of RTS,S/AS01 by 27 months of age. The secondary feasibility objectives measure, in implementation and comparison areas, the coverage of recommended EPI vaccines; the coverage and utilization of ITN/LLIN and IRS; changes in malaria diagnosis and treatment practices; and the patterns of health-seeking behaviour for febrile children. In addition to ongoing monitoring of facility-based administrative uptake and coverage data, three cross-sectional household surveys will be conducted in each pilot country over the course of the programme.

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

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

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

b) Evaluate the vaccine's impact on severe malaria and all-cause mortality²⁰

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

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

c) Further characterize vaccine safety in the context of a routine immunization programme, with special attention to the safety signals observed in the Phase 3 trial

In addition to data collected by the ministries of health through strengthened routine pharmacovigilance, and through the GSK Phase 4 study (see #3 below), safety data will be captured in up to 24 sentinel hospitals across the three pilot countries by means of systematic, prospective, monitoring of all paediatric admissions, paying particular attention to meningitis and cerebral malaria. Safety data will be reviewed regularly by a Data Safety and Monitoring Board (DSMB).

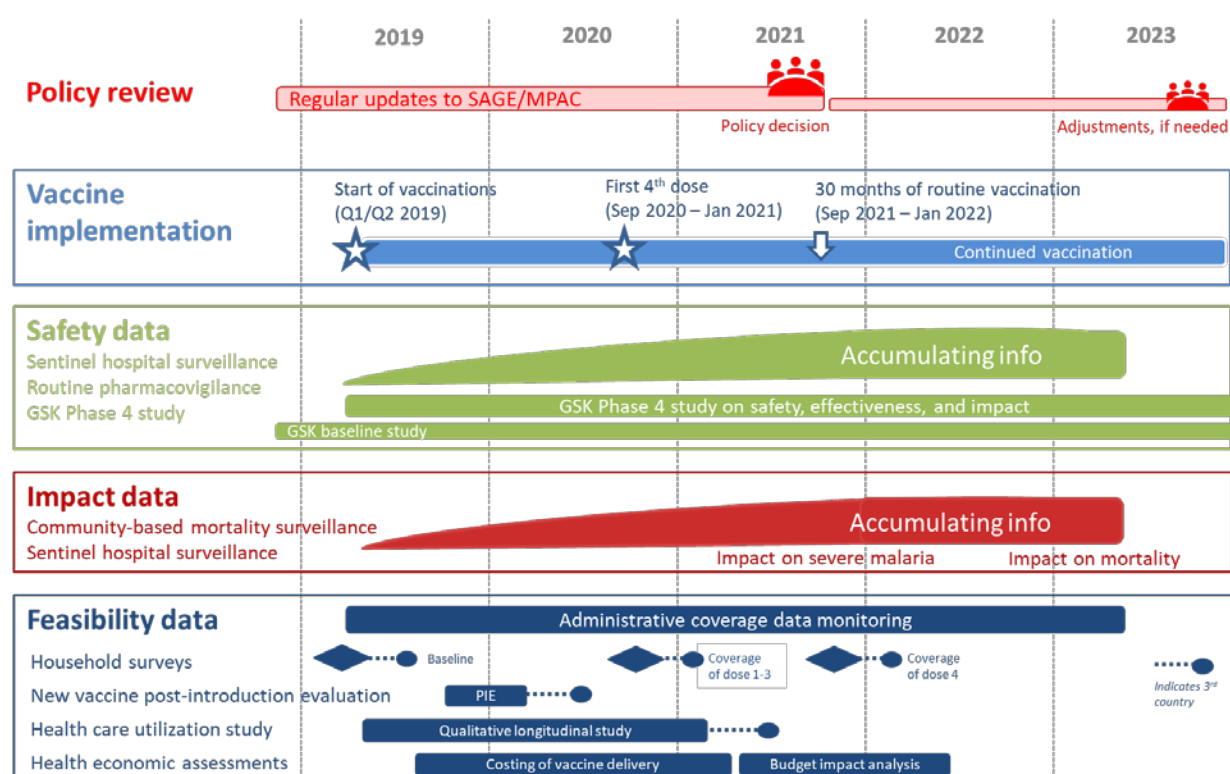
3) GSK-sponsored Phase 4 study

The GSK-sponsored Phase 4 studies form part of the RTS,S/AS01 Risk Management Plan agreed between GSK and EMA to further assess vaccine safety, effectiveness and impact in routine use. In addition to enhanced hospitalization surveillance, the Phase 4 study will include active surveillance through home visits and continuous monitoring of outpatient visits and hospitalisations at health care facilities in a subset of vaccinating and comparison areas. The WHO-sponsored pilot evaluation has been designed to complement the GSK-sponsored Phase 4 study which will take place in a small subset of the pilot area of each country.

Evidence and experience from the pilot implementations will be provided to the SAGE and MPAC to inform recommendations on the vaccine's potential use on a wider scale in Africa. (See Figure 2)

²⁰ The evaluation of impact will depend on community mortality surveillance and is powered to detect a 10% reduction in all-cause mortality in each country. This is expected to be complete in 2023.

Figure 2: Timeline of MVIP data generation and review



V. DATA AND INFORMATION USED BY THE WORKING GROUP TO INFORM RECOMMENDATIONS

A. New data available since the 2015 SAGE/MPAC recommendation for pilots

Results from Phase 3 long-term follow-up study (MAL-076)

MAL-076 was a long-term open-label follow-up study conducted in 3 out of the 11 Phase 3 trial sites (Korogwe [Tanzania], Kombewa [Kenya] and Nanoro [Burkina Faso]). Children 5–17 months of age at first vaccination who were enrolled in the trial were followed for a median of four years during the Phase 3 trial and then followed for an additional three-year period for the MAL-076 study (for a total follow-up time of approximately seven years after administration of the first three RTS,S/AS01 doses) [11]. The primary objective of the MAL-076 study was to describe incidence of severe malaria over the additional three-year follow-up period. Secondary objectives were to assess clinical malaria incidence, malaria hospitalization, fatal malaria, and cerebral malaria during the additional three-year period and overall seven years of follow-up. Selected serious adverse events (SAEs) were also recorded during follow up. In addition to prospective data collection, retrospective data were collected during the gap period between the end of the Phase 3 MAL-055 and the start of MAL-076 study.

The three MAL-076 study groups were comprised of children who were participants in the Phase 3 trial at these three long-term follow up sites and whose parents had consented to their participation in the long-term study follow-up. Children who had been randomized to the 4-dose and the 3-dose malaria vaccine groups or the control group for both age categories were eligible to participate in MAL-076. Out of the 2512 children aged 5–17 months vaccinated in the 3 participating sites from Phase 3 MAL-055 trial, 1739 were enrolled in the MAL-076 study. The incidence of severe malaria was low in all study sites for both age categories during the three-year period of long-term follow up. In the 5–17-month age group vaccine efficacy (VE) against severe malaria decreased over time, and overall during the seven years of follow-up was 37% (95%CI: 15; 53) in the 4-dose group and 10% (95% CI: 18; 32) in the 3-dose group (Table 3). VE against clinical malaria also decreased over time; overall during the seven years of follow-up in the 5–17 months age category, VE against clinical malaria was 24% (95% CI: 16; 31) in the 4-dose group and 19% (95% CI: 11; 27) in the 3-dose group. In the 5–17 months age category, a statistically significant increased incidence of clinical malaria in RTS,S/AS01 recipients versus controls was observed over the last three years of the seven year follow-up only in Nanoro (VE: -37% [95% CI: -44; 73]), an area of highly seasonal malaria transmission, and only for the 3-dose group. VE against malaria hospitalizations was similar to the VE against severe malaria.

Table 3. Results for Severe Malaria* in the MAL-076 study, 5–17 month age category

Group	4 doses RTS,S/AS01			3 doses RTS,S/AS01			Control
N	594			561			593
Period	n	% VE	(95% CI)	n	% VE	(95% CI)	n
M0-M20							
Mal-055 pre-dose 4	32	50.58	(24.52; 67.65)	57	10.61	(-27.6; 37.38)	65
M21-M48 (SE)							
Mal-055 post dose 4	31	-2.28	(-68.3; 37.85)	28	6.06	(-56.7; 43.67)	31
M48 - 3 years							
Mal-076 only	7	53.68	(-13.7; 81.13)	11	23.33	(-67.1; 64.82)	15
Total (overall 7 years)	70	36.69	(14.6; 53.07)	96	10.14	(-18.1; 31.64)	111

*Case definition 2: *P. falciparum* asexual parasitemia >0 (within -1 to +3 days of admission) and at least one marker of severe disease **OR** SAE report (within -1 to +3 days of admission) including preferred term of “Malaria”, “*P. Falciparum* infection” or “Cerebral malaria”

SAEs were similar between 4 dose, 3 dose, and control groups; none were vaccine-related. Fatal SAEs were reported in 1/2/2 (R3R/R3C/C3C) children in the 5–17 months age category. One case of meningitis was reported in the control group of the 5–17 months age category and was not fatal. No cases of cerebral malaria were reported.

Based on these results, VE against severe malaria remains positive during the 7 years following initial vaccination when 4 doses are provided and VE against clinical malaria remains positive for 7 years when 3 or 4 doses are provided. MAL-076 data indicate no indication of an age shift (or rebound) of severe malaria following 4 vaccine doses. The observed age shift in severe malaria following vaccination among children who received only 3 vaccine doses in MAL-055 was limited in time. Furthermore, over the entire period, there was no excess in severe malaria cases. Incidence of severe malaria declined considerably when children grew older regardless of the study/vaccine group. This decline was observed in the Phase 3 trial as well (Figure 3). One site with strong seasonal malaria (Nanoro, Burkina Faso) showed a period of increased risk for uncomplicated malaria, but this was not preceded by, nor did it result, in an increased risk for severe malaria.

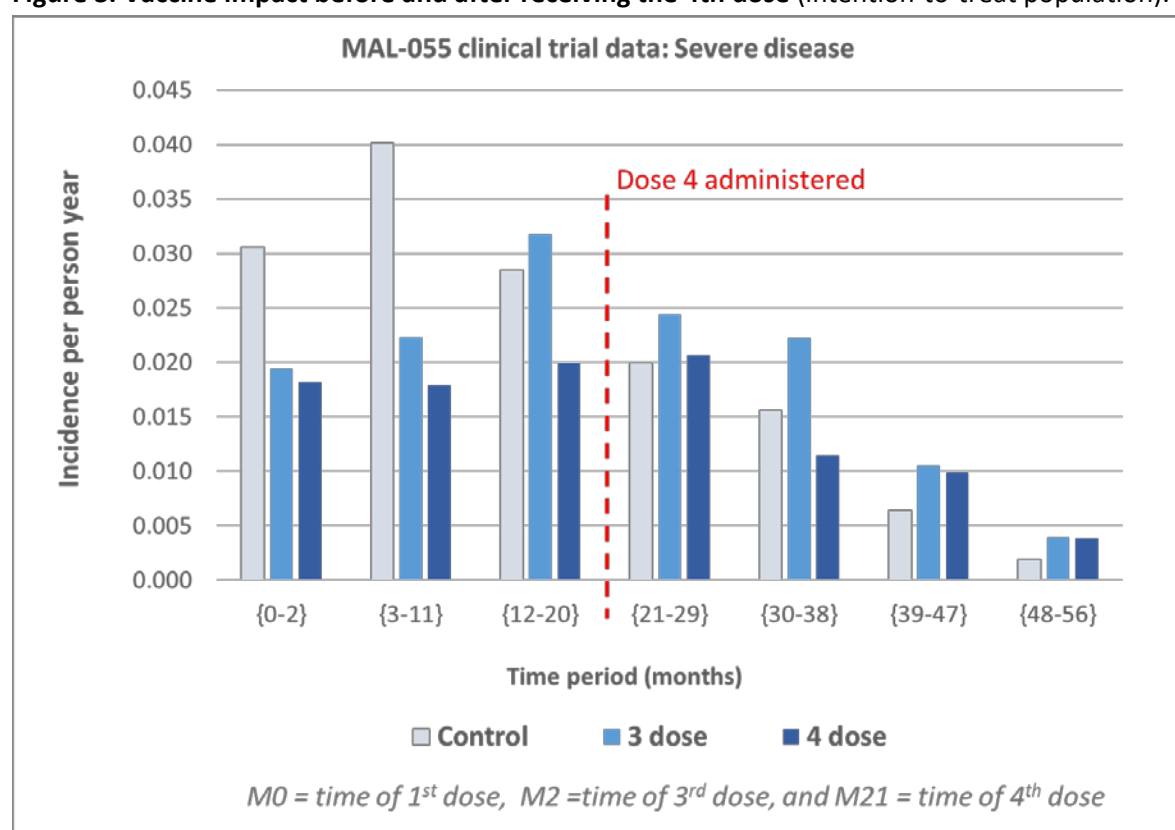
Further analysis of MAL-076 and MAL-055 data

The modelling groups at Swiss TPH and Imperial College were engaged to estimate thresholds of vaccine coverage that predict impact—in particular, on what levels of coverage (overall and for the fourth dose) are sufficiently high to be considered good public health value. The models (which were validated with MAL-076 data) predict small incremental impact of the fourth dose, with over 90% of impact achieved with the administration of the first 3 doses. The modelers were unable to reproduce the extent of the rebound observed in the Phase 3 trial. These estimates and inability to reproduce the extent of the rebound are consistent with the 2015 modelling analysis.

Data presented from the Phase 3 trial, showing severe malaria incidence per person-year, plotted in 6-monthly intervals show a marked decline in severe malaria incidence, with very low incidence of severe malaria by months 48-56 months follow-up in all three study arms (Figure 3).

After reviewing the modelling results and data from the MAL-076 study, the Working Group requested from GSK additional statistical analysis of the MAL-055 data (1) to better understand the difference between modelling results and Phase 3 trial results, and (2) to try to quantify the incremental benefit of the fourth dose for clinical or severe malaria relative to the first three doses, over time and to end of MAL-055. The additional analysis was reviewed by the Working Group, but provided little definitive information to better understand the benefit of the fourth dose.

Figure 3. Vaccine impact before and after receiving the 4th dose (intention-to-treat population).



Source: Modelling groups with permission from GSK

Severe disease incidence per person year plotted every 6 months after dose 3 is administered. The dotted line represents when the fourth dose is given. We see a difference between the 3-dose and 4-dose groups before the fourth dose is given. Additional analyses did not reveal a reason for this difference, which is considered a chance finding.

B. Policy considerations for the Working Group

Annex 5 includes the full summary of the malaria intervention policy background, prior SAGE policy decisions on vaccines, and considerations around operational feasibility.

Standards applied for other vaccine policy recommendations

Prior SAGE policy decisions on other vaccines were reviewed to inform questions pertinent to RTS,S/AS01 with attention to the type and quality of data available at the time of a recommendation. Rotavirus vaccines, PCVs, and dengue vaccine case studies were the most relevant examples for this exercise. Specifically the group focused on the following issues in prior policy decisions:

- Assessment of safety signals for risk-benefit assessment
- Availability of mortality impact data
- Consideration of disparate efficacy or impact results across study sites/countries
- Availability of feasibility and cost-effectiveness data

As illustrated by the case studies in the Annex, global policies for vaccine use evolve after initial licensure, prequalification, and SAGE recommendations, as additional information, including mortality data, are generated over time.

Malaria intervention policy recommendations

The Malaria Policy Advisory Committee advises WHO on recommendations for malaria control interventions. Currently recommended malaria prevention tools include long lasting insecticidal nets (LLINs), Intermittent Preventive Treatment in infants (IPTi), Intermittent Preventive Treatment in pregnancy (IPTp), indoor residual spraying (IRS), and in areas with highly seasonal malaria, seasonal malaria chemoprevention (SMC). Increased rollout of malaria control methods had led to over 50% reduced malaria mortality in sub-Saharan Africa since 2000 [2], but ongoing gaps in access to preventive, diagnostic and treatment measures continue to exist.

C. Operational feasibility: Expected MVIP coverage based on Immunization coverage trajectories over time following new vaccine introductions

Definition of “high” coverage

The JTEG has recommended that “high” immunization coverage be documented in order to recommend continued implementation. However, as the SAGE has previously recognised (SAGE, April 2018), the relatively low coverage levels of the second dose of measles-containing vaccine (MCV2) provided to children aged 15–18 months in MVIP countries could indicate challenges in reaching children in the second year of life with the fourth dose of RTS,S/AS01. Receiving all four doses of the vaccine provides optimal benefit of the vaccine and appears to prevent the age-shift in timing of severe disease that was observed in the Phase 3 trial among children randomized to receive only 3 vaccine doses. Long-term follow up data from the MAL-076 study are reassuring, showing no excess risk of severe malaria among those who receive only 3 doses and modeling estimates based on Phase 3 data predict that the added benefit of a fourth dose may be small compared to that of the first three doses. Nonetheless, given uncertainty around the added benefit of a fourth dose, efforts at maximizing coverage of the full four dose series during the Programme is desirable.

Considering experience with introduction of other childhood vaccines, the definition of “high” coverage is challenging, and would be expected to differ for the third and fourth doses of RTS,S/AS01. Coverage is expected to be lower for the fourth dose of RTS,S/AS01 compared to the third dose because of healthcare visits during the second year of life are less well established than those in infancy. Examples from other vaccine introductions were reviewed to determine realistic goals for coverage based on the strength of the immunization system to support the additional vaccine introduction and new immunization schedule.

Documentation of achieving high coverage is not typically a prerequisite for a WHO policy recommendation for vaccine introduction (see section V), unless there is an epidemiological rationale. For example, with vaccines that induce population-level protection (“herd immunity”), suboptimal childhood vaccination coverage can lead to an age shift in disease at the population level, but this principal does not apply to malaria vaccination as the RTS,S/AS01 vaccine is expected to provide individual protection only and not expected to have an effect on malaria transmission.

