



**World Health  
Organization**

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

**SAGE**  
**October 2017**

**Strategic Advisory Group of Experts  
on Immunization  
17 - 19 October 2017**

**Executive Boardroom  
WHO HQ, Geneva**



**World Health  
Organization**

## **SAGE October 2017**

This booklet contains key background documents for the  
meeting of the  
Strategic Advisory Group of Experts (SAGE) on immunization  
17 - 19 October 2017

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

[SAGE/meetings/2017/October](#)

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**Agenda**

**Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization  
17 - 19 October 2017**

**Executive Board Room, WHO Headquarters, Geneva, Switzerland**

**Tuesday, 17 October 2017**

<b>Time</b>	<b>Session</b>	<b>Purpose of session, target outcomes and questions for SAGE</b>	<b>Duration</b>
8:30	<b>Welcome – introduction of participants</b> A. Cravioto, Chair of SAGE.		20 min.
8:50	<b>Report from Director, IVB - Session 1</b> Global report including key updates and challenges from regions. J.-M. Okwo-Bele, WHO. 30 min. Discussion: 1h	<b>FOR INFORMATION</b>	1h 30 min.
<b>10:20</b>	<b>Coffee/Tea break</b>	<b>Break</b>	<b>30 min.</b>
10:50	<b>Report from Gavi, the Vaccine Alliance - Session 2</b> Report from Gavi, the Vaccine Alliance. TBD, Gavi, the Vaccine Alliance. 15 min. Discussion: 15 min.	<b>FOR INFORMATION</b>	30 min.
11:20	<b>Reports from other Advisory Committees on Immunization – Session 3</b> Global Advisory Committee on Vaccine Safety (GACVS). R. Pless, Chair of GACVS. 10 min. Discussion: 10 min. Product Development for Vaccines Advisory Committee (PDVAC). D. Kaslow, Chair of PDVAC. 10 min. Discussion: 10 min.	<b>FOR INFORMATION</b>	1h

	<p>Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC). P. Beutels, IVIR-AC. 10 min.</p> <p>Discussion: 10 min.</p>		
12:20	<b>Lunch</b>		<b>1h 30 min.</b>
13:50	<p><b>Typhoid vaccines - Session 4</b></p> <p>Introduction. I. Jani, Chair of SAGE Working Group on Typhoid Vaccines. 5 min.</p> <p>Overview of the epidemiology and global disease burden of typhoid fever. J. Crump, Member of SAGE Working Group on Typhoid Vaccines. 15 min.</p> <p>Current control strategies, antimicrobial resistance of <i>S. Typhi</i> and implications for typhoid control. Z. Bhutta, Member of SAGE Working Group on Typhoid Vaccines. 15 min.</p> <p>Discussion: 20 min.</p> <p>Evidence review on the immunogenicity, efficacy/effectiveness and safety of typhoid conjugate vaccines. M. Levine, Member of SAGE Working Group on Typhoid Vaccines. 20 min.</p> <p>Conclusions and proposed recommendations of the SAGE Working Group on Typhoid Vaccines. I. Jani, Chair of SAGE Working Group on Typhoid Vaccines. 15 min.</p> <p>Discussion: 30 min.</p>	<p><b>Break</b></p> <p><b>FOR DECISION</b></p> <p>Present SAGE with the report of the SAGE Working Group on Typhoid Vaccines, including:</p> <ul style="list-style-type: none"> <li>The evidence review on disease and economic burden, increasing threat of antimicrobial resistance (AMR) and effectiveness and safety of typhoid vaccines.</li> <li>Draft recommendations on vaccine use for typhoid control (in context of other interventions), with a focus on newly licensed typhoid conjugate vaccines, as well as an update on the currently recommended Vi polysaccharide (ViPS) and Ty21a vaccines.</li> </ul> <p>Updated SAGE recommendations on typhoid vaccine use will be used to update the 2008 WHO position paper on typhoid vaccines.</p>	2h
15:50	<b>Coffee/tea break</b>		<b>30 min.</b>
16:20	<p><b>Polio eradication initiative - Session 5</b></p> <p>Overview of Global Polio Eradication Initiative. M. Zaffran, WHO. 25 min.</p> <p>Risk assessment and prioritization of Inactivated polio vaccine (IPV) supply and implementation of fractional IPV (fIPV) in the routine immunization. D. Chang Blanc, WHO. 20 min.</p> <p>Post certification strategy (PCS). B. Burkholder. 15 min.</p> <p>Report from SAGE Polio Working Group. Y. AL-Mazrou, Chair of the SAGE Polio Working Group. 20 min.</p> <p>Discussion: 70 min.</p>	<p><b>Break</b></p> <p><b>FOR INFORMATION AND DECISION</b></p> <p><b>For information</b> To update SAGE on:</p> <ul style="list-style-type: none"> <li>The current status of the polio eradication program, including the IPV supply situation, risk assessment of types 1 and 3 before bivalent oral polio vaccine (bOPV) withdrawal and the post certification strategy.</li> <li>The status of implementation of fractional IPV in the routine immunization.</li> <li>The preliminary discussions on assessment criteria for OPV withdrawal.</li> </ul> <p><b>For decision</b> To seek SAGE's recommendations on:</p> <ul style="list-style-type: none"> <li>Proposed approach to prioritize IPV allocation in tier 3 and</li> </ul>	2h 30 min.

		<ul style="list-style-type: none"> <li>4 countries, based on the risk ranking.</li> <li>IPV catch-up for children in countries which delayed the introduction of IPV or had stock out due to supply shortage.</li> </ul>	
<b>18:50</b>	<b>End of Day</b>		
<b>19:00</b>	<b>Cocktail</b>		

**Wednesday, 18 October 2017**

<b>8:00</b>	<b>Global Vaccine Action Plan (GVAP): Progress report - Session 6</b>	<p>Update from the GVAP Secretariat, including on the 2017 World Health Assembly 70.14 Global Vaccine Action Plan resolution. T. Cherian (on behalf of the Secretariat of the SAGE Decade of Vaccines Working Group), WHO. 10 min.</p> <p>Summary of GVAP implementation progress review and recommendations for corrective actions. N. MacDonald, Chair of SAGE Decade of Vaccines Working Group. 30 min.</p> <p>Discussion: 1h 20min.</p> <p>Immunization related Sustainable Development Goals indicator options and proposal retained by the Decade of Vaccines Working Group. N. Arora, Member of SAGE Decade of Vaccines Working Group. 10 min.</p> <p>Discussion: 20 min.</p> <p>Presentation of proposed process to develop a Global Immunization Strategy 2021-2030. C. Mantel, on behalf of WHO. 10 min.</p> <p>Discussion: 20 min.</p>	<p><b>FOR DECISION</b></p> <p>SAGE will be expected to produce an independent annual report on progress with the Decade of Vaccines Global Vaccine Action Plan.</p> <p>Specially, SAGE will be asked to:</p> <ul style="list-style-type: none"> <li>Review the DoV WG "Assessment report on DoV progress 2017" based on the "GVAP Secretariat report 2017", regional reports on the implementation of regional vaccine action plans, priority country reports and some independent stakeholder submissions.</li> <li>Make recommendations on any necessary changes to the formulation of the indicators, operational definitions and/or the processes for data collection.</li> <li>Identify successes, challenges and areas where additional efforts or corrective actions by countries, regions, partners, donor agencies or other parties, are needed.</li> </ul> <p>Provide recommendations and corrective actions for Member States, regions, partners, donor agencies "SAGE Assessment report on the Decade of Vaccines progress" which will be the basis of the "progress report" for the 2018 WHO Executive Board and World Health Assembly.</p> <p>Review the immunization related indicators proposed as part of the Sustainable Development Goals indicator and make a final decision on these indicators.</p> <p>SAGE will further be presented with the preliminary plans for Global Immunization Strategy 2021-30.</p>	3h
<b>10:00</b>	<b>Coffee/tea break</b>		<b>Break</b>	<b>30 min.</b>
10:30	<b>Global Vaccine Action Plan (GVAP): Progress report, contd.</b>			