Strength of routine immunization in the pilot countries

After responding to call for expressions of interest, Ghana, Kenya, and Malawi were selected for participation in the pilot implementations based on standardized criteria, including demonstration of a strong EPI programme. Coverage levels for diphtheria-tetanus-pertussis (DTP) and MCV are considered indicators of health system performance. Vaccines given in the second year of life, such as MCV2 and meningococcal A vaccine are relevant when considering potential RTS,S/AS01 coverage (see Table 7 in Annex 5). The additional visits to be introduced for RTS,S/AS01 can be leveraged as opportunities to reach children at critical time points for well child exams, including weight monitoring, and to provide vitamin A and deworming recommended at two years of age.

Table 4. Integration of RTS,S/AS01 into the childhood vaccination schedule /1

Child Age Vaccine/1	Birth	6 wks	10 wks	14 wks	5 mo	6 mo	7 mo	9 mo	12 mo	18 mo	22 mo	24 mo
BCG	①											
Oral polio	①	①	②	③								
DTP-HepB-Hib (penta)		①	②	③								
Pneumococcal conj.		①	②	③								
Rotavirus		①	②									
Inactivated Polio				①								
Meningococcal A conj.										①		
Measles-Rubella								①		②		
Yellow Fever								①				
Vitamin A						①			②	③		④
RTS,S/AS01 in Ghana						①	②	③				④
RTS,S/AS01 in Kenya						①	②	③				④
RTS,S/AS01 in Malawi					①	②	③				④	

1/ The upper part of the table reflects Ghana’s vaccination schedule

Based on the WHO recommendations, the EPI Programmes defined the most appropriate target age for children to receive each dose of RTS,S/AS01 given the existing routine immunization schedule (see Table 4). Ghana and Kenya will provide the four doses at 6, 7, 9, and 24 months of age. Delivery of the second dose at 7 months of age will be a new vaccination contact point in these two countries.

Malawi opted for a different schedule with the four doses given at 5, 6, 7, and 22 months of age, in an effort to administer the primary vaccination series- and partial protection against malaria- as early as possible; this requires three new vaccination contacts.²¹

ACKNOWLEDGEMENTS

The WHO secretariat would like to thank the FPD Working Group members, and Professor Peter Smith as chair, for their thoughtful deliberations in the development of the Framework for Policy Decision on RTS,S/AS01. This document reflects their expertise in child health, insight into the policy process, and critical thinking around the questions and data presented for their consideration. WHO also appreciates the MVIP Programme Advisory Group for their review of the document, and the input from Drs. Laurence Slutsker and Scott Gordon of PATH. WHO appreciates the technical and administrative support provided by Cynthia Bergstrom, PATH, to ensure effective delivery on the Working Group's Terms of Reference.

The FPD Working Group would like to acknowledge the openness and responsiveness of the manufacturer in providing access to data and performing additional analyses requested by the Working Group and the WHO secretariat.

The Working Group thanks Dr. Melissa Penny and colleagues from the SwissTPH as well as Drs. Azra Ghani and Alexandra Hogan from Imperial College, with coordination from Farzana Muhib of PATH, for analysis and modelling of the MAL-076 and MAL-055 data that spurred Working Group discussions and input into this document.

Furthermore, there were several valuable contributions to the content of this document. Drs. Jenny Waldorf and Rebecca Casey of the United States Centers for Disease Control and Prevention prepared the policy precedent on immunization and presented to the Working Group. Key inputs on the malaria policy precedent were prepared by Ryan Thompson of the Johns Hopkins Bloomberg School of Public Health.

²¹ Malawi decided to schedule the first dose at 5 months in order to reach children at the earliest age for which the vaccine is recommended. The target age of 22 months for the fourth dose reflects the minimal interval of 15 months from the third dose.

Annex 1: FPD Working Group Terms of Reference

World Health Organization
Terms of Reference
Malaria Vaccine Implementation Programme
Framework for Policy Decision – Working Group

Background on the Malaria Vaccine Implementation Programme

In January 2016, following a joint review of evidence by WHO's Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC), WHO published its policy recommendation for RTS,S/AS01, the first malaria vaccine. WHO recommended pilot implementation of the RTS,S/AS01 vaccine in distinct settings in sub-Saharan Africa in order to generate critical evidence to enable decision-making about potential wider scale use.

The Malaria Vaccine Implementation Programme (MVIP) has been developed to execute the 2016 WHO recommendation for pilot implementation of the of the RTS,S/AS01 malaria vaccine to address several outstanding questions related to the public health use of the vaccine. The MVIP supports routine introduction of the malaria vaccine in selected areas of 3 countries (Ghana, Kenya and Malawi) and rigorous evaluations to:

- Assess the programmatic feasibility of delivering a four-dose schedule, including new immunization contacts, in the context of routine health service delivery;
- Evaluate the vaccine's impact on severe malaria and all-cause mortality; and
- Further characterize vaccine safety in the context of a routine immunization programme, with special attention to the safety signals observed in the Phase 3 trial.

As part of the 2015 review process, the Joint Technical Expert Group (JTEG), comprised of MPAC and SAGE members, advised WHO to monitor emerging data from the MVIP; "If concerns about safety are resolved, implementation data are favourable and fourth dose coverage is high, WHO might recommend broader introduction prior to pilot end."

WHO assumes the overall scientific and technical leadership and is responsible for coordinating and overseeing all activities corresponding to the RTS,S/AS01 implementation and evaluation in the context of the MVIP. The Programme is jointly led by the Global Malaria Programme (GMP) and the Immunization, Vaccines & Biologicals (IVB) departments at WHO, collaborating closely with AFRO and country offices, ministries of health in pilot countries, and PATH, as well as coordinating relevant activities with the vaccine manufacturer, GlaxoSmithKline Biologicals.

Purpose of the MVIP Framework for Policy Decision

During their April 2017 meetings, MPAC and SAGE endorsed the establishment of a joint working group to develop a MVIP Framework for Policy Decision for RTS,S/AS01. Through the Framework, MPAC and SAGE will be able to consider, align on, and document in advance, how data collected through the MVIP might be used to answer the key outstanding questions on feasibility, impact, and safety of RTS,S/AS01 to inform WHO policy on broader use of the vaccine. The Framework will consider the use and relative weight of data collected through the pilot (1) at the pilot end, when final results are available; (2) during the course of the MVIP, when emerging data might suggest earlier broader

introduction; and (3) after approximately 30 months of pilot introduction, when the vaccine could be expanded to the comparator areas of the pilot if data indicate a positive benefit-risk profile.

The Framework serves several important functions: it will prompt WHO advisory groups and policy makers to consider the data being collected at this early stage to assure the data to be collected are sufficient to support a policy decision; it will enable MPAC and SAGE to refine their understanding of the relative contribution of the collected data (feasibility, safety, impact) to a future policy recommendation; and it will document the expected use of the data in anticipation of changes in MPAC and SAGE membership between the time the MPAC/SAGE recommendations were made (2015) and when MVIP data are available.

Purpose of the MVIP Framework for Policy Decision Working Group

The development of the MVIP Framework for Policy Decision on RTS,S/AS01 will be a collaborative process among representatives from advisory bodies involved in malaria vaccine policy decision making. The role of the MVIP Framework for Policy Decision Working Group (Working Group) is to deliberate on the use of the data collected through the MVIP in the context of the SAGE/MPAC recommendations on pilot introduction, and to make recommendations to the PAG. The deliberations will be recorded, as will recommendations, and shared with the MVIP Programme Advisory Group for consideration, then SAGE and MPAC for their endorsement and advice to WHO leadership (including the ADGs of FWC and HTM and the RD of AFRO, and the Directors of IVB, GMP and AFRO) and the MVIP Programme Coordination. Specific responsibilities of the Working Group include:

- Consider the JTEG, SAGE/MPAC and WHO recommendations around the use of data on feasibility, safety and impact and discuss and recommend the relative contribution of the collected data to a future policy decision
- Consider and discuss specific questions on the use of the data for policy decision and consider whether there are other important questions that should be considered
- Discuss any unintentional consequences that might come from particular decisions around the use of the data (e.g. undue delay in vaccine availability; expansion too early; impact on supply from the manufacturer)
- Determine most appropriate means to translate the above considerations into a framework, set of recommendations to WHO advisory bodies, or key considerations for WHO advisory bodies
- Discuss how the Framework for Policy Decision should be made available and/or utilized
- Provide regular updates to their respective WHO advisory bodies on the Framework for Policy Decision progress and Working Group deliberations
- Participate in the presentation of the Framework for Policy Decision for review and endorsement of their respective advisory bodies

The Working Group has no executive, regulatory or decision-making functions. The Framework and guidance provided by the Working Group will be non-binding on WHO and the Working Group will not directly analyze or review MVIP data.

Working Group Membership

The Working Group will have representation from the WHO advisory bodies that will monitor MVIP progress and/or make recommendations on future use of the malaria vaccine based on MVIP data:

- Malaria Policy Advisory Committee (MPAC) – up to 3 members
- Strategic Advisory Group of Experts (SAGE) on Immunization – up to 3 members
- MVIP Programme Advisory Group (PAG) – up to 3 members
- Immunization & vaccines related implementation research advisory committee (IVIR-AC) –1
- Modelling groups that generate estimates to inform policy decisions – 1 member

Framework for Policy Decision Working Group members will be selected based on recommendations from the chairs of the respective advisory groups. Members will serve in their personal capacities for their scientific and technical knowledge and experience, as well as their commitment and willingness to volunteer the necessary time and effort. Members must respect the impartiality and independence required of WHO, as it also applies to their membership on their respective advisory bodies. When traveling for Working Group activities, members will be reimbursed for travel costs and accommodation according to WHO standard procedures.

Members should be free of any real, potential or perceived conflict of interest. In performing their work, they may not seek or accept instructions from any Government or from any authority external to the Organization, with respect to the matters to be discussed by the Working Group. Members are required to complete a declaration of interest form prior to their appointment and each meeting and their participation is subject to the evaluation of completed forms by the WHO Secretariat.

Working Group Meetings and Operations

The Working Group is expected to meet once in 2018 and once in 2019. Teleconferences will be called as needed until the Framework is finalized, in 2019. Additional meetings may be called if required.

Information and documentation to which members may gain access in performing MVIP related activities should be considered as confidential and proprietary to WHO and parties collaborating with WHO. Working Group members shall not purport to speak on behalf of, or represent, the MVIP or WHO to any third party. All proposed members will be required to sign an appropriate confidentiality undertaking and provisions on ownership.

WHO, as the secretariat, will provide technical and administrative support to the Working Group to ensure effective delivery on its Terms of Reference.

Presentation of Working Group's Deliberations and Recommendations

The Framework, together with a report of the deliberations and any accompanying recommendations generated by the Working Group will be presented to the MVIP Programme Advisory Group to consider prior to presentation to MPAC and SAGE for their consideration and advice to WHO.

WHO will retain control over the conduct of the MVIP and any subsequent recommendations, decisions, or actions by WHO regarding any proposals, policy issues, or other matters considered by the Working Group. WHO retains full control over the publication of reports from the Working Group meetings, including whether to publish them.

Annex 2: FPD Working Group membership and convenings

A. Working Group Members

Immunization and vaccines related implementation research advisory committee (IVIR-AC)

Quique Bassat, ISGlobal Institute for Global Health Hospital Clinic, Universitat de Barcelona

Malaria Policy Advisory Committee (MPAC)

Gabriel Carrasquilla, Asesorias e Investigaciones en Epidemiologia Salud Y Medio Ambiente (ASIEALAUD), Colombia

Umberto D'Alessandro, Medical Research Council Unit, The Gambia and LSHTM United Kingdom

Modelling groups (SwissTPH and Imperial College)

Melissa Penny, Swiss Tropical and Public Health Institute, Switzerland

MVIP Programme Advisory Group (PAG)

Eusebio Macete, Centro de Investigaçao da Manhica (CISM), Mozambique

Kim Mulholland, London School of Hygiene and Tropical Medicine, United Kingdom/MCRI, Australia

Peter Smith, London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom - **Chair**

Strategic Advisory Group of Experts (SAGE) on Immunization

Terry Nolan, Murdoch Children's Research Institute, Australia

Fred Were, University of Nairobi, Kenya (also PAG member)

B. Working Group convenings

The Working Group has been convened three times: an initial teleconference on 17 July 2018, a face-to-face meeting in Geneva on 3 to 4 December 2018, and a teleconference on 11 February 2019.

Members completed a declaration of interest form prior to each meeting, which the WHO secretariat evaluated and determined there to be no conflicts.

Annex 3: Questions presented to FPD Working Group

Discussion during the Working Group's meeting on 3-4 December 2018 was structured around the below key questions to consider in the context of RTS,S/AS01.

<p>Key questions A – policy recommendation for broader use across sub-Saharan Africa: <i>The Joint Technical Expert Group on Malaria Vaccines (JTEG) noted in its report (Sept 2015): It would be appropriate for WHO to recommend countrywide introduction if concerns about safety have been resolved, and if favourable implementation data become available, including high coverage of the fourth dose.</i></p>
<p>1. What would be considered “resolved” safety concerns? (a) Meningitis: what level of increased risk would need to be ruled out (8:1; ...2:1, other?) (b) Cerebral malaria: what level of increased risk would need to be ruled out? (c) Sex-specific mortality: what level of increased risk would need to be ruled out? (d) What if safety signal(s) get confirmed but a favourable benefit risk profile persist?</p>
<p>2. What would be considered “high coverage of the fourth dose”? (a) Can a threshold of coverage be defined above which sufficient impact would be predicted? (b) If a threshold for predicting impact cannot be defined, a recommendation might rely on trial data (~90% 4 dose coverage) prior modelling data (72% 4 dose coverage) or impact findings from the pilot, (impact on severe malaria or mortality).</p>
<p>3. What would be considered “favourable” implementation data, and what would be required for an early policy recommendation? (a) No or little adverse effect on coverage of other vaccines? Or timing of other vaccines? (b) Continued use of ITNs (or if reduced use, impact data still positive)? (c) No change in health seeking behaviour for fever? (d) Cost effectiveness?</p>
<p>4. What criteria, if met, would likely lead to a recommendation <u>not</u> to implement the vaccine</p>
<p>5. What is role of data to measure impact on all-cause mortality? (a) MPAC states not required for policy recommendation; severe malaria is marker of mortality.</p>
<p>Key questions B – expansion within the three MVIP countries: <i>The WHO Research Ethics Review Committee emphasizes that if the RTS,S/AS01 vaccine is seen as beneficial, it should be offered in the comparator areas as soon as possible (i.e. when comparator areas are no longer required for assessment of safety or impact, approximately 30 months after vaccinations begin)?</i></p>
<p>1. What criteria should be met before expansion of RTS,S/AS01 into pilot comparator areas can be considered?</p>
<p>2. What about expansion beyond the pilot areas in the three MVIP countries? Would this necessarily be tied to a policy recommendation for broader use across Sub-Saharan Africa?</p>
<p>Key questions C - conflicting or delayed data: <i>The MVIP takes place in Ghana, Malawi and Kenya. Current target start dates are close together, all expected in Q1 2019. Safety endpoints are powered based on pooled data from all three countries; impact endpoints are powered based on each country.</i></p>
<p>1. How would conflicting data from different countries be considered?</p>
<p>2. How would data be considered if data from one of the 3 countries was delayed?</p>

Annex 4: Expected timing of availability of pilot implementation evidence

Based on current assumptions across the three MVIP countries' related to the expected rate of accumulating events malaria prevalence and vaccine introduction timings, the Working Group received a summary of the expected timing of availability of evidence around 24 months after the start of vaccine introduction in the first country.

Based on the assumption that the mortality rate is 8.5/1000/year, and the size of each cluster is as described in the protocol with an assumed annual birth cohort of 4000, it is expected that enough events will have accrued by month 24 to have about 90% power to exclude the female:male mortality ratio being 20% higher in the RTSS arm than in the control arm (if there is no interaction by sex) (using the method for power calculation for interaction described by Cheung et al., Tropical Medicine and International Health 13:247d In, 2008).

Using a similar method, comparing between arms the differences in rates in vaccine-eligible and non-eligible age groups within clusters, and assuming rates of 0.4/1000/year for meningitis, and 2/1000/year cerebral malaria, there is about 80% power to rule out a 3-fold or greater increased rate of meningitis associated with introduction of RTSS vaccine (if RTSS does not increase the risk of meningitis); and about 90% power to rule out a 2-fold or greater increase in risk of cerebral malaria (if there is no effect (increase or decrease) on cerebral malaria incidence), by month 24. There is over 80% power to detect a 30% reduction in severe malaria by month 24 by country, or a 10% reduction in mortality by month 24 across all countries combined.

Updated calculations will be done when preliminary data on actual event rates are available, four to five months after vaccinations start. These estimates will be included in the MVIP Statistical Analysis Plan, under development, as will case definitions and indicators.

Annex 5: Prior vaccine and malaria intervention policy decisions and considerations

A) Standards applied for other vaccine policy recommendations

The Working Group reviewed prior SAGE policy decisions on other vaccines to inform questions pertinent to RTS,S/AS01 with attention to the type and quality of data available at the time of a recommendation. Rotavirus vaccines, pneumococcal conjugate vaccines, and dengue vaccine case studies were the most relevant examples for this exercise. Specifically the group focused on the following issues in prior policy decisions:

- Assessment of safety signals for risk-benefit assessment
- Availability of mortality impact data
- Consideration of disparate efficacy or impact results across study sites/countries
- Availability of feasibility and cost-effectiveness data

As illustrated by the case studies below, global policies for vaccine use evolve after initial licensure, prequalification, and SAGE recommendations, as additional information, including mortality data, are generated over time.

Pneumococcal conjugate vaccine (PCV)

WHO's initial recommendation for PCV use in 2003 was informed by evidence on efficacy, effectiveness and safety from industrialized settings, but the recommendation did not extend to resource-poor countries. The WHO recommendation for use broadly in national immunization programs was made in 2007 based on review of efficacy, safety and limited mortality impact data from a secondary analysis of one study in the Gambia (16% reduction in all-cause mortality).