11:30	<p><b>Report of activities from international immunization partners – Session 7</b></p> <p>Developing Country Vaccine Manufacturers Network (DCVMN). M. Datla, Director DCVMN. 20 min.</p> <p>Discussion: 20 min.</p> <p>International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). L. Bigger, IFPMA. 20 min.</p> <p>Discussion: 20 min.</p>	<p><b>FOR INFORMATION AND DISCUSSION</b></p> <p>Continuation of the series of presentations initiated in October 2015 to be held at SAGE meetings on the immunization-related activities of partners working in the field of immunization.</p>	1h 20 min.
<b>12:50</b>	<b>Lunch</b>	<b>Break</b>	<b>1h</b>
13:50	<p><b>Rabies vaccines - Session 8</b></p> <p>Overview of the global rabies situation. B. Abela-Ridder, WHO. 10 min.</p> <p>Presentation of evidence on vaccination for pre-exposure rabies prophylaxis (PREP) (Question 1,2,3,4). A. Tarantola, Member of SAGE Rabies Working Group. 15 min.</p> <p>Conclusions and proposed recommendations. K. O'Brien, Chair of the SAGE Rabies Working Group. 10 min.</p> <p>Discussion: 30 min.</p> <p>Presentation of evidence on vaccination for post-exposure rabies prophylaxis (PEP) (Question 5,6,7,8,9). A. Tarantola, Member of SAGE Rabies Working Group. 20 min.</p> <p>Conclusions and proposed recommendations. K. O'Brien, Chair of the SAGE Rabies Working Group. 10 min.</p> <p>Discussion: 30 min.</p> <p>Presentation of evidence on rabies immunoglobulins (RIG) for PEP (Questions 10,11,12,13,14). A. Tarantola, Member of SAGE Rabies Working Group. 15 min.</p> <p>Conclusions and proposed recommendations. K. O'Brien, Chair of the SAGE Rabies Working Group. 10 min.</p> <p>Discussion: 30 min.</p>	<p><b>FOR DECISION</b></p> <p>Based on the evidence presented, SAGE is expected to review and endorse draft recommendations related to the following questions:</p> <p><b>Question 1:</b> Does novel evidence support the use of PREP in particular sub-populations, apart from persons bearing an occupational rabies exposure risk?</p> <p><b>Question 2:</b> Does novel evidence support the need for rabies booster doses in persons at continual or frequent risk of occupational rabies exposure?</p> <p><b>Question 3:</b> Can the duration of the entire course of current PREP regimens be reduced while maintaining immunogenicity and clinical protection?</p> <p><b>Question 4:</b> Can the number of doses administered in current PREP regimens be reduced while maintaining immunogenicity and clinical protection?</p> <p><b>Question 5:</b> Which (operational) parameters affect cost-effectiveness of intradermal (ID) compared to intramuscular (IM) administration route of PEP? a. in urban settings; b. in rural settings.</p> <p><b>Question 6:</b> Can the duration of the entire course of current PEP regimens be reduced while maintaining immunogenicity and clinical protection?</p> <p><b>Question 7:</b> Can the number of doses administered in current PEP regimens be reduced while maintaining immunogenicity and clinical protection?</p> <p><b>Question 8:</b> Does novel evidence support recommendations on modified PEP protocols vs current PEP protocols for specific risk groups of rabies exposed patients, such as: Immuno-compromised patients (e.g. HIV-infected); patients concurrently using antimalarial</p>	3h