Like malaria, pneumonia and pneumococcal disease account for a large proportion of child mortality globally. The 7-valent pneumococcal conjugate vaccine (PCV7) was first licensed in the United States in 2000, and included serotypes covering 65–80% of the serotypes associated with invasive pneumococcal disease among children in the United States and Western Europe. However, serotype coverage was thought to be less compatible for other parts of the world, and the first WHO position paper (2003) [12] did not recommend routine use of PCV in developing countries due to lack of evidence of efficacy and feasibility in those settings. The WHO position at that time was as follows *“Large-scale childhood immunization using the conjugate vaccine has been highly effective in reducing the burden of invasive pneumococcal disease among infants and young children in the United States... Hence, where control of invasive pneumococcal disease in childhood is a public health priority and the vaccine serotypes are shown to match the most important local serotypes, the conjugate vaccine merits consideration for inclusion in national childhood immunization programmes”*. In 2003, the future recommendations for routine use of pneumococcal vaccines in developing countries was deemed to be dependent largely on the demonstration of protective efficacy against pneumonia. At that time, more information was noted to be required by SAGE to assess the impact of conjugate vaccines on the incidence and mortality of pneumonia among infants and other high-risk groups in developing countries.

The first WHO recommendation for introduction of PCV in national immunization programmes was made in 2007 [13], noting priority in countries with high prevalence of child mortality: “*WHO considers that pneumococcal conjugate vaccine should be a priority for inclusion in national childhood immunization programmes. Countries with mortality among children aged <5 years of >50 deaths/1000 births or with more than 50,000 children’s deaths annually should make the introduction of PCV-7 a high priority for their immunization programmes*”. This recommendation was based on Phase 3 trial vaccine efficacy and safety data for PCV-9 from developing settings. Vaccine impact data were available from industrialized settings that had introduced vaccine previously and were accruing post-marketing data.

At the time of the 2007 recommendation data were available from a Gambian randomized clinical trial (RCT) showing that the efficacy of 3 doses of PCV-9 against vaccine-type invasive pneumococcal disease was 77% (95% CI, 51–90%), and efficacy against invasive disease regardless of pneumococcal serotype was 50% (95% CI, 21–69%). Another RCT in South Africa found 83% (95%CI, 39–97%) protective efficacy against vaccine-type invasive pneumococcal disease in HIV-negative children and 65% (95% CI, 24–86%) efficacy in HIV-positive children. The efficacy of conjugated pneumococcal vaccine against pneumonia has also been documented in developing countries. In the PCV-9 studies mentioned above, efficacy was 35% (95% CI, 26–43%) in the Gambia and 20% (95% CI, 2–35%) in South Africa using WHO’s standards for radiologically confirmed pneumonia.

At the time of the 2007 recommendation, mortality data were available from the Gambian clinical trial of 9-valent PCV described above which showed a 16% (95%CI, 3–28%) reduction in all-cause child mortality. All-cause mortality was not a primary endpoint in any of the PCV trials. However, in the Gambia trial, the baseline mortality rates were high enough to perform a secondary analysis. Despite the reduction in overall mortality, the Gambian study showed little or no protection against clinically diagnosed pneumonia.

Rotavirus vaccine

WHO initial recommendation in 2007 to introduce rotavirus vaccine if data suggest significant public health impact was based on clinical efficacy data from the United States, Europe, and Latin America; and did not recommend global inclusion of rotavirus vaccines into national immunization programmes given the lack of data from other regions. In 2009, this recommendation was extended to all regions based on the available efficacy data from African and Asian countries.

As with malaria and pneumonia, diarrhea is one of the leading causes of death in children worldwide. Rotavirus is the causative agent for a significant proportion of severe diarrhea in children under five years of age, and especially under one year of age. WHO policy recommendations for rotavirus vaccination have evolved with accrual of evidence since the initial publication of guidance in 2007. At that time, WHO recommended [14] inclusion of rotavirus vaccination in national immunization programs in regions and countries where vaccine efficacy data were available to suggest significant public health impact and where appropriate infrastructure and financing mechanisms were available to sustain vaccine utilization. ‘Significant public health impact’ and ‘appropriate infrastructure’ were not explicitly defined. Clinical efficacy data for Rotarix (RV1) and Rotateq (RV5) were available primarily from the United States, Europe, and Latin America. WHO did not recommend global inclusion

of rotavirus vaccines into national immunization programmes given the lack of data from other regions. In 2007 no increased risk of intussusception in vaccinated groups with either RV1 or RV5 was observed. Given the concern about risk of intussusception from experience with Rotashield where it had been pulled from the market in 2000, WHO also recommended that rotavirus vaccine introduction should be accompanied by careful post-marketing national surveillance to evaluate impact and any potential association between rotavirus vaccines and intussusception in the concerned age group [14].

A revision of the 2007 policy was published in 2009 [15] extending the recommendation for routine rotavirus vaccine introduction globally: “WHO recommends that rotavirus vaccine for infants should be included in all national immunization programmes. In countries where diarrhoeal deaths account for $\geq 10\%$ of mortality among children aged <5 years, the introduction of the vaccine is strongly recommended”. This recommendation was based on new efficacy data available from trials in African (Malawi, South Africa, Kenya, Ghana, Mali) and Asian (Bangladesh, Viet Nam) countries representing multiple mortality strata. In a large RCT of RV1 in Malawi (high mortality rate among children aged <5 years) and South Africa (intermediate mortality rate among children aged <5 years) after 1 year of follow up, the efficacy against severe rotavirus gastroenteritis (RVGE) was 61% (95% CI, 44–73%) in the combined study populations, 77% (95% CI, 56–88%) in South Africa and 50% (95% CI, 19–68%) in Malawi). Despite lower efficacy in Malawi, the number of episodes of severe RVGE prevented by vaccination was higher (3.9/100 vaccinees) than in South Africa (2.5/100 vaccinees) because of the higher incidence of severe RVGE in young infants in Malawi. Initial Phase 3 efficacy results were also available for RV5 in Africa and Asia. The RCT was designed to separately analyse the combined results for the sites in three countries in Africa (Ghana, Kenya and Mali) and the combined results for the sites in two countries in Asia (Bangladesh and Viet Nam). The efficacy of a 3-dose regimen of the vaccine against severe RVGE during the first year of follow-up was 64% in Africa (95% CI, 40–79%). When results are reviewed separately by country, vaccine efficacy at 1 year varied greatly: Ghana 65% (95%CI 35.5–81.9), Kenya 83% (95%CI 25.5–98.2), Mali 1% (95%CI -431.7–81.6) [16]. Upon subsequent review of the Mali results, it was determined that children enrolled in the study were infrequently being brought to medical attention when they became ill and instead were being taken to traditional healers so that very few cases of RVGE were identified. In the second year of the study sensitization of participants was increased, leading to an increase of reported cases and a higher point estimate for vaccine efficacy (19.2% (95%CI -23.1–47.3)) [17]. Despite the variation in findings across sites, the pooled efficacy was considered and cited in the global policy recommendation.

At the time of the 2009 recommendation, post-marketing safety monitoring data were available and showed no increased risk of intussusception in the US, Australia, and Latin America. Data available were sufficient to rule out the level of risk of intussusception that had been seen with Rotashield (attributable risk of 1 case per 10,000 individuals vaccinated). Clinical trials had not been powered to rule out a smaller risk of intussusception. No evidence of mortality impact due to rotavirus vaccine was not available or required for this policy recommendation [15].

A 2013 position paper broadened the policy recommendation for global use of rotavirus vaccines [18]. At the time of this decision, limited evidence of mortality impact had become available from observational studies in Brazil and Mexico. In Brazil, vaccination resulted in 22–28% reduction in diarrhoea-related deaths in children ≤ 2 years. In Mexico, there was a relative reduction in the rate of diarrhoea-related deaths among infants <11 months of age (41%; 95% CI: 36%–47%) and among children aged 12–23 months (29%; 95% CI: 17%–39%). However, secondary analysis of mortality impact was not consistent across trials and study designs were not intended to look at mortality

impact. Although the Brazil and Mexico observational data were considered, the WHO evidence-to-recommendation tables at the time of the 2013 position paper were as follows:

- We are not certain about the effect of use of RV1 on all-cause death in low mortality countries
- We are not certain about the effect of use of RV1 on all-cause death in high mortality countries
- We are not certain whether the use of RV5 in low mortality countries has any effect on all-cause death
- We are not certain whether the use of RV5 in high mortality countries has any effect on all-cause death

In 2013, extensive clinical data supported the safety of both RV1 and RV5 and the benefits of rotavirus vaccination for children. The 2013 WHO position paper noted that the benefits of vaccination far outweigh any currently known risk associated with use of either rotavirus vaccine despite the fact that the RCTs conducted lacked power to rule out very small relative risks of association. No increased risk of intussusception was detected with either RV1 or RV5 in 2 RCTs, each of which including approximately 60 000–70 000 infants and designed to detect a risk similar to that seen with Rotashield (attributable risk 1 per 10 000). Following clinical trials, post-marketing surveillance intussusception data has accrued indicated attributable risk of 1-2 per 100,00 at the time of the 2013 position paper; intussusception surveillance data continues to accrue and attributable risk varies by setting but has remained in the range of 1-5 per 100,000 children [18]. The SAGE recommended that country-specific plans for rotavirus vaccine introduction consider not only potential public health impact and risk, but also cost-effectiveness, affordability, and financial and operational impact on the immunization delivery system.

The FPD Working Group discussed the utility of comparing relative and attributable risk of intussusception in relation to impact on rotavirus hospitalizations and deaths averted as a potential threshold that could be applied when considering RTS,S/AS01 meningitis and cerebral malaria risk. Table 1 provides reference data from the Mexican and Brazilian studies described above as well as from Australia and the USA.

Table 1. Risk–benefit estimates of rotavirus disease and intussusception outcomes by country (adapted from Table 2, Rha et al. *Expert Reviews Vaccines* 2014 [19])

Country	Outcome	Rotavirus outcomes averted	Intussusception outcomes caused	Rotavirus outcome averted: intussusception outcome caused	Ref
Mexico	Hospitalizations	11,551	41	282:1	[20]
	Deaths	663	2	331:1	
Brazil	Hospitalizations	69,572	55	1265:1	[20]
	Deaths	640	3	213:1	
Australia	Hospitalizations	6,528	14	466:1	[21]
	Deaths	NR	NR	NR	
USA	Hospitalizations	53,444	35-166	322-1530:1	[22]
	Deaths	14	0.1-0.5	28-134:1	
Estimates based on one vaccinated birth cohort to age 5 years. NR: Not reported					

Dengue vaccine

In 2016, WHO recommended that countries should consider introduction of the dengue vaccine CYD-TDV in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease. The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination. In 2017, SAGE considered newly available safety data which showed an increased risk of hospitalized and severe dengue in seronegative individuals after year 3 to 66 months of follow-up, and in 2018 recommended that countries using the vaccine for dengue control should implement pre-vaccination screening so that only seropositive individuals are vaccinated.

Dengue is a mosquito-borne illness that causes both asymptomatic infection and in some cases can cause severe hemorrhagic disease and death. Four viral serotypes exist; infection leads to development of temporary protective immunity to the infecting serotype. After an initial infection, as immunity wanes, individuals are at risk for severe disease [23]. In contrast to malaria, there is no specific treatment for clinical dengue disease. CYD-TDV (Dengvaxia®) is a live attenuated (recombinant) tetravalent vaccine, licensed in December 2015 for individuals 9 to 45 years of age in geographic settings with high burden of disease and dengue seroprevalence 70% or greater. It is recommended as a 3 dose series with doses 6 months apart. As of June 2018, CYD-TDV has been approved for licensure by regulatory authorities in 20 countries.

In July 2016, WHO published the first position paper on dengue vaccine [23] with a recommendation as follows *“Countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease... The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination... Use of CYD-TDV in populations in which seroprevalence is low in the age group considered for vaccination is not recommended because of low efficacy and potential longer-term risks of severe dengue in vaccinated seronegative individuals”*.

This WHO position was informed by clinical trial and safety data, mathematical modelling and cost-effectiveness analyses which suggested that the public health benefits of vaccination could be maximized if dengue seropositivity was high in the age group targeted for vaccination. Data on CYD-TDV was available from two parallel Phase 3 randomized clinical trials, known as CYD14 and CYD15. CYD14 was conducted at sites in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Viet Nam), with 10 275 participants aged 2–14 years at first vaccination. CYD15 was conducted at sites in 5 countries in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico (USA)), with 20 869 participants aged 9–16 years at first vaccination. Vaccine efficacy against virologically-confirmed dengue illness was assessed during the active phase of surveillance (25 months post-enrolment). Per protocol vaccine efficacy against virologically-confirmed symptomatic dengue illness of any serotype was 56.5% (95% CI 43.8%–66.4%) in CYD14, and 60.8% (95% CI 52.0%–68.0%) in CYD15 (from one month post dose 3 for 12 months). Vaccine efficacy varied by country, with efficacy ranging from 31.3% (95% CI 1.3%–51.9%) in Mexico to 79.0% (95% CI 52.3%–91.5%) in Malaysia.

The lower limit of the licensed indication at 9 years of age was chosen due to a safety concern identified in the Phase 3 clinical trials. During hospital-based surveillance, a signal emerged in the 2–5

year age group (age group only included in CYD14). While the cumulative relative risk of hospitalized dengue illness between vaccine and placebo arms in the 2–5 year age group during the entire trial period to date was not statistically significant (1.3 (95% CI 0.8–2.1)), a statistically significant RR of 7.5 (95%CI 1.3–313.8) was observed among 2-5 year olds only in the period in year 3 after dose 1. There were 15 hospitalized dengue cases in vaccinated children versus 1 in unvaccinated children [23]. Several hypotheses have been suggested to explain the results, including that in seronegative children, of whom there is a higher percentage in the younger age groups, the vaccine may act as a silent natural infection that primes seronegative vaccinees to experience a secondary-like infection upon their first exposure to dengue virus. At the time of the April 2016 SAGE meeting and July 2016 WHO position, this increased risk had not been observed in those aged 9 years and older. At that time, the SAGE noted the limited safety data in seronegative populations and recommended post-marketing safety surveillance to monitor hospitalized and severe dengue illness in vaccinated persons.

Feasibility data were available nor cited as a requirement for the policy recommendation despite challenges associated with implementation of the 3-dose vaccination schedule in the target population of older children and the multiple new visits required to meet the schedule.

A revision to the SAGE recommendation occurred following the April 2018 SAGE meeting due to new safety data from November 2017 showing that while overall population level benefit was favourable, there was an increased risk of hospitalized and severe dengue in seronegative individuals after year 3 to 66 months of follow-up [24]. 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. The SAGE considered the safety data as well as feasibility of individual pre-vaccination screening, and recommended that countries using the vaccine for dengue control should implement pre-vaccination screening so that only seropositive individuals are vaccinated.

Neither the original policy recommendation for use nor the recent revision considered mortality impact as mortality impact data were not available.

B) Standards applied for malaria intervention policy recommendations

In contrast to the process for SAGE vaccine policy decisions published in position papers, malaria intervention policy decisions have not followed a consistent procedure or format for publication. Currently recommended malaria prevention tools include long lasting insecticidal nets (LLINs), Intermittent Preventive Treatment in infants (IPTi), Intermittent Preventive Treatment in pregnancy (IPTp), indoor residual spraying (IRS), and in areas with highly seasonal malaria, seasonal malaria chemoprevention (SMC). Increased rollout of malaria control methods had led to over 50% reduced malaria mortality in sub-Saharan Africa since 2000 [2], but ongoing gaps in access to preventive, diagnostic and treatment measures continue to exist.

Insecticide Treated-Nets (ITNs)

ITNs and specifically, LLINs have been shown to cause a reduction in both malaria disease and childhood mortality in randomised controlled trials. A Cochrane Review estimated 50% efficacy of ITNs against uncomplicated malaria episodes and 17% efficacy of ITNs against all-cause under five mortality (compared to no nets) in areas of high transmission [25]. The impact of ITNs is based not only on

individual-level protection but also on community-level transmission reduction [26]. However, ITN use and protection wanes over time in the absence of new distributions and it is therefore important that countries maintain distribution of replacement nets at least every 3 years [27], including in areas implementing malaria vaccination.

Early support for vector control activities began after WHO hosted a convention in 1992 to increase attention on malaria prevention measures with acknowledgement of ITNs as the most promising strategy. At this point, data were available to show that use of pyrethroids were safe, effective to decrease mosquito bites and repel and kill mosquitoes, effectiveness could be optimized based on the quantity of pyrethroid used, and cost-effective [25]. At the time of the convention, data from a study in the Gambia were also available showing a 42% reduction in all-cause mortality among children 1–59 months after implementation of ITNs [28]. Subsequently in 1993, WHO reported on Implementation of the Global Malaria Control Strategy and noted that “Impregnated bednets have proved their efficacy in reducing morbidity and mortality in certain areas, but more research is needed.... efficacy under local conditions ... sustainability” [29]. In this period, before the large malaria policy and funding initiatives had been established, there was no mechanism in place to incentivize ITN production and roll-out. Four additional RCTs with mortality impact endpoints were published in 1995 [30], 1996 [31, 32], and 1997 [33]. These additional data contributed to the basis for the recommendation for additional scale up of ITNs [34].

Table 2. Insecticide-treated net data for policy recommendation

Data Available at Time of Policy Statement:	Data Unavailable at Time of Policy Statement:
<ul style="list-style-type: none"> • Pyrethroids safe • ITN’s decrease mosquito bites, and repel and kill mosquitoes • Cost-effectiveness of ITN’s • Impact on overall mortality (42% in The Gambia, 1991)—more data was requested 	<ul style="list-style-type: none"> • Feasibility • Impact on resistance

Drug-based malaria prevention tools (IPTp, IPTi, SMC)

Key drug-based malaria preventive tools include IPTp to prevent malaria in pregnancy, IPTi to prevent malaria in the first year of life (which has not been widely adopted) and, SMC, limited to areas with highly seasonal malaria. All of these rely on inexpensive, well-tolerated antimalarial drugs.