		<p>drugs; pregnant women; bat exposures (i.e. for bat lyssavirus)?</p> <p><b>Question 9:</b> Does a change in route of administration (IM or ID) during a single course of a PEP regimen affect immunogenicity of PEP?</p> <p><b>Question 10:</b> Are there novel approaches to RIG (-sparing) injection vs current practice as part of PEP for category III exposed patients?</p> <p><b>Question 11:</b> Is there clinical equivalence in the safe use of eRIG compared to hRIG in category III exposed patients?</p> <p><b>Question 12:</b> Is there clinical equivalence in the efficacious use of eRIG compared to hRIG in category III exposed patients?</p> <p><b>Question 13:</b> Can monoclonal antibodies be safely and efficaciously administered in category III exposed patients compared to standard RIG?</p> <p><b>Question 14:</b> In cases of RIG shortage and constraints, can subcategories of patients be identified who should be given highest priority for RIG administration?</p>	
<b>16:50</b>	<b>Coffee/ tea break</b>		<b>30 min.</b>
17:20	<p><b>Pneumococcal conjugate vaccines (PCV) - Session 9</b></p> <p>Introduction. A. Pollard, Chair of the PCV Working Group. 2 min.</p> <p>Current status of PCV usage and current recommendations. K. O'Brien, SAGE PCV Working Group member. 10 min.</p> <p>Review of PRIME systematic review. M. Knoll, Johns Hopkins Bloomberg School of Public Health. 35 min.</p> <p>Review of modelling on catch-up immunization. S. Flasche, London School of Hygiene and Tropical Medicine. 10 min.</p> <p>Questions for clarification: 10 min.</p> <p>Conclusions and proposed recommendations. A. Pollard, Chair of the SAGE PCV Working Group. 13 min.</p> <p>Discussion: 40 min.</p>	<p><b>FOR INFORMATION AND DECISION</b></p> <p>SAGE will be expected to review evidence related to the following questions and update recommendations on the use of Pneumococcal conjugate vaccines accordingly:</p> <ol style="list-style-type: none"> <li>1) In the general population, what overall effectiveness and impact does a 2p+1 PCV dosing schedule elicit as compared to a 3p+0 PCV dosing schedule?</li> <li>2) In the general population, what overall effectiveness and impact does PCV10 elicit as compared to PCV13?</li> <li>3) In the general population, what additional value does catch-up vaccination with 1 or 2 doses of PCV in vaccine-naïve children above the birth cohort have as compared with vaccination of only the birth cohort at the time of introduction (or PCV product switch)?</li> </ol>	2h
<b>19:20</b>	<b>End of day</b>		

**Thursday, 19 October 2017**

<p>08:00</p>	<p><b>Measles and rubella elimination – Session 10</b></p> <p>Introduction. N. Turner, Chair of the SAGE Measles and Rubella Working Group. 5 min.</p> <p>Global update and progress on the implementation of recommendations from the midterm review. A. Dabagh, WHO. 20 min.</p> <p>Discussion: 30 min.</p> <p>Critical immunity threshold for measles elimination. S. Funk, London School of Hygiene and Tropical Medicine. 20 min.</p> <p>Discussion: 20 min.</p> <p>Measles in infants less than 6 months of age and effectiveness and safety of vaccination. N. Crowcroft, Member of SAGE Measles and Rubella Working Group. 25 min.</p> <p>Discussion: 20 min.</p>	<p><b>FOR INFORMATION AND DECISION</b></p> <p>For information:</p> <ul style="list-style-type: none"> <li>• Global update on measles and rubella</li> <li>• Progress on the implementation of recommendations from the midterm review.</li> <li>• Global criteria for country categorization.</li> </ul> <p>For recommendations on:</p> <ul style="list-style-type: none"> <li>• What level of population immunity is needed to achieve herd immunity (age-specific immunity thresholds).</li> <li>• The possibility and eventual need to vaccinate infants less than 6 months of age.</li> <li>• Review evidence and provide policy guidance related to revaccination of HIV infected adults.</li> </ul>	<p>2h 45 min.</p>
<p><b>10:20</b></p>	<p><b>Coffee/tea break</b></p>	<p><b>Break</b></p>	<p><b>30 min.</b></p>
<p>10:50</p>	<p><b>Measles and rubella elimination –Session 10, contd.</b></p> <p>Revaccination of HIV infected adults. W. Moss, Member of SAGE Measles and Rubella Working Group. 10 min.</p> <p>Discussion: 15 min.</p>		
<p>11:15</p>	<p><b>Bacille Calmette-Guérin (BCG) vaccines -Session 11</b></p> <p>Introduction T. Goodman, WHO. 10 min.</p> <p>Effectiveness, duration of protection and impact of BCG vaccination against TB. P. Mangtani, LSHTM, 15 min.</p> <p>Safety of vaccination and implications on HIV-infected and exposed children. K. Johansen, Member of SAGE BCG Working Group. 10 min.</p> <p>Use of BCG for the prevention of leprosy. L. Gillini, WHO. 15 min.</p>	<p><b>FOR DECISION</b></p> <p>Present SAGE with the report of the SAGE BCG Working Group and request SAGE's consideration of the proposed recommendations.</p> <p>SAGE will particularly be asked to consider the optimal timing of vaccination, the vaccination of HIV exposed and HIV infected children, the duration of protection and need for revaccination, the effect of BCG co-administration with other vaccines, and the potential role of BCG in the control of leprosy.</p> <p>SAGE recommendations on vaccine use will then be used to update the WHO Position Paper on BCG.</p>	<p>2h 20 min.</p>