IPTp is the distribution of a complete dose of an antimalarial medicine to pregnant women at different intervals during pregnancy, usually during ANC visits, regardless of disease status. The original WHO policy recommendation (2004) on IPTp was: *“All pregnant women in areas of stable malaria transmission should receive at least two doses of IPT after quickening...IPT-SP doses should not be given more frequently than monthly. Currently, the most effective drug for IPT is sulfadoxine-pyrimethamine (SP) because of its safety for use during pregnancy, efficacy in reproductive-age women and feasibility for use in programmes as it can be delivered as a single-dose treatment under observation by the health worker.”*

At the time of the initial (2004) recommendation, there were two major topics addressed by the Technical Expert Group (TEG) regarding IPTp that needed further information: SP use in IPTp in areas with high SP resistance, and the impact of IPTp in the presence of high coverage of other interventions [35]. Data of SP efficacy in high resistance areas was available for children, but there was not data

available on in vivo protective efficacy in pregnant women [35]. The TEG also requested further studies to determine: the optimal dose and dose interval, effect of seasonal malaria transmission on SP effectiveness, impact (and validation of results) of IPTp on low birth weight, maternal anaemia, and peripheral and placental parasitemia, and whether SP should be replaced with another antimalarial (superiority RCT, dose/schedule for other antimalarials, effectiveness, etc). No thresholds for parasite prevalence were established regarding when to halt or initiate IPTp use. No recommendations were made on IPTp use outside of Africa.

In 2012, following a subsequent evidence review on dose-dependent efficacy of SP and the impact of IPTp in regions with high prevalence of sulphadoxine pyrimethamine (SP)-resistant parasites, WHO made the following updated recommendation: *“The [Evidence Review Group] (ERG) advises that an update to the WHO policy on IPTp is needed and recommends that all pregnant women in areas of stable (high or moderate) malaria transmission should receive SP at each scheduled ANC visit. IPTp-SP doses should be administered as early as possible during the 2nd trimester of gestation, with each dose given at least 1 month apart from any other and continuing up to the time of delivery [36].”*

The updated policy recommendation concluded that IPTp was effective even in areas with high SP resistance, but recommended that SP should not be used as a monotherapy in malaria treatment outside of IPTp to avoid resistance.² The dose-dependent recommendation was based on the results of a meta-analysis that looked at 2 dose versus 3 dose regimens of SP in 7 RCT's (6281 pregnancies) [36]. The analysis showed a reduction in risk of low birth weight of 21% (95 CI: 8-32) for a three dose regimen versus a two dose regimen. The update also cited new cost-effectiveness data showing IPTp to be cost effective against in high malaria transmission areas for prevention of neonatal mortality and maternal malaria.

The recommendation called for further data on: IPTp-SP use outside of Africa; information on effectiveness at different transmission levels; programmatic effectiveness of IPTp service delivery at ANC visits and barriers to uptake [36]. There was insufficient evidence available for WHO to make a policy recommendation on what level of malaria transmission should serve as the threshold for halting IPTp. A subsequent 2013 draft recommendation suggested halting IPTp-SP when *P. falciparum* prevalence stayed below 5% in children under-15 for three years [37]. However, this threshold has yet to be formally included in WHO policy, and the 2014 WHO policy brief requested more information before selecting a threshold below which IPTp use should be halted [38].

Table 4. Intermittent Preventive Treatment in Pregnancy (IPTp) data for policy recommendation

	Data Available at Time of Policy Decision:	Data Unavailable at Time of Policy Decision:
2004	<ul style="list-style-type: none"> • 1 RCT, Shulman C., 1999: maternal anaemia & birthweight • At least two SP doses needed to be beneficial • In HIV+ women, monthly dose of SP needed • Cost-effectiveness data • No signs of additional risk or benefit from a third dose of SP 	<ul style="list-style-type: none"> • Feasibility, efficacy and safety of alternative antimalarials for IPTp • Efficacy in areas with high SP resistance • Impact of IPTp in areas with high coverage of other malaria interventions

2012 update	<ul style="list-style-type: none"> • IPTp still effective in areas with high SP resistance • New dose-dependent results, based on a meta-analysis of 2-dose vs. 3-dose regimens (<u>7 RCT's, 6281 pregnancies</u>): 21% reduction in low birth weight (95 CI: 8%-32%) with three doses • IPTp shown to be cost-effective for preventing maternal malaria and neonatal mortality in areas with high malaria transmission 	<ul style="list-style-type: none"> • IPTp impact outside of Africa • Effectiveness of IPTp at different transmission levels • Programmatic effectiveness of IPTp delivery at ANC visits • Level of malaria transmission where IPTp should be implemented or halted
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IPTi is a malaria prevention intervention that involves the distribution of SP through EPI programs alongside routine vaccines. WHO's current policy recommendation (2010) on IPTi is: *"The co-administration of SP-IPTi with DTP2, DTP3 and measles immunization to infants, through routine EPI in countries in sub-Saharan Africa, in areas with moderate-to-high malaria transmission (Annual Entomological Inoculation Rates >10), and where parasite resistance to SP is not high –defined as a prevalence of the pfdhps 540 mutation of <50%"* [39]. At the time of the policy recommendation, the available evidence showed that initial concerns around severe skin reactions seen in some of the early studies were not observed in larger trials or the IPTi Consortium's analysis. A pooled analysis of the six original trials showed 30% efficacy (19.8%-39.4%) against clinical malaria, 21.3% (8.3%-32.5%) against anaemia, and an all-cause decline in hospital admissions of 23% (10.0%-34.0%). There was one additional study presented for consideration whose results were published after the pooled analysis that showed IPTi efficacy of 6.7% (-45.9% –22.0%) against clinical malaria. The pooled analysis showed no signs of a rebound effect, though further observation was recommended following reports of increasing anaemia, high density parasitemia and severe malaria-associated anaemia in the SP arms of three of the RCT's. Implementation study results showed SP to be cost-effective and help increase EPI coverage.

At the time of the policy recommendation, it was unknown what parasite SP resistance threshold made IPTi ineffective. Additionally, there was uncertainty on the impact of IPTi on severe malaria incidence and malaria mortality, and there was a noted need for evidence for IPTi use in areas with low malaria transmission rates.

Table 5. Intermittent Preventive Treatment in infants (IPTi) data for policy recommendation

Data Available at Time of Policy Decision:	Data Unavailable at Time of Policy Decision:
<ul style="list-style-type: none"> • 6 RCT's: 30% efficacy (95 CI: 19.8-39.4) against clinical malaria, 21.3% (95 CI: 8.3-32.5) against anaemia, 23% (95 CI: 10.0-34.0) against all-cause hospital admissions • No signs of rebound (call for further data) • No serological interactions with response to EPI vaccines • Operational experience from pilot implementation • Low cost, and helped increase coverage of EPI vaccines • Initial safety concern of severe skin reaction resolved when not observed in large IPTi Consortium studies 	<ul style="list-style-type: none"> • Threshold of SP resistance where IPTi becomes ineffective / not cost-effective • Efficacy on severe malaria incidence and malaria mortality • IPTi impact in areas with low malaria transmission

SMC, also known as Intermittent Preventive Treatment in children (IPTc), is the provision of antimalarial treatment courses to children under five in the Sahel region of Africa, where there are large seasonal variations in malaria transmission rates between the rainy and dry seasons. The current WHO policy on SMC (2012) is: *"SMC is recommended in areas of highly seasonal malaria transmission across the Sahel sub-region. A complete treatment course of amodiaquine plus sulfadoxine-pyrimethamine (AQ+SP) should be given to children aged between 3 and 59 months at monthly intervals, beginning at the start of the transmission season, to a maximum of four doses during the malaria transmission season (provided both drugs retain sufficient antimalarial efficacy)"* [40].

The 2012 policy recommendation was based on evidence available from 8 RCT's (7 sets of results had been published) that looked at monthly and two monthly dose regimens across a cumulative 900,000 treatment courses [41]. Efficacy from these studies looked at: uncomplicated malaria, severe malaria, moderate anaemia and all-cause mortality. Pooled results showed that monthly and bimonthly SMC regimens (any antimalarial) had an efficacy of 78% (95 CI: 69 – 84) against uncomplicated malaria, and this immunity lasted for approximately 4 weeks following each dose. Monthly SMC regimens (any antimalarial) showed efficacy of 61% (95 CI: 15 – 82) against severe malaria, and 20% (95 CI: -5 – 38) against severe anaemia. There were not many reported deaths across the eight studies, making evaluations of impact on all-cause mortality unreliable, but the pooled analysis showed an efficacy of 18% (95 CI: -69 – 61) against all-cause mortality. No serious adverse events were attributed to SMC across the eight studies. There was no association between efficacy and the SP dose (half or whole tablet).

Cost-analysis data was also considered, and showed SMC to be highly cost-effective in areas with attack rates greater than 0.2 clinical attacks per transmission during the rainy season, and cost-

effective at rates from 0.1 to 0.2 clinical attacks per transmission. SMC was not cost-effective at attack rates below 0.1 clinical attacks per transmission season.

This 2012 WHO recommendation was made without evidence on efficacy of alternative dose regimens, safety risks of repeated AQ doses (specifically neutropenia and hepatotoxicity), impact in other age groups, impact on malaria transmission, and without defined thresholds for initiating, altering or stopping SMC in a particular area. Due to the lack of data to answer these questions, the WHO policy also contains the caveat: *“While there are several potential approaches to implementing SMC, there is presently insufficient evidence to recommend a standard deployment strategy and individual approaches best suited to local conditions should be used.”*

Table 6. Seasonal Malaria Chemoprevention (SMC) data for policy recommendation

Data Available at Time of Policy Decision:	Call for further data at Time of Policy Decision:
<ul style="list-style-type: none"> • 8 RCT's, 900k treatment courses • 78% efficacy (95 CI: 69-84) against uncomplicated malaria; protection lasted about 4 weeks • 61% (95 CI: 15-82) against severe malaria, 20% (95 CI: -5.0-38.0) against severe anaemia, 18% (95 CI: -69 -61) mortality • No AEFI reported • No association observed between SP dose and efficacy • Highly cost-effective at attack rates greater than 0.2 clinical attacks per transmission season, cost-effective at attack rates of 0.1-0.2 	<ul style="list-style-type: none"> • Efficacy of alternative dose regimens • Safety risk of repeat AQ doses (neutropenia and hepatotoxicity) • Impact in different age groups • Impact on malaria transmission • Data for starting and stopping thresholds of malaria transmission

Impact of RTS,S/AS01 on utilization of other malaria interventions will be assessed during the household surveys by measuring and comparing prevalence estimates in vaccination and comparator areas. Communication will be a key component of any RTS,S/AS01 introduction plan to maintain use of other malaria control tools, including emphasis on the partial protection of the vaccine and the need to continue sleeping under and an ITN and the need to seek diagnosis and treatment for fever early.

C) Operational feasibility: Expected MVIP coverage based on Immunization coverage trajectories over time following new vaccine introductions

Definition of “high” coverage

The JTEG has recommended that “high” immunization coverage be documented in order to recommend continued implementation. However, as the SAGE has previously recognised (SAGE, April 2018), the relatively low coverage levels of MCV2 provided to children aged 15–18 months in MVIP countries could indicate challenges in reaching children in the second year of life with the fourth dose of RTS,S/AS01.

The WHO recommendation acknowledged that receiving all four doses of the vaccine ensures optimal benefit of the vaccine and avoids an age-shift in timing of severe disease that was observed in the

Phase 3 trial among children randomized to receive only 3 vaccine doses. However, subsequent long-term follow up data from the MAL-076 study are reassuring, showing no excess risk of severe malaria among those who receive only 3 doses and modelling estimates based on Phase 3 data predict that the added benefit of a fourth dose may be small compared to that of the first three doses. Nonetheless, given uncertainty around the added benefit of a fourth dose, efforts at maximizing coverage of the full four dose series during the Programme is desirable.

Considering experience with introduction of other childhood vaccines, the definition of “high” coverage is challenging, and would be expected to differ for the third and fourth doses of RTS,S/AS01. Coverage is expected to be lower for the fourth dose of RTS,S/AS01 compared to the third dose because of healthcare visits during the second year of life are less well established than those in infancy. Examples from other vaccine introductions were reviewed to determine realistic goals for coverage based on the strength of the immunization system to support the additional vaccine introduction and new immunization schedule.

Documentation of achieving high coverage is not typically a prerequisite for a WHO policy recommendation for vaccine introduction, unless there is an epidemiological rationale. For example, with vaccines that induce population-level protection (“herd immunity”), suboptimal childhood vaccination coverage can lead to an age shift in disease at the population level, but this principal does not apply to malaria vaccination as the RTS,S/AS01 vaccine is expected to provide individual protection only and not expected to have an effect on malaria transmission.

Strength of routine immunization in the pilot countries

After responding to call for expressions of interest, the pilot countries were selected for participation in the pilot implementations based on standardized criteria, including demonstration of a strong EPI programme. Coverage levels for diphtheria-tetanus-pertussis (DTP) and measles-containing vaccine (MCV) are considered indicators of health system performance. Vaccines given in the second year of life, such as MCV2 and meningococcal A vaccine, were assessed as relevant by the Working Group when considering potential RTS,S/AS01 coverage. The additional visits to be introduced for RTS,S/AS01 can be leveraged as opportunities to reach children at critical time points for well child exams, including weight monitoring, and to provide vitamin A and deworming recommended at two years of age. Based on the WHO recommendations, the EPI Programmes defined the most appropriate target age for children to receive each dose of RTS,S/AS01 given the existing routine immunization schedule.

Expected coverage trajectory over time following new vaccine introduction

Vaccine coverage rates for second year of life vaccines are generally suboptimal in Africa. As of 2016, WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) average MCV2 coverage was 74% with many countries having introduced more than 5 years ago. Coverage for vaccines administered at the same or similar times points as RTS,S/AS01: MCV1, MCV2 and Meningococcal serotype A (MenA) (introduced in Ghana only) vary greatly among pilot countries (Table 7).

Table 7. Immunization programme performance in MVIP countries: 2017 vaccine coverage estimates*

	Ghana	Kenya	Malawi
DTP-HepB-Hib, first dose, at 6 weeks	99%	93%	93%
DTP-HepB-Hib, third dose, at 14 weeks	99%	82%	88%
Measles-containing vaccine (MCV1) 1st dose, 9 months	95%	89%	83%
Measles-containing vaccine (MCV2) 2nd dose, 18 months	83%	35%	67%
Meningococcal conjugate serotype A vaccine, 18 months	82%**	NA	NA

*according to WHO/UNICEF coverage estimates, as of 15 July 2018

**Country reported estimate, first full year after introduction

Vaccine coverage trends increase over time following introduction. The trajectory in coverage for first year of life vaccines has been increasing since the start of the EPI program. Since the 1980's trends in coverage over time for infant DTP, MCV, and oral polio vaccines have been observed and found to vary considerably by region and country; however, generally, the acceleration in coverage is highest when national coverage levels are between 25-30%, and where there is investment in the immunization system. Coverage levels tends to level off when they are high, e.g. over 80% [42].

In the pilot countries, increasing trends have been observed in average WUENIC estimates [43] for vaccines given during the first year of life (third dose pneumococcal vaccine, Haemophilus influenza type b vaccine, second dose rotavirus vaccine) during the first three years after introduction (Figure 1a). When MCV2 as a second year of life (2YOL) vaccine is considered, increasing trends are also observed though the highest coverage achieved has been lower than for vaccines given in the first year of life (Figure 1b).

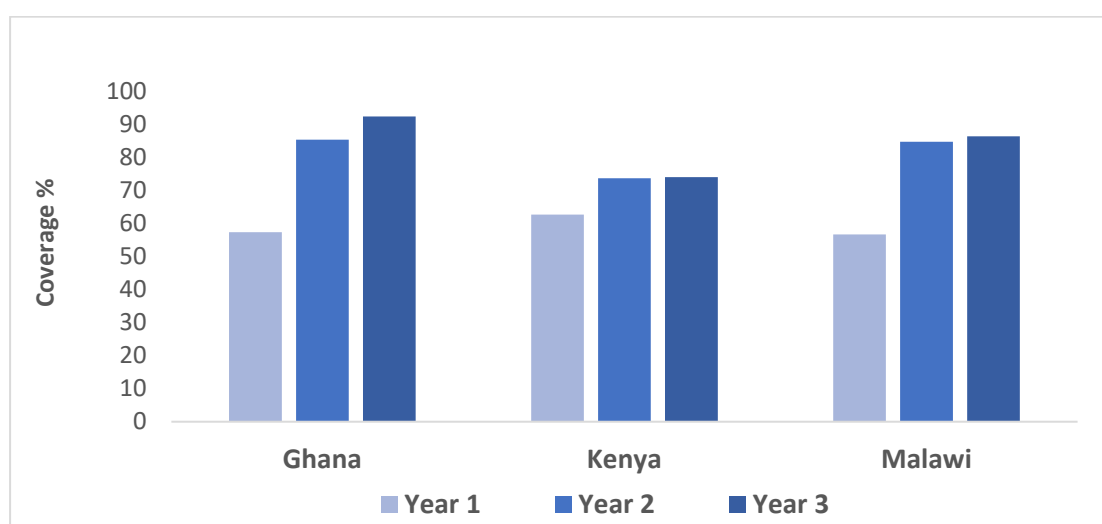


Figure 1a. Average WHO/UNICEF (as of 15 July 2018) estimated first year of life vaccine coverage in Ghana, Kenya, and Malawi during first 3 years following introduction, including the year of introduction (third dose pneumococcal vaccine, Haemophilus influenza type b vaccine, and second dose rotavirus vaccine)

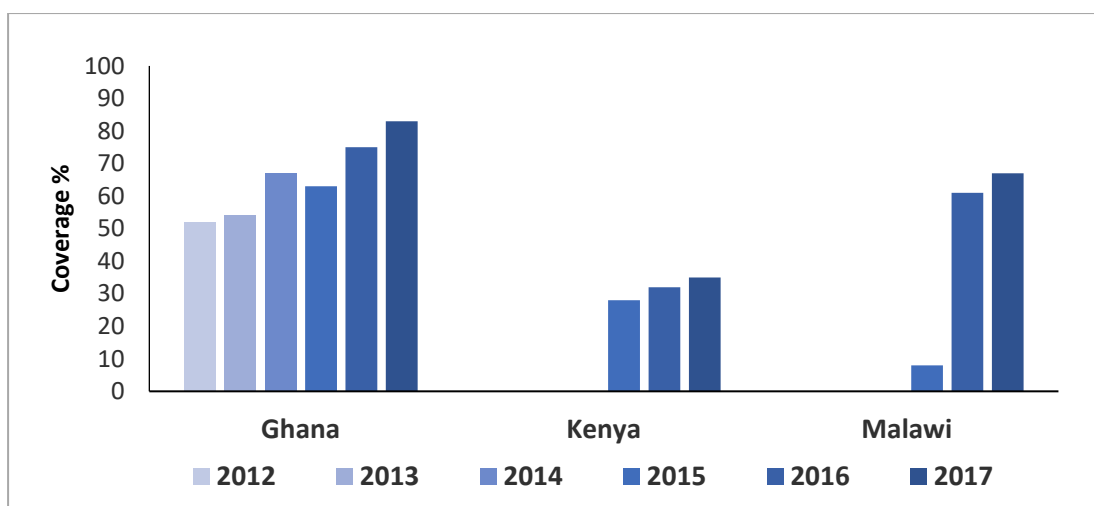


Figure 1b. **Second dose measles-containing vaccine** WHO/UNICEF estimated coverage (as of 15 July 2018) in Ghana, Kenya and Malawi, 2012-2017. The first year shown for each country is the year of introduction.

A preliminary analysis performed by CDC using the WHO/UNICEF coverage data (2016) [43] of the time needed to attain various MCV2 coverage levels showed that among 22 countries in AFRO who have introduced MCV2, 17 have achieved coverage of at least 60%. Among the 13 countries that had reported at least five years of data, attaining 60% coverage took an average of 1.4 years. Attaining 70% and 80% coverage took 2 and 3.9 years respectively (Table 8).

Table 8. Average time to reach target MCV2 coverage in years, as of 2016

	Average time (years) to reach MCV2 target coverage, as of 2016*			
	60%	70%	80%	90%
WHO African Region	1.4	2	3.9	5
Number of countries** (%)	13 (59)	11 (50)	7 (32)	4 (18)

* Among total 22 countries in AFRO who have introduced MCV2 as of 2016, 17 have achieved coverage of at least 60%.

** Excludes countries who didn't report for >5 years

Note: This reflects first time countries hit the selected target coverage. Many countries hit 70% or 80% one year and then the next year (or few years) they were back down in the 60% range.

The meningococcal serotype A conjugate vaccine (MenA) is another example of a 2YOL vaccine that has recently been introduced in multiple countries in the meningitis belt, including in Ghana. The MenA coverage trajectory experience may be informative for potential coverage expected for RTS,S/AS01 and the impact on other routine EPI vaccines. MenA vaccination campaigns in Africa since 2010 have led to dramatic reductions in meningococcal meningitis and community acceptance of vaccination was observed to be high [44]. Burkina Faso introduced MenA into the routine EPI in March 2017 at age 15-18 months, concomitantly with MCV2. A coverage survey was recently conducted one year after introduction in Burkina Faso to examine MCV2 coverage in pre- and post-MACV introduction cohorts to assess changes regionally and nationally, with the hypothesis that introduction of MenA, highly desirable by endemic communities, might lead to an improvement of MCV2 coverage, available to children at the same vaccination visit. Results of the survey showed that after one year of introduction, MenA coverage reached 58% (95%CI 56-61), much lower than the 96% coverage that has been achieved during the mass vaccination campaign conducted in Burkina Faso in 2010 [45].

MCV2 coverage did increase significantly by about 5% compared to pre-MenA introduction coverage (Table 9). Given the methodology of the survey, the increase in MCV2 coverage cannot be attributed to the introduction of MenA into the routine EPI schedule. While MACV introduction may have contributed, it cannot be separated from the expected modest increase in coverage during the first few years post-introduction. The introduction of RTS,S/AS01 coinciding with other 2YOL vaccines might present a similar opportunity for improvement of other immunization or coverage.

Table 9. Measles-containing vaccine dose 1 (MCV1), MCV2, and meningococcal serotype A conjugate vaccine (MenA) coverage before and after MenA introduction in routine childhood immunization, Burkina Faso, 2018*

% Coverage (95% CI)	Pre MenA Introduction Age Group (30-41 months)	Post-MenA Introduction Age Group (18-26 months)	Change in Coverage
MCV1	88 (87, 90)	89 (87, 91)	1.0 (-0.8, 2.8)
MCV2	62 (59, 65)	67 (64, 69)	4.5 (1.3, 7.7)
MenA	NA	58 (56, 61)	na

*Burkina Faso introduced MenA vaccine into the EPI in March 2017; the coverage survey was conducted 12 months after introduction in March 2018. Data from Zoma, Walldorf et al, manuscript in preparation.

Assessment of coverage during the MVIP evaluation period

Administrative coverage data will be available monthly after the start of RTS,S/AS01 vaccination based on routine reports from vaccination facilities up to the district and national levels. However, administrative coverage data has well-known limitations for over or underestimation [46, 47]; reliability of administrative data depend greatly on completeness and timeliness of reporting and accuracy of population denominator estimates for the age group eligible for vaccination. Administrative coverage estimates may become more reliable over time. Given the limitations to administrative coverage data, household survey data will a more reliable source of RTS,S/AS01 and other vaccine coverage [48] but will not be available as early and will only be available intermittently following the conduct of a coverage survey and subsequent statistical analysis. Representative population-based survey data that would include the fourth RTS,S/AS01 dose will be estimated at the coverage survey planned to occur at 30 months after vaccine introduction with results available approximately 2 months later depending on the time needed for analysis.

The full evaluation period of approximately 50 months may be sufficient for scale up and achievement of “high” coverage for first year of life RTS,S/AS01 doses 1, 2, and 3, with less certainty for the fourth dose considering experience with other 2YOL vaccines. In contrast, evaluation at 18-24 months following the first RTS,S/AS01 fourth dose administration may not allow enough time for the trajectory towards high coverage, especially for the fourth dose. Similar to the trends observed for MCV2, achievement of fourth dose RTS,S/AS01 vaccine coverage comparable to the third dose will likely take several years.

During the course of the evaluation, the immunization program will have the opportunity to strengthen procedures around the new immunization visits and respond to early challenges identified

through the planned post-introduction evaluation and through the Health Care Utilization Qualitative Longitudinal evaluation (HUS). The HUS will inform interpretation of coverage estimates, and will explore contextual and behavioural factors that might impede or facilitate RTS,S/AS01 uptake in terms of: delivery and integration, community reception and acceptability, and vaccine uptake and consequences.

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Executive summary

outlining the key aspects of the session and related background material

Meningitis remains a major public health challenge in regions and countries around the world. Cases and outbreaks continue to be highly feared. The magnitude of the problem varies dramatically globally, but deaths and long-term sequelae endure a heavy legacy in all settings. Developing countries and vulnerable communities suffer from the highest burden, and they face the biggest challenges in accessing vaccines, diagnoses and care. Yet the current remarkable success observed toward the elimination of meningitis in many countries, notably the elimination of epidemic meningitis A in the century-old meningitis belt of Africa, is a fundamental source of optimism.

A global strategy to ‘defeat meningitis by 2030’ is being developed by a WHO-led multi-organization partnership assembled into a Technical Taskforce. The fight against meningitis fits strategically in the WHO thirteenth General Programme of Work, structured around prioritizing universal health coverage and health security, with a three-fold mission to ‘Promote health, Keep the world safe, Serve the vulnerable’. This strategy, integrated into a global roadmap, covers the organisms responsible for most of acute bacterial meningitis, namely *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Streptococcus agalactiae* (Group B Streptococcus). The vision of the roadmap is a world free of meningitis. The proposed goals to be achieved by 2030 are: (1) Eliminate meningitis epidemics; (2) Reduce cases and deaths from vaccine-preventable meningitis by 80%; and (3) Decrease the impact of sequelae by 50%.

The roadmap is based on five strategic pillars: (1) Prevention and epidemic control - through development and enhanced access to affordable vaccines, effective prophylactic measures and targeted control interventions; (2) Diagnosis and treatment – achieving access to the right diagnostic test from remote health facilities to city hospitals, to enhance surveillance and ensure patients can be promptly treated through effective antibiotics and adjunctive care; (3) Disease Surveillance - encompassing all main causes of bacterial meningitis and their sequelae in order to guide meningitis control policies and accurately monitor progress; (4) Support and aftercare for survivors and their families - so that the heavy burden of meningitis sequelae is recognized and alleviated in every community around the world; and (5) Advocacy and Information - to raise public and political awareness of meningitis as a health priority and improve health-seeking behaviour and access to control measures.

The major steps for the development of the roadmap include: the development of a baseline situation analysis (completed in February 2019) and a large iterative consultation process, including stakeholders and technical advisory groups. Initial steps in the consultation process have included convenings of the Technical Taskforce (July 2018 and February 2019), which focused on defining the main components of the baseline situation analysis and on developing a draft of the roadmap. The roadmap will then be subject to a web-based public consultation (May-June 2019), followed by a large stakeholders' consultation (September 2019). The overall intention is to submit the Global Roadmap for adoption at the seventy-second World Health Assembly (WHA) in May 2020, and regionally adapted versions at the subsequent WHO Regional Committees in September 2020.

The purpose of the first session is to inform SAGE members on this initiative to defeat meningitis by 2030 and present them with the progress and main elements of the initiative. A second session will be held in October 2019 for their recommendations.

There are two background documents for this session:

- (1) Defeating meningitis by 2030: baseline situation analysis, WHO 20 February 2019 available at <https://www.who.int/immunization/research/en/> . (Website)

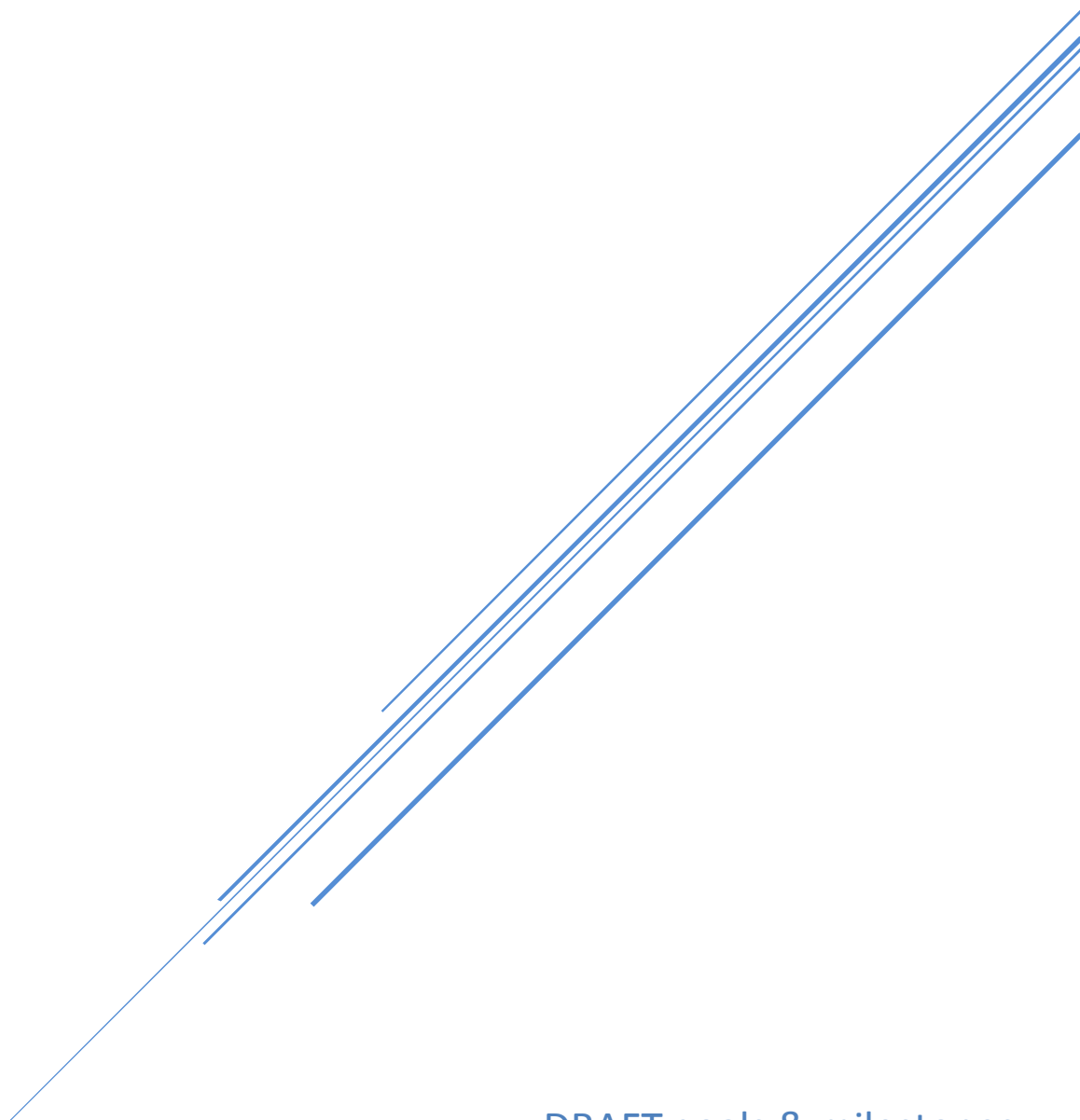
The document is the result of contributions from over 50 reviewers and authors, including Technical Taskforce members and subject experts and is key to inform direction and priorities for the roadmap. It summarizes the outlines the global and regional burden of meningitis, the recommended practice, research and implementation status, barriers and gap analysis for the five pillars.

- (2) Defeating meningitis by 2030: draft goals and milestones, WHO 20 February 2019. (Yellow Book)

The document is an early draft of the global roadmap and does not include the propositions of adjustments and other inputs provided during the extended Technical Taskforce meeting held at the end of February 2019.

“DEFEATING MENINGITIS BY 2030”: A ROADMAP

Draft goals and milestones



DRAFT goals & milestones
20 Feb 2019

Introduction

Meningitis is a devastating disease affecting all populations and remains a major public health challenge in regions and countries around the world. Cases and outbreaks continue to be highly feared. Together with neonatal sepsis, meningitis is estimated to cause more deaths in children under 5 years of age than malaria, with the highest impact on the poorest communities. The fight against meningitis fits strategically in the WHO 13th General Programme of Work, set to drive progress towards the United Nations Sustainable Development Goals for 2030, and structured around prioritizing universal health coverage and health security, with a three-fold mission to ‘Promote health, Keep the world safe, Serve the vulnerable’.

Meningitis can be caused by many different organisms, notably bacteria, viruses, protozoa and fungi. The highest global burden is seen with bacterial meningitis, though cryptococcal meningitis, a fungal infection, has emerged in recent years as an important cause of meningitis among adults linked to HIV infection.

This roadmap covers the organisms responsible for the majority of acute bacterial meningitis, namely *Neisseria meningitidis* (Nm), *Streptococcus pneumoniae* (Spn), *Haemophilus influenzae* (Hi) and *Streptococcus agalactiae* (commonly referred to as Group B Streptococcus (GBS). Other important causes of meningitis, such as tuberculosis (TB) or Cryptococcus are not a focus of this roadmap, as they are already included in other preventive strategies. However, several goals directed at reducing the burden of disease will be equally applicable to other causes of meningitis, particularly in support, after-care, advocacy and information.

The number of deaths from bacterial meningitis in all ages was estimated by WHO as around 300,000 in 2015, with close to 100,000 deaths in children between one month and 5 years of age. Mortality rates varied by organism and by WHO region, with the highest overall burden in Africa. Global estimates of GBS meningitis cases in young babies aged up to 3 months were similar in number (70,000) to estimates of pneumococcal meningitis cases in 1-59 month old children.

All the leading causes of bacterial meningitis were estimated to result in a high degree of disabling sequelae among survivors of meningitis. The proportion of survivors with severe after-effects varied by organism, being highest for pneumococcal meningitis (25%) and GBS disease (32%), and by setting, with survivors in low income countries being the worst affected. Meningitis sequelae can have an enormous emotional, social and economic impact on individuals, families and communities.

Vision

Our vision is **a world free of meningitis**.

This roadmap sets out a global strategy to achieve the following goals by 2030:

- **Eliminate meningitis epidemics**
- **Reduce cases and deaths from vaccine-preventable meningitis by 80%**
- **Decrease the impact of sequelae by 50%**

The global roadmap

The global strategy sets a path, for the first time, to tackle the four main causes of acute bacterial meningitis. Achieving these goals will rely on strong commitments from countries, partners, and donors to collectively engage in defeating meningitis.

The Global Roadmap is based on **five pillars**:

- **Pillar 1:** Prevention and epidemic control
- **Pillar 2:** Diagnosis and treatment
- **Pillar 3:** Disease surveillance
- **Pillar 4:** Support and aftercare for families and survivors
- **Pillar 5:** Advocacy and information

All five pillars need to be developed together and implemented globally in order to achieve the overall goals. The strategic goals, milestones and priority activities outlined below will also need to be tailored to the context of each region and coordinated across regions.

Pillar 1: Prevention and epidemic control

through development and enhanced access to affordable vaccines, effective prophylactic measures and **targeted** control interventions

Enhanced efforts are needed to advocate for immunization. This includes (i) encouraging vaccine introduction and sufficient vaccine coverage especially in lower- and middle-income countries where the burden of meningitis is greatest, (ii) promoting the development of vaccines to address the residual disease burden due to pathogens, serogroups or serotypes not covered by existing vaccines and (iii) ensuring equitable access to affordable vaccines. Polysaccharide-conjugate vaccines are dramatically reducing the global burden of disease caused by Nm, Spn and Hi but their global impact needs to be considerably enhanced. No vaccine exists for the prevention of GBS disease, but GBS conjugate vaccine candidates are in advanced development. Several Nm and Spn conjugate vaccine candidates are also in late stage development including multivalent products with broader serogroup/type coverage than existing vaccines. Novel protein-based vaccines against NmB disease are now being used at public health scale in some countries. In addition, several protein vaccine candidates against Nm, Spn and GBS are in development. Enhanced and sustained use of vaccines will allow vaccines to play an increasingly important role in strategies for controlling antimicrobial resistance.

Chemoprophylaxis is generally used for close contacts of cases of meningococcal meningitis, but needs further evaluation, particularly in the context of epidemics in the African meningitis belt. Screening and intra-partum antibiotic prophylaxis are recommended for GBS infection during pregnancy, but this policy is rarely implemented in low and middle-income countries because of cost and logistic issues.

The most important challenges in the response to Nm or Spn meningitis epidemics include the lack of laboratory capacity to confirm the epidemic pathogen and of timely access to sufficient quantities of affordable vaccines for response, and, for Spn meningitis outbreaks, guidance on response is lacking.

1. 1. Strategic Goals

- SG 1: Development, licensure and WHO pre-qualification of affordable and accessible new vaccines targeting more causal agents for meningitis
- SG2: Optimization of vaccination strategies that result in individual and community protection (where feasible to do so)
- SG3: Achieving and maintaining high coverage of current and new vaccines in all countries
- SG 4: Implementing screening and chemoprophylaxis against GBS infection in pregnant women where not already introduced (before vaccine introduction)
- SG 5: Optimization of strategies for outbreak prevention and response including vaccination and chemoprophylaxis

1.2. Milestones

1.2.1. By 2020, rollout of preventive vaccination against Nm serogroup A in EPI will have been completed in meningitis belt countries as appropriate; by 2023, at least three countries in the meningitis belt will have started preventive vaccination against Nm serogroups A, C, W, X and Y; and by 2030 all countries will have done so as appropriate. In parallel, a strategy to maintain coverage is implemented, reinforcing and complementing other such strategies

1.2.2. By 2020, the stockpile of meningococcal conjugate vaccines will be appropriately replenished (quantity, composition, timeliness) to enable an early response to outbreaks

1.2.3. By 2021, WHO strategy for pneumococcal meningitis outbreak prevention and response will be available

1.2.4. By 2022, at least one additional affordable pneumococcal conjugate vaccine, with coverage consistent with emerging data on serotypes causing disease, will be licensed and WHO prequalified

1.2.5. By 2022, a policy will be available on GBS screening in pregnant women and intrapartum antibiotic prophylaxis, considering highest needs and feasibility; by 2030 all countries will have implemented this policy unless superseded by a vaccination programme (see 1.2.7.)

1.2.6. By 2025, all countries will have introduced pneumococcal and *H. influenzae* type b conjugate vaccines with locally-relevant strategies; and with a >90% vaccine coverage by 2030. In parallel, a strategy to maintain coverage is implemented, reinforcing and complementing other such strategies

1.2.7. By 2026, at least one vaccine against GBS will be licensed and WHO prequalified; and by 2030, at least 10 countries will have introduced the vaccine, consistently with a WHO policy

1.2.8. By 2026 at least one additional affordable new MenB vaccine will be licensed and WHO pre-qualified

Pillar 2: Diagnosis and treatment

achieving access to appropriate diagnostic tests at all levels of care, to enhance surveillance and ensure patients can be promptly treated through effective antibiotics and adjunctive care

Laboratory confirmation is well defined for the main bacterial pathogens (real time PCR and culture being the gold standards), but health workers especially in lower- and middle- income countries (LMICs) may not be trained or resourced to identify cases of meningitis, cerebrospinal fluid (CSF) sampling is often not undertaken, and laboratory capacity is often weak. There is a lack of quality assured affordable high performance rapid diagnostic tests (RDTs), and in 2018, use cases (describing use, impact, target population, skill level) were developed for three RDTs to improve case management of meningitis and strengthen surveillance. Antibiotic treatment regimens are well established, but WHO guidelines for treatment of adults with bacterial meningitis are not currently available and recommended antibiotics are not always available. Adjunctive therapies need further evaluation in some settings.

2. 1. Strategic Goals

- SG6: Increase confirmation of bacterial meningitis and make diagnostic tools available at the appropriate level of care to initiate recommended treatment as early as possible and to improve surveillance
- SG7: Provide appropriate quality-assured treatment and supportive care to every patient to reduce sequelae and deaths

2.2. Milestones

2.2.1 By 2023 a quality assured multiplex diagnostic test will be available to identify the main pathogens responsible for meningitis (bacterial, viral, fungal) that is affordable for LMICs

2.2.2 By 2026 a quality assured, affordable and accessible point of care (POC) diagnostic test will be developed for individual case management

2.2.3 By 2026, guidance on antimicrobial and adjunctive supportive therapy covering all meningitis bacterial pathogens will be published

Pillar 3 Disease Surveillance

encompassing all main causes of bacterial meningitis and their sequelae to guide meningitis control policies and accurately monitor progress toward goals

Guidelines for national surveillance of meningitis pathogens are not uniformly implemented and there are no recommended guidelines for GBS surveillance. In many countries, weak surveillance systems hamper prompt outbreak detection and response. In addition to the limited diagnostic capacity, needed for effective surveillance, laboratory capacity for molecular characterization and whole genome sequence based global surveillance for meningitis pathogens needs to be advanced. Disease data reporting to the international level is incomplete. There is very limited guidance and implementation of surveillance of sequelae in all regions.

3.1. Strategic Goals

- SG8: Strengthen country surveillance of meningitis pathogens to guide epidemic control, and case management, and to evaluate the impact of vaccine programmes and vaccination policies
- SG9: Develop guidance and implement surveillance of (i) GBS disease and (ii) sequelae from meningitis
- SG10: Improve disease data reporting to the international level to strengthen regional and global monitoring and estimation of the disease burden

3.2. Landmark goals / Milestones

- 3.2.1 By 2021, surveillance guidance is available in all regions for all main bacterial meningitis pathogens
- 3.2.2 By 2022, assessment of the impact and the additional burden of sequelae after meningitis
- 3.2.3 By 2024, a global genome library (GGL) is functional for each of the four pathogens
- 3.2.4 By 2025, 60% of Member States have implemented the minimum package of meningitis surveillance that includes complications / sequelae associated with bacterial meningitis, reaching 80% of Member States by 2030
- 3.2.5 By 2025, 90% of Member States report meningitis surveillance data (annual incidence for each pathogen) to WHO Regional level

Pillar 4: Support and aftercare for survivors and their families

so that the heavy burden of meningitis sequelae is recognized and alleviated in every community around the world.

It is estimated that at least one third of people surviving an episode of bacterial meningitis have enduring after-effects. Aftercare has a high cost and may not be affordable for families. Common sequelae include seizures, hearing and vision loss, cognitive impairment, neuromotor disability, memory and behavior changes, as well as limb amputations after meningococcal sepsis. Policies for assessment of sequelae, treatment and follow up are often absent or insufficient with inequitable access. Community-based rehabilitation is infrequently provided, with a lack of targeted interventions. Training on disability and bereavement for health care professionals and community workers is limited, with inadequate numbers of trained staff both in hospital and in the community. Given the ongoing global burden of bacterial meningitis, it is essential to build and strengthen health systems to provide the necessary care and programmatic support.

4.1 Strategic Goals

- SG11: Strengthen recognition of sequelae both in hospital and by follow up after discharge
- SG12: Increase availability and access to appropriate care for survivors with sequelae
- SG13: Empower survivors and their families to maximize their health and quality of life

4.2 Milestones

4.2.1. By 2023, guidelines for systematic follow-up of bacterial meningitis to diagnose, monitor and manage sequelae developed; and by 2028, implemented in all countries

4.2.2. By 2025, education about sequelae and disability integrated into training of health workers

4.2.3. By 2028, access to psychosocial support and rehabilitation services increased by 30%

Pillar 5: Advocacy and Information

to raise public and political awareness of meningitis as a health priority and improve health-seeking behavior and access to control measures

Advocacy can drive lasting change and makes the case for that change. Advocacy goals for meningitis include better protection against meningitis, better diagnosis and treatment, and better support and aftercare for those who have experienced meningitis and their families. Suitable awareness information and resources for populations, at-risk groups, and health workers, as well as specific information for people who have directly been affected by meningitis, their families and communities, can play an important role in defeating meningitis, but are often lacking. Meningitis poses specific information challenges. Its rapid onset leaves little time to act, increasing the need for good, targeted information. It is frequently confused with other fever-causing diseases, such as malaria, increasing the need for health worker resources and training. Disability is a common feature of life after meningitis, meaning good aftercare information is essential.

Effective information can make people aware of the need to seek help based on awareness of the signs and symptoms and to increase demand from populations for vaccination. Clinical guidelines are often not available to help ensure that health workers and clinicians are trained and resourced to respond. Information is generally lacking to help signposting of patients to support services.

5.1 Strategic Goals

- SG14: Improve recognition among policymakers at national, regional and global level that meningitis and the roadmap to defeat meningitis should be prioritized
- SG15: Ensure awareness among all populations of meningitis signs, symptoms, sequelae and - seeking of healthcare as appropriate
- SG16: Ensure health workers are trained and provided with suitable resources to enable them to appropriately identify, diagnose, treat and support people with and surviving meningitis
- SG17: Ensure that the right to meningitis prevention and services is valued and demanded by communities
- SG18: Maintain high vaccine confidence

5.2. Milestones

5.2.1. By 2021 meningitis is included in all relevant WHO (Global and Regional) and donors' strategic and operational plans and budgets

5.2.2. By 2022 all countries have a meningitis action plan aligned to their national health strategy and global roadmap through to 2030

5.2.3. By 2023 all countries are conducting meningitis awareness campaigns appropriate to country burden and integrated with existing health awareness campaigns

5.2.4. By 2025 all countries have meningitis training for suitable relevant health care workers

5.2.5. By 2025 80% of countries have citizen representation and input to national meningitis annual plans

EVALUATION OF THE STRATEGIC ADVISORY GROUP OF EXPERTS (SAGE) ON IMMUNIZATION

Initial draft report of the
Expert Advisory Group on SAGE Evaluation (EAGSE)

Hanna Nohynek, Narendra Arora, Fred Binka, Lisa Cairns, Kathryn Edwards, Bruce Gellin, Anna
Lena Lopez, Ezzeddine Mohsni

supported by MMGH Consulting (Carsten Mantel, Stefano Malvolti)

Geneva, 11 March 2019

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2. List of Abbreviations

The following abbreviations can be found in the document:

AC – Advisory Committee
AMR – Antimicrobial Resistance
BMGF – Bill & Melinda Gates Foundation
CoI – Conflict of Interest
CSO – Civil Society Organization
DG – Director General
DoV – Decade of Vaccines
EAGSE – Expert Advisory Group on SAGE Evaluation
ECDC – European Centre for Disease Prevention and Control
ETR – Evidence to Recommendations
GACVS – Global Advisory Committee on Vaccine Safety
GPEI – Global Polio Eradication Initiative
GPW – Global Programme of Work
GRADE – Grading of Recommendations Assessment, Development and Evaluation
GVAP – Global Vaccine Action Plan
HIC – High Income Country
HSS – Health System Strengthening
IPAC – Immunization Practices Advisory Committee
IVB – Immunization Vaccines & Biologicals
IVIR-AC – Immunization and Vaccines Related Implementation Research Advisory Committee
LIC – Low-income Country
LMIC – Lower Middle-Income Country
M&RI – Measles and Rubella Initiative
MIC – Middle-Income country
MNCAH – Maternal Neonatal Child and Adolescent Health
NCD – Non-communicable Disease
NGO – Non-Governmental Organization
NITAG – National Immunization Technical Advisory Group
PDVAC – Product Development of Vaccines Advisory Committee
PHC – Primary Health Care
R&D – Research and Development
RITAG – Regional Immunization Technical Advisory Group
SAGE – Strategic Advisory Group of Experts on Immunization
SDG – Sustainable Development Goals
SIVAC – Supporting Independent Immunization and Vaccine Advisory Committees
SOP – Standard Operating Procedure
TAG – Technical Advisory Group
ToR – Terms of Reference
UHC – Universal Health Coverage
UMIC – Upper Middle-Income Country
UNICEF – United Nations International Children Emergency Fund
US CDC – United States Centers for Disease Control and Prevention
VPD – Vaccine Preventable Disease
WASH – Water, Sanitation and Hygiene
WER – Weekly Epidemiological Records
WG – Working Group
WHA – World Health Assembly
WHO – World Health Organization

3. Introduction and background

The Strategic Advisory Group of Experts (SAGE) on Immunization was established in 2005 as the principal advisory group to the World Health Organization (WHO) for vaccines and immunization. The group is charged with advising the Director General (DG) of the 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"*¹.

The first evaluation of SAGE was published in 2007 as part of a broader exercise looking at the overall immunization advisory architecture in support of the WHO Immunization, Vaccines and Biologicals (IVB) department. With specific reference to SAGE, the outcome of that review was synthesized into the following five recommendations²:

- *"That SAGE be recognized as the key committee which reviews and/or makes recommendations to the DG of WHO on all aspects pertaining to immunization policies.*
- *That SAGE and its working groups be adequately supported in order to meet the expectations placed upon it, including and especially the need for SAGE to have the necessary multidisciplinary expertise.*
- *That a much stronger connection be established between the regional Technical Advisory Groups (TAGs) and SAGE (along with the rest of the IVB's advisory structure). Immediate steps should be taken in this regard that would include strengthening of the regional TAGs.*
- *That IVB should implement a comprehensive communication strategy.*
- *That the independence of advisory committees be affirmed as essential for their success, including the independence of committees from donors and from the advocacy functions of WHO itself".*

Since its creation, the scope and expectations for normative and strategic guidance by SAGE have expanded considerably in response to the expanding contribution of immunization to global health and global health security and to the evolving goals and objectives of the WHO. For instance, SAGE also assumes advisory functions for the Global Polio Eradication Initiative (GPEI), SAGE recommendations are essential to inform Gavi policies and SAGE exerts an oversight function of the Global Vaccine Action Plan (GVAP). Over time, SAGE has progressively adapted its functions and processes. Today, the group is widely recognized as a model for other WHO advisory bodies and is highly influential with a number of different stakeholders, some of whom use the SAGE recommendations to frame their own organizational policies and strategies.

After a decade of operations, and a common overview that SAGE is performing well, the Director IVB, the SAGE Secretariat and SAGE members agreed on the need to ensuring that SAGE is not only fit for today's challenges but also well-prepared to fulfil its mission into the next decade. In early 2018, it was decided that an evaluation of SAGE be conducted, aimed at appraising the committee's functions and priorities and at identifying areas where processes may require improvements.

This second evaluation of SAGE has been carried out starting in April 2018 and ending in June 2019. (ref. Appendix 8.3 for the evaluation ToR). A set of initial scoping questions was developed by the Director of WHO IVB with input provided by WHO regional staff during a kick-off consultation in April 2018, to steer the evaluation process (ref. Appendix 8.1 for the scoping questions and appendix 8.4 for the notes of the consultation).

¹ SAGE Terms of Reference - February 2016.

² "Report of the Independent Review Team examining the Advisory Committees of the WHO Department of Immunization", Vaccines and Biologicals, January 2007, World Health Organization, p.6-7. The report included an additional 5 recommendations related to more general issues or did not refer to the SAGE

3.1. Objective and scope of the 2018-2019 SAGE Evaluation

The evaluation reviewed the appropriateness of the current Terms of Reference (ToR)³ and working processes of SAGE, including those of the SAGE Working Groups (WGs)⁴. It included SAGE's relationship with key actors in the immunization community, including country Ministries of Health and National Immunization Technical Advisory Groups (NITAGs), WHO Regions and Regional Immunization Technical Advisory Groups (RITAGs), major partners, donors and other stakeholders. It also included a review of the approaches currently used for communicating and disseminating SAGE outputs. The scope of the evaluation did not include the functioning of RITAGs and NITAGs. However, it covered the functioning of other WHO committees advising the IVB department as they are related directly to SAGE.

SAGE's role and function was assessed taking into consideration key strategies within e.g., Global Vaccine Action Plan (GVAP), and beyond the immunization field e.g., the focus on Universal Health Coverage (UHC), Health Security, and non-communicable diseases of the 13th Global Programme of Work and of the Sustainable Development Goals (SDG), as well as emerging themes of the post-2020 immunization agenda. Special emphasis was placed on the role that SAGE should play in a likely future scenario where immunization policies and services will be integrated to a greater extent with other health services.

3.2. Desired outputs of the SAGE Evaluation

The Director of IVB, considering input provided by WHO senior regional staff, advised that the evaluation should aim at:

- Ascertaining SAGE's role in relation to the evolving immunization and health agenda.
- Identifying the optimal interfaces with other WHO immunization and public health decision making and advisory bodies.
- Ensuring the optimal coordination with WHO Regions and regional immunization committees, as well as key partners and stakeholders.
- Ensuring that SAGE works effectively and is able to meet the highest quality standards.
- Ensuring the effective presentation and dissemination of SAGE and WHO recommendations.
- Revisiting the WHO SAGE Secretariat composition and resource needs.

4. Methodology of the evaluation

4.1. Evaluation governance

The evaluation was performed under the guidance and oversight of the Expert Advisory Group on SAGE Evaluation (EAGSE)⁵, tasked with the appraisal of the evaluation's methodology and findings and with the development of recommendations (ref. Appendix 8.2 for the EAGSE ToR). The group, established in June 2018, provided technical and strategic input and guidance throughout the evaluation process. Its membership was constituted by invitation from the Director of IVB, and to ensure a balanced representation of experience, skills, regions, gender and background.

³ https://www.who.int/immunization/sage/SAGE_TORs_Full_21_11_08.pdf

⁴ https://www.who.int/immunization/sage/SAGE_Working_Groups_general_information.pdf?ua=1

⁵ https://www.who.int/immunization/policy/sage/sage_wg_evaluation_may2018/en

The EAGSE specifically reviewed the evaluation methodology, including the selection and adaptation of the appropriate tools, and guided the interaction of the evaluation team with identified stakeholders. The EAGSE reviewed summaries of results and of interim reports across the phases of the evaluation and developed the set of final recommendations. The EAGSE held two face-to-face meetings - in July 2018 and in February 2019 - and ten video or teleconferences in August, September, and November 2018, as well as in January, February and March 2019.

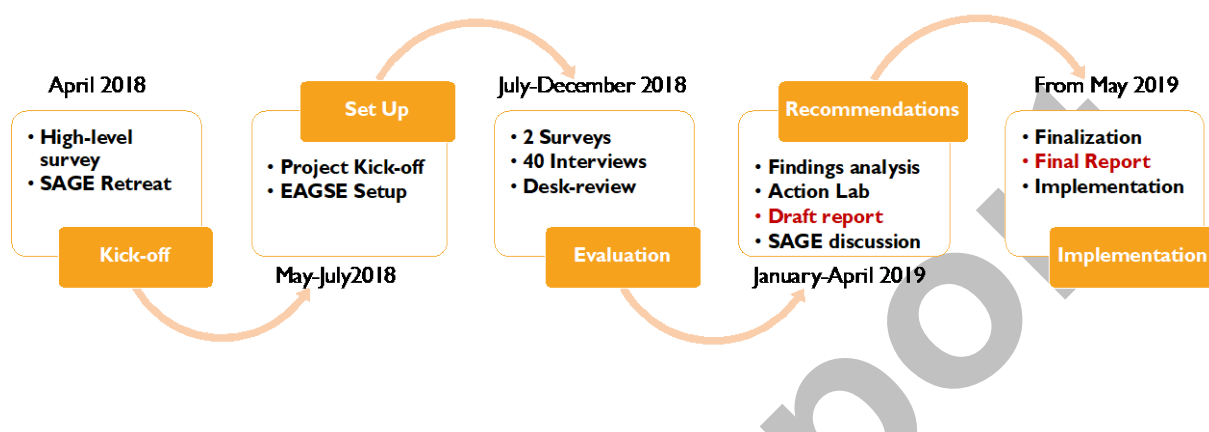


Figure 1: SAGE Evaluation Timeline.

MMGH Consulting, a consulting and advisory group with specific knowledge and experience of the SAGE functions and processes and familiarity with the key immunization stakeholders, was selected through a competitive bidding process to support the EAGSE in the evaluation (ref. appendix 8.7 for the ToR of the consulting group). Under the supervision of the WHO SAGE Secretariat and guided by the EAGSE, the consulting firm was tasked with preparing and facilitating meetings, administering online surveys, questionnaires and interviews, analysing the data and drafting documents.

4.2. Evaluation design

After definition of the evaluation's goals and ToR, the evaluation process was formally launched in April 2018 during a retreat with participation of the members of SAGE, the chairs of other WHO immunization advisory committees, the chairs of the RITAGs and senior WHO staff at Headquarters and regional levels. The meeting served to identify the critical areas to be analysed and provided input on the evaluation's design, tools and timelines.

Based on those inputs, and in consultation with the EAGSE and the SAGE Secretariat, the consultants refined the evaluation design, identified the appropriate tools, and defined a detailed project timeline. The approach was endorsed by the EAGSE during a 2-day face-to-face meeting in early July 2018. The evaluation process started thereafter and consisted of 4 phases.

An initial **fact-finding and insight generation** phase took place between August and December 2018 and was comprised of multiple activities:

- a **desk review** including the review of the prior SAGE evaluation, the review of all SAGE outputs between 2010 and 2017 and the resulting products (ref. appendix 8.5. for the SAGE product table); a descriptive analysis of SAGE agenda items, recommendations and position papers and decisions on cross-cutting issues, including the dissemination of outputs and the reach or influence of these - to the extent that this could be assessed - on initiatives, partners, and countries;
- an **in-depth interview** process with the WHO SAGE Secretariat, including a review of the SAGE ToR; guidance documents, standard operating procedures (SOP) and other specific working processes as well

as of the WHO Secretariat support, aimed at identifying areas where SAGE processes could benefit from improvements;

- c) the administration of two **online anonymized surveys** via a dedicated survey tool (off-the-shelf tool Qualtrics™) sent to 110 stakeholders closely involved with SAGE, those forming the 'inner circle' during SAGE meetings (defined as SAGE members and stakeholders regularly and directly impacted by SAGE's work including staff from WHO Headquarters, WHO regional and country offices, UNICEF, Gavi, Bill & Melinda Gates Foundation (BMGF), as well as RITAG and NITAG representatives) and to 120 additional immunization and Global Health stakeholders. The surveys, based on an adaptation and extension of the standard NITAG evaluation tool developed by the Strengthening of Immunization and Vaccines Advisory Committees (SIVAC) Initiative⁶, aimed at collecting views on SAGE performance in different areas of work. Some 58% of the 'inner circle' stakeholders (n=64) and 37% of Global Health stakeholders (n=42) responded to the survey.
- d) conducting **interviews** with a subset of stakeholders of both the 'inner circle' as well as the wider stakeholder group, selected in agreement with the EAGSE with respect to global, regional / country as well as institutional representation, who provided additional in-depth insights into thematic areas that were emerging as critical for the evaluation. A total of 40 interviews were performed during the months of December 2018 and January 2019, equivalent to 65% of the sample of targeted respondents.

A second phase was aimed at identifying areas for improvement. The EAGSE reviewed the findings arising from the first phase and defined **14 thematic areas for potential improvements** to be analysed during the subsequent phase. The six desired outputs of the evaluation (see 3.2.) are fully covered by these themes (see table 1):

Desired Outputs of the Evaluation		Thematic Areas identified for intervention	
1	Ascertaining SAGE's role in relation to the evolving immunization and health agenda.	1	SAGE goals, mandate, mission and scope
		2	SAGE in the next decade
		3	Research and development
2	Identifying optimal interfaces with other WHO immunization and Public Health decision-making and advisory bodies.	4	SAGE and other WHO Advisory Committees
3	Ensuring the optimal coordination with WHO Regions and regional committees, as well as key partners and stakeholders.	5	Principles of working with Regions and countries
		6	SAGE - RITAG – NITAG policy making chain
		7	Relations with global stakeholders
4	Ensuring the SAGE working mechanisms' effectiveness and ability to meet the highest quality standards.	8	Membership and chair selection
		9	SAGE agenda setting
		10	Decision-making and Working Group processes
		11	SAGE meeting setup and modus operandi
		12	Conflict of interest management
5	Ensuring effective presentation and dissemination of SAGE and WHO recommendations.	13	Communication and dissemination of SAGE output
6	Revisiting the WHO SAGE Secretariat composition and resource needs.	14	Secretariat resources

Table 1: Thematic Areas for Intervention and desired outputs of the evaluation

A third phase, in February 2019, during which a subset of 28 experts including SAGE Members, former SAGE Chairs, WHO Regional Advisors, RITAG and NITAG chairs, and major immunization partners (UNICEF, Gavi) - i.e. the group

⁶ SIVAC tool for evaluating NITAGS - <http://www.nitag-resource.org/media-center/document/3473>

most intimately involved in all practical dealings of SAGE and as such considered ‘process owners’ - came together by invitation of WHO IVB. Together with the EAGSE this group **prioritized the areas requiring focused attention** and suggested potential organizational and process changes. These activities were carried out as part of an Action Lab⁷, a two-day facilitated meeting focused on identifying concrete and actionable interventions for the 14 thematic areas for intervention identified in the prior phase. The approach consisted of an iterative facilitated process that moved between the broader global policy dimensions, the goal of SAGE’s work, and the technical details of the chosen interventions with a strong focus on their implementation. During the Action Lab, the group confirmed the thematic areas and extensively discussed interventions across a number of topics which had emerged in those areas.

A fourth and last phase focused on the **prioritization of recommendations**. During this phase, the EAGSE reconvened, during a face-to-face meeting in February 2019, to critically review the numerous recommendations emerging from the Action Lab and from the prior phases. The EAGSE performed a prioritization of those recommendations across the thematic areas, taking into account their relative impacts, their “implementability” and the urgency for their implementation. Detailed recommendations are currently being prepared by EAGSE for consideration by the Director of IVB.

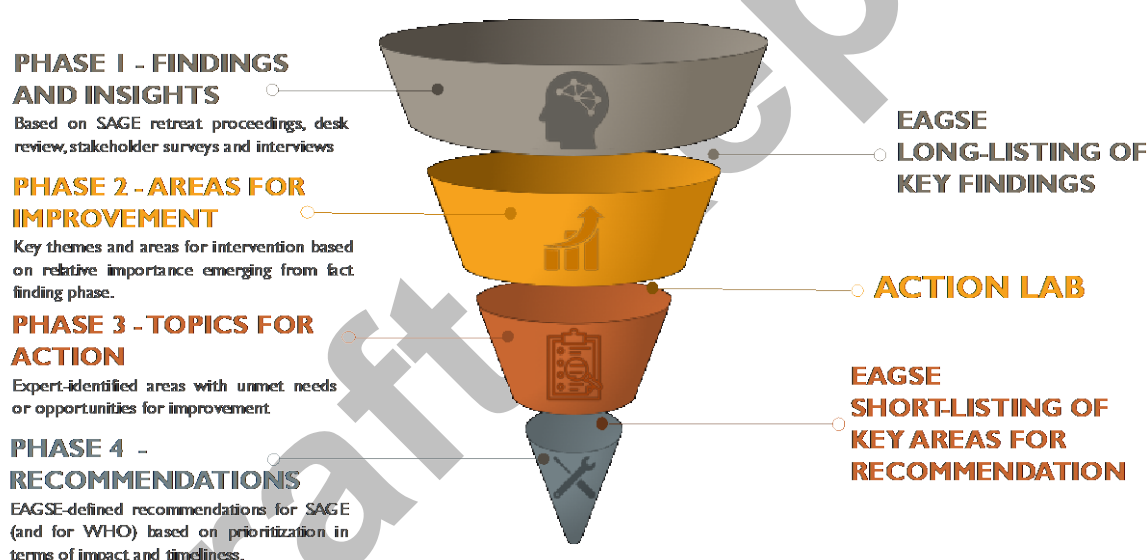


Figure 2: Evaluation Process Steps

5. SAGE retrospective: a descriptive analysis

The initial desk review provided an overview of the topics discussed in the SAGE meetings over the period from 2010-2017. The analysis of the 17 SAGE meetings during this period highlighted that two categories of topics - vaccine-specific topics and reports (see tables 3 and 4) - were the most frequently discussed, representing 72% of sessions in that period. When reviewing the type of sessions, there was an almost equal split between topics “for decision”, “for discussion” and “for information” with a slight predominance of topics for decision (38% of sessions) - (Ref. Appendix 8.6. for desk review questions).

Topic	# sessions	%	# for decision	# for discussion	# for information
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⁷ The Action Lab is an approach to organizational redesign developed originally for the private sector – Richard T. Pascale and Anne H. Miller, “The Action Lab. Creating a greenhouse for organizational change”, Strategy, Management and Competition, Issue 17, Fourth Quarter 1999. In the last 10 years, the approach has been applied successfully in the public sector by its creator.

Vaccine-specific	68	40	51 (75%)	14 (21%)	3 (4%)
Reports	54	32	0	7 (13%)	47 (87%)
Programmatic challenges	20	12	5 (25%)	14 (70%)	1 (5%)
DoV/GVAP	12	7	7	1	4
Financing	4	2	0	4	0
Vaccine safety	4	2	1	3	0
General policy	3	2	0	3	0
SAGE process	2	1	0	2	0
Surveillance	2	1	0	2	0
TOTAL	169	100%	64 (38%)	50 (30%)	55 (32%)

Table 2: Topics discussed at SAGE meeting 2010-2017

Polio was the most frequent agenda item, with at least one session devoted to this topic in each of the 17 meetings, emerging as de-facto standing agenda item. Measles-rubella and influenza vaccine issues were each discussed five times.

Number of sessions	Vaccine-specific topics
17 sessions	Polio
5 sessions each	Measles – rubella, influenza
3 sessions each	Ebola, Pertussis, Pneumococcal disease
2 sessions each	Cholera, Dengue, Hepatitis A, Human Papillomavirus, Meningococcal disease, Tuberculosis, Typhoid, Yellow Fever
1 session each	Diphtheria, Hepatitis B, Hepatitis E, Haemophilus influenza type b, Human Immunodeficiency Virus, Japanese Encephalitis, Malaria, Measles, Rabies, Respiratory Syncytial Virus, Rotavirus, Rubella, Smallpox, Tetanus, Tick-borne Encephalitis, Varicella

Table 3: Vaccine specific topics and numbers of sessions

With regard to the second most frequently discussed category of topics, i.e., reports, those from the IVB Director, Gavi and other advisory committees were again de-facto standing-agenda items during the entire period. In addition, regular annual sessions on DoV / GVAP were held (see table 1) for 5 years in preparation of World Health Assembly (WHA) discussions.

Number of sessions	Subject matter
16 sessions each	Reports from IVB Director, Gavi, other Advisory Committees
3 sessions each	Reports from Regions on regional priorities and updates and from international immunization partners

Table 4: Reports and numbers of sessions, n=54

Finally, with reference to the programmatic challenges, 2 sessions each were dedicated to (a) impact of new vaccine introduction on health and immunization systems; (b) humanitarian emergencies; (c) vaccine hesitancy; and (d) immunization supply chain and logistics. One session each was focused on the following topics: epidemiology of the unimmunized and gender-related issues; integration of immunization and child health care services; administration of multiple injections; reducing pain at the time of vaccination; maternal vaccination; implementation in the context of health systems strengthening and UHC; strengthening NITAGs; pre-empting responding to vaccine shortages; missed opportunities for vaccination (MOV); second year of life platform; national immunization programme management; and private provider engagement in immunization.

6. Evaluation findings by thematic areas

Across the four phases of the evaluation and as previously stated, findings, derived from the desk review, the surveys and the in-depth interviews had been organised into 14 thematic areas which were the basis for the formulation of recommendations (see table 1). Details of findings by theme are provided in the following.

6.1. SAGE goals, mandate, mission and scope

SAGE is considered by the stakeholders surveyed as extremely valuable, well-respected and playing a critical support role for global immunization. It has a direct and **relevant influence** on multiple areas of work for almost all key stakeholders: WHO, UNICEF, Gavi, BMGF, health ministries of low- (LIC) and middle-income countries (MICs) and for manufacturers. Its influence is deemed slightly less impactful, but still important for high-income countries (HICs), for non-governmental organizations (NGOs) and civil society organizations (CSOs), and for research or regulatory agencies.

SAGE is considered strong in accomplishing its main tasks of **providing evidence-based recommendations** even for complex issues. However, in light of the evolving global immunization space, there is a general consensus among the stakeholders for revisiting SAGE's scope of work as well as the committee's mission statement.

In this respect, the majority of inner circle respondents (57% of the survey respondents) are concerned about an expansion of the role and scope of SAGE since this may dilute its impact, while there is some appetite by the wider stakeholder group (52% of the survey respondents) to extend SAGE's **scope** beyond immunization, i.e. in linking with the Primary Healthcare (PHC) and UHC agenda and with broader health issues such as antimicrobial resistance (AMR). At the same time, there is general consensus among both groups that SAGE should consider both vaccines and immunization programmes and all types of vaccination strategies against vaccine preventable diseases (VPDs).

Finally, there is agreement across stakeholder groups on the need for a better synthesis and balance between scientific advice on vaccines and immunization and policy guidance on overall **programmatic issues**, with the latter to be especially focused on the efforts necessary to reach vulnerable populations and strengthening capacities of the weaker systems and the "implementability" of SAGE's recommendations. Any increased consideration of programmatic issues should, however, be done without reducing the scientific rigor of present SAGE deliberations. Issues related to the practical implementation of recommendations are considered by respondents beyond the scope of SAGE and best dealt with by other Advisory Committees, e.g., the Immunization Practices Advisory Committee (IPAC) and the Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC).

6.2. SAGE in the next decade

There is general agreement (80% of the 'inner circle' survey respondents and 74% of the broader stakeholder group respondents) that SAGE can accommodate future immunization challenges. At the same time there is consensus that **SAGE will need some adaptation** in its composition and modus operandi to address emerging needs and trends. In the next decade, the field of immunization will undergo significant changes to the context within which it operates, including urbanization, humanitarian emergencies, ageing populations, climate change and a shift of focus from mortality to morbidity reduction. These changes will necessarily require SAGE functioning and expertise to adapt. In addition, a variety of immunization-specific issues are on the horizon: legal and social frameworks for vaccination to address immunization as a human right, the growing focus on vaccine hesitancy as well as the arrival of additional new vaccines and new technologies to advance delivery. All of these are issues that SAGE will need to consider and for which adaptations in mission and operations will likely be required.

In this changing world, there is consensus among stakeholders for the need for SAGE to further **enhance its "brand"** to become the entity to which the world looks for guidance across a broad spectrum of strategic topics. To do so, respondents saw a need to better align the SAGE agenda, role and processes with the Sustainable Development Goals (SDGs) and to address major shifts in the health agenda of UHC. SAGE will also need to deal with aspects of integration of immunization with other primary care programmes, particularly in Maternal Neonatal Child and Adolescent Health (MNCAH), including life-course vaccination approaches. Also, further intensified interactions will be needed within the WHO with departments dealing with health systems strengthening (HSS), emergencies, non-communicable diseases, water, sanitation and hygiene (WASH), cervical cancer, malaria, rabies, tuberculosis, neglected tropical diseases, and regulatory aspects, including prequalification.

Finally, it was stated that there will likely be even more demand for **monitoring and accountability**, with the present role of SAGE in translating and monitoring the GVAP to be aligned with the post-2020 global immunization strategy.

6.3. Research and Development

There is general consensus among those surveyed that SAGE is not a committee focusing or advising on research and development (R&D) in immunization. However, as part of the development of recommendations and position papers, SAGE is dependent on research results as generated or assessed by other WHO advisory groups (see 6.4.). When collating available evidence, or when discussing policy recommendations, SAGE often identifies knowledge gaps which require further R&D, i.e., including results emanating from upstream vaccine research as well as from operational research and implementation science.

6.4. SAGE and other WHO Advisory Committees

While the role of the other WHO Advisory Committees (ACs)⁸ to SAGE functioning and their complementarity is acknowledged, the general perception is a lack of clarity about SAGE's relationship with these advisory bodies (by almost half, 47% of the 'inner circle' respondents). In particular, their mandates, functions and activities as well as their positioning in **relation to the SAGE decision-making processes** (e.g., their reporting lines to the Director of IVB as well as their reporting to SAGE during meetings) appear not to be well understood by many stakeholders.

A lack of clarity is also felt by stakeholders on a possible overlap of **roles and responsibilities** of the ACs themselves and on how SAGE could benefit more from their work. In particular, there seems to be space for better alignment of topics and a for joint management of critical issues between SAGE and the ACs. Workplans between SAGE and ACs seem not to be harmonized and linkages are not immediately apparent.

As a result, SAGE seems not to utilize the AC mechanism effectively and the possibility of delegating responsibility to specific committees is not being fully exploited.

6.5. Principles of working with regions and countries

General consensus emerged among the stakeholders that SAGE should be more systematic in considering **regional and country needs** (54% of the 'inner circle' respondents), and in particular in ensuring that its focus extends to all countries, recognizing that, increasingly, some of the greatest needs may not necessarily be concentrated in the LICs and LMICs. For this purpose, the strengthening of existing channels or the definition of new ones (such as more direct country participation with SAGE or more effective translation of SAGE output via Regional Offices) is suggested to ensure that appropriate consideration is given to country needs in defining the SAGE agenda and in formulating SAGE guidance or specific recommendations.

Country-level dimensions such as local disease burden evidence of VPDs, HSS, country decision-making processes, financial and political priorities including Gavi eligibility, and local acceptance and handling of vaccine hesitancy are all context-specific themes that will require additional attention to ensure that SAGE recommendations remain relevant for countries. Respondents saw regional offices to have the main responsibility in ensuring that appropriate visibility of country specific issues is achieved.

It was also pointed out that low-income, middle-income and high-income countries will require a **differentiation** of recommendations and a sweeping approach will no longer be useful in the future. Increasingly, country choices and adaptations from a broader menu of options will likely be required. SAGE will therefore increasingly need to provide guidance for decision-making rather than off-the-shelf recommendations. This is becoming more

⁸ Product Development for Vaccines Advisory Committee (PDVAC); Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC); Immunization Practices Advisory Committee (IPAC); Global Advisory Committee on Vaccine Safety (GACVS)

important as a result of the trend in which major donors appear to be reducing their engagement, increasing sustainability risks in some countries.

Finally, the ability to synthesize **best practices in the delivery** of vaccines and addressing any emerging challenges with the 'implementability' of SAGE decisions are also seen as important tasks of SAGE, necessitating a more functional feedback-loop from countries.

6.6. SAGE – RITAG – NITAG policy-making chain

Relations between SAGE, RITAGs and NITAGs are key to the success of SAGE. The 'implementability' of SAGE recommendations is dependent on the RITAGs' ability to tailor SAGE outputs to the specifics of each Region and on the NITAGs' ability to effectively advise Ministries of Health on applying these recommendations in the management of country immunization programmes. There is a general consensus that **SAGE relationships with RITAGs** and NITAGs should be rendered more functional (64% of the 'inner circle' survey respondents and 54% of the broader stakeholder group respondents) and roles, responsibilities and interactions further clarified with the aim of a more effective bidirectional engagement and information sharing across the three levels.

The fact that SAGE and the RITAGs occasionally operate in parallel was indicated as a source of concern: technical discussions happening at the SAGE meetings appear to sometimes be repeated at RITAG meetings. While there are established **communication links between SAGE, RITAGs and NITAGs**, with SAGE members participating in RITAG meetings (albeit not sufficiently), and RITAG and some NITAG chairs attending SAGE meetings, it was suggested by survey respondents that these links could be better used to align committee operations. This should allow for informing the SAGE agenda setting and for taking up region-specific questions at SAGE, while ensuring each committee's respective level of responsibility. At the same time, these links could be used to ensure that SAGE output is taken up in RITAG deliberations without necessarily repeating the technical discussions preceding these outputs.

Respondents also asked for a mechanism of systematic **feedback on how SAGE and RITAG recommendations have been considered, adjusted to local needs and implemented** to assist with SAGE's continuous quality improvement.

6.7. Relations with global stakeholders

SAGE's role is known in the global immunization community and the reach of its engagement with stakeholders is seen as a key strength of the committee. A variety of stakeholders in and outside of the field of immunization refer to SAGE decisions and use them as key triggers or inputs for their decisions. Gavi, UNICEF, the GPEI and the Measles and Rubella Initiative (M&RI) operations are directly advised by SAGE deliberations. SAGE, in addition, exerts influence on other stakeholders, including the BMGF, the US Centers for Disease Control and Prevention (CDC) the European CDC (ECDC), the World Bank, bilateral donors, academia, industry, regulators, NGOs / CSOs and professional organizations.

A clearer **definition of the role of 'inner circle' stakeholders** – e.g. the ones directly impacted by SAGE decisions and that depend on the downstream policy implementation processes – was called for to clarify the modalities and the extent of their contributions to the SAGE meetings. Suggestions were made by survey respondents that the purpose, method and process of obtaining their views and that of other stakeholders participating in the meetings should be more clearly differentiated and clarified.

The potential **risk of disproportionate influence** directly or indirectly exerted by some stakeholders and by WHO focal points on SAGE and WG dealings and decisions was indicated by many as an area of concern. This applies in particular to the engagement of representatives of donors / funders and of industry with participation of the latter in SAGE sessions considered as particularly critical for discussions about vaccine products. However, such an engagement demands utmost transparency and pre-defined contours of engagement.

Finally, there is consensus that SAGE could further benefit from the establishment of a more formal **stakeholder feedback** process.

6.8. SAGE membership and chair selection

There is consensus that the fundamental **areas of expertise** needed for SAGE operations are well covered (70% of the broader stakeholders group survey respondents), however a need was voiced for additional skills and competencies in areas such as primary healthcare, ethics, health economics, social science, communication science, obstetrics and maternal health. This would not necessarily require an extension of SAGE membership, as WGs potentially play an important role in providing the SAGE decision-making process with such added competencies.

Moreover, SAGE membership is considered adequate by most stakeholders (75% of both inner circle and broader stakeholders group respondents indicate SAGE membership as consistent with its goals and functions), with appropriate technical, geographic and gender diversity. However, a potential area for attention is the need for regional representation while maintaining the greatest **technical expertise**. The latter can lead to some regions (in particular Americas and Europe) and high-income countries (HICs) to be overrepresented in SAGE. Furthermore, an increased representation from implementers and CSOs, particularly from LICs & LMICs, was seen as desirable. The opportunity for establishing a mentoring programme for SAGE members or future members was proposed as an option for creating a more diversified membership, capable of participating fully and contributing to all discussions.

The current practice of **rotating membership** was perceived by the stakeholders as appropriate to ensure the dynamic adaptation of the mix of expertise represented in the committee and to allow for transition in case of performance issues.

Finally, the very high **workload of the chair** and the currently ill-defined role of the vice-chair were seen as problematic by several stakeholders. The chair's role – and the time necessary to dedicate to SAGE – is widely recognized as critical to the success of the committee, hence there is a need for realistic requirements in terms of time commitment so that the widest pool of strong candidates may retain an interest in the post. In this respect the clarification of the role of the vice-chair – for which ToR do not yet exist – is indicted as an area worth exploring.

6.9. SAGE agenda setting

Although the topics included in the agenda of SAGE meetings are considered adequate and relevant by the large majority of stakeholders, some stakeholders perceive the agenda setting to not be fully **transparent** and not to result from a thorough approach to prioritization (55% of the inner circle survey respondents to the survey). Specifically, concerns are raised by some survey respondents about the influence of some stakeholders and about the limited consideration given to country delivery needs. Consultation with Regional Offices and RITAGs appears not to be functioning as required (see 6.6.), considering the limited input provided to the agenda from regions. A more transparent SAGE agenda-setting process was also suggested as providing an opportunity for positively influencing similar exercises in the regions.

Overall, the agenda topics selection was felt to be lacking a prescribed **process** (e.g., SOP). There is consensus that this process should be part of a structured work planning exercise, taking into account need, urgency, and expected impact.

Finally, there were suggestions that a more open consultation process involving other stakeholders in a formalized manner could be beneficial, however, in those circumstances care would be required to avoid the agenda-setting being driven or influenced by individual stakeholders' interests.

6.10. Decision-making and Working Group processes

The current **consensus-based SAGE process of decision-making** is deemed optimal by the vast majority of stakeholders (88% of the 'inner circle' survey respondents); however, some concerns exist about the process of formulating SAGE recommendations (52% of the 'inner circle' respondents): several stakeholders pointed out that the decision-making process does not always appear transparent and raised concerns on, at times, 'influential' or 'vocal' stakeholders exercising unjustifiable influence (see 6.11.). In particular, more clarity on how SAGE arrives

at its decisions is thought to be needed with increased transparency by the immunization community on the decision-making criteria used.

Working Groups (WG) are seen as a key feature in the SAGE decision-making architecture, allowing the committee to expand its expert knowledge and competencies beyond its membership and as a major mechanism for the synthesis of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Evidence to Recommendations (EtR) framework. Overall, WGs are considered as working well and appropriately structured. The standard composition with one or two SAGE members and a Secretariat-identified panel of experts is considered appropriate, allowing to factor-in geography as well as gender and expertise even if efforts for further improvement regarding diversity are recommended. There is full consensus on their time-limited nature (100% of 'inner circle' survey respondents) and on the fact that standing WGs (such as the ones on polio, measles-related issues and GVAP) have a member rotation policy. During the interviews, the process of setting up WGs has been indicated by some stakeholders as an area where improvements can be made, in particular related to the occasionally long lead-time required for their establishment. Some concerns were raised about the lack of uniformity of the functioning of various WGs. Finally, the role of other partner and donor agencies in this process can be clarified on certain aspects, e.g., their active involvement in funding or conducting research for WGs.

The **GRADE approach** is considered adequate by the vast majority of respondents (79% of the 'inner circle' and 87% of the broader stakeholder group respondents), as is the use of the EtR framework. The publication of the GRADE tables is deemed appropriate with a request made to present them during the meetings where recommendations are discussed. However, questions were raised by some stakeholders during the interview process on the suitability of GRADE for the assessment of operational studies with a call for alternative mechanisms to be explored.

Most respondents felt that **SAGE's recommendations** were appropriately timely (79% of the 'inner circle' survey respondents) and, as a result, SAGE is seen as providing sensible answers to emerging issues and to be adequately responsive to urgent matters. Nevertheless, a more regular update of the position papers to remain current on evolving vaccine developments was solicited by several stakeholders, with the request for SAGE to seamlessly implement minor reviews of earlier decisions with minimal delay.

6.11. SAGE meeting setup and Modus Operandi

There is a general consensus (86% of the 'inner circle' and 75% of the broader stakeholder respondents) that the present SAGE modus operandi works reasonably well, allowing opportunities for **participation** of the 'inner circle' and of other stakeholders, including the invitation of comments from a wider audience.

Specifically, while the overall **setup** with plenary meetings and consensus voting is considered appropriate in terms of transparency, modifications that can possibly facilitate a more 'honest and robust' discussion were indicated as an area for improvement. Despite the fact that SAGE is seen as working effectively as a team, not all SAGE members actively participate in all 'decision' sessions. Members may, at times, be hesitant to speak up in public on highly technical issues. A more active role for the chair in engaging all inner circle members during the public discussion was suggested, as well as the adoption of a more structured approach to engage members before the meeting. The establishment of longer closed-door sessions, during which SAGE members could preview detailed findings ahead of the open sessions and have frank discussions on controversial topics, was suggested by several parties during the interview process.

The limited proactive **regional participation** (WHO Regional Advisors and RITAGs) was also pointed out during the interviews as an area to be addressed. Short regional presentations related to specific issues could be valuable to raise the profile of regional needs and priorities. Similarly, input from countries, private sector providers and civil society should be increased, creating specific appropriate spaces for their public comments.

On the **operational side**, it was noted that a large part of SAGE meetings is spent on sessions 'for information' and reports, that SAGE sessions are often very long, and that presentations are sometimes not clear or harmonized.

Concerns were voiced by some interview participants that during SAGE meetings **advocacy efforts** may occur and that SAGE members should be shielded from any such lobbying to the extent possible.

The **communication technology** in use is widely perceived as not appropriate to enable good preparation of SAGE members or to promote quality member interaction. The use of state-of-the-art video and audio technology was requested by most stakeholders in their comments in the survey and during the interviews, highlighting the positive impacts that such a move would allow, including a wider participation of experts and possibly obviating the need for travel.

Finally, suggestions were made for the establishment of an **evaluation process** for SAGE meetings providing immediate feedback for their further 'improvement.

6.12. Conflict of Interest management

The **Conflict of Interest (Col) management** is considered appropriate by the vast majority of the stakeholders (78% of the 'inner circle' survey respondents). However, the opportunity for and desirability of even more transparency was highlighted.

The precise **definition of what constitutes a Col** was seen as an area deserving special attention to uphold SAGE independence. There is consensus on the need for extending the scope of Col beyond simple financial interests and a focus on commercial enterprises. Other institutions beyond industry (e.g., academia, donors) and other interests beyond the financial ones (e.g., research) carry a relevant risk of undue influence on SAGE decisions and ought to be disclosed and appropriately managed. Any revision of Col will need to encompass WGs. It was noted that sufficient attention should be paid to the need for any revised Col mechanism to be consistent with the general WHO Col practices, and to being applicable to all other WHO IVB advisory committees. Additionally, caution was voiced against too strict a Col management, which would make it difficult to find subject-matter experts and to have meaningful discussion with all stakeholders concerned.

6.13. Communication and dissemination of SAGE output

There is general consensus (80% of the 'inner circle' respondents) on the need for improvement of the dissemination of SAGE decisions. The main **output of SAGE work**, the Weekly Epidemiological Records (WER) position papers and Vaccine publications, and the SAGE meeting notes and presentations are well known in the immunization field. Detailed background documents are considered as highly valuable but less well known with broader availability to be sought.

While the **quality of position papers** is rated as very high by most stakeholders, there are voices which consider SAGE outputs as being 'too difficult' and not easily 'digestible' by many practitioners in the immunization world. Use of more effective communication tools and approaches as well as the generation of documents using more plain language was indicated by many as a possible way forward to achieve a broader reach. This would also require a constituency-tailored approach that goes beyond the traditional focus on immunization stakeholders and extends to policy and decision-making bodies including finance ministries, donors, CSOs, academics and media. Policy briefs for decision-makers, guidelines for implementers and additional communication channels to medical associations are suggested.

An improved **communication and dissemination strategy** would thus need to be more proactive to allow a wider audience in regions and countries to benefit from the SAGE output. Such a strategy will have to consider a number of components such as an improved WHO website, a smarter use of social media, and the partial webcasting of SAGE sessions (or at least a possibility for download of some sessions). It was highlighted that RITAGS and NITAGs will also have an instrumental role in enhancing communication of key recommendations to ministries of health.

Finally, the briefing with WHO DG and the higher-level WHO management is deemed important by those surveyed and should be continued. More direct involvement at the Assistant Director General level in WHO could allow for tighter links with areas beyond immunization.

6.14. Secretariat role and resources

While there is wide consensus on the adequacy of the support provided by the SAGE Secretariat (71% of the inner circle survey responders), several comments were provided about the currently available **financial resources** for the SAGE Secretariat and its various WGs being inadequate and - as only partly coming from WHO core funding – potentially rendering SAGE vulnerable to influence from selective funders. The support of donors and funders for SAGE is welcome but needs to be managed – e.g. not being earmarked to a specific WG or topic – to avoid any possibility of undue influence. Specific budgets were suggested to be allocated to all WGs to ensure their effective functioning.

The ability of the SAGE Secretariat to provide sufficient **data collection and analysis** prior to SAGE deliberations (e.g., by performing or overseeing systematic reviews) appears to be inadequate in view of its limited size and large administrative burden. It was noted that the Secretariat will likely be even more stretched once some of the areas for improvement identified in this evaluation will be addressed. Most stakeholders called for an increase in size of the SAGE Secretariat in the context of the further refinement of SAGE's roles and modus operandi.

7. Next steps

The EASGE is presently preparing detailed recommendations related to SAGE's mission and scope, relations and modus operandi in each of the 14 thematic areas for consideration by the Director IVB.

These recommendations will be presented to SAGE for information in its April 2019 meeting.

8. Appendixes

The following reference documents will be made available on the SAGE website for background materials in advance of the April 2019 meeting:

8.1. Evaluation scoping questions

8.2. TOR of the EAGSE

8.3. TOR of the SAGE evaluation

8.4. SAGE product table 2010-2017

8.5. Desk review impact table

8.6. TOR of the Consulting Group