	Conclusions and proposed recommendations. C. Wiysonge, Chair of the SAGE BCG Working Group. 20 min. Discussion: 1h 10 min		
<b>13:35</b>	<b>Closing</b>		20 min.
<b>13:55</b>	<b>End of meeting</b>		

**Meeting of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization  
17-19 October 2017  
Geneva, Switzerland**

**SAGE members**

<p><b>Dr Rakesh Aggarwal</b> Professor Department of Gastroenterology <b>Sanjay Gandhi Postgraduate Institute of Medical Sciences</b> Lucknow <b>India</b></p>
<p><b>Dr Yagob Yousef Al-Mazrou</b> Secretary General <b>Council of Health Services</b> Riyadh 12628 <b>Saudi Arabia</b></p>
<p><b>Dr Alejandro Cravioto (SAGE Chair)</b> Consultant <b>Facultad de Medicina Universidad Nacional Autónoma de México</b> Ciudad de México <b>Mexico</b></p>
<p><b>Dr Ilesh Jani</b> Director General <b>Instituto Nacional de Saúde (INS)</b> Maputo <b>Mozambique</b></p>
<p><b>Dr Jaleela Jawad</b> Head, Immunization Group and EPI Manager Public Health Directorate <b>Ministry of Health</b> Manama <b>Bahrain</b></p>
<p><b>Dr Youngmee Jee</b> Director Center for Immunology and Pathology <b>Korea Centers for Disease Control &amp; Prevention</b> Cheongju <b>Republic of Korea</b></p>
<p><b>Dr Kari Johansen (SAGE-Vice Chair)</b> Expert Influenza and other Vaccine Preventable Diseases Surveillance and Response Support Unit <b>European Centre for Disease Prevention and Control</b> Stockholm <b>Sweden</b></p>
<p><b>Professor Noni MacDonald</b> Professor of Pediatrics Division Pediatric Infectious Diseases <b>Dalhousie University</b> Halifax <b>Canada</b></p>
<p><b>Professor Terence Nolan</b> Head, Department of Public Health Melbourne School of Population Health <b>The University of Melbourne</b> Melbourne <b>Australia</b></p>



<p><b>Dr Katherine L. O'Brien</b>  Professor  Department of International Health  <b>John Hopkins Bloomberg School of Public Health</b>  Baltimore  <b>United States of America</b></p>
<p><b>Professor Andrew Pollard</b>  Professor of Paediatric Infection and Immunity  Department of paediatrics  <b>University of Oxford</b>  Oxford  <b>United Kingdom</b></p>
<p><b>Dr Firdausi Qadri</b>  Senior Director  Infectious Diseases Division  <b>International Centre for Diarrhoeal Diseases Research, Bangladesh</b>  Dhaka  <b>Bangladesh</b></p>
<p><b>Dr Nikki Turner</b>  Associate Professor, Director Immunisation Advisory Centre  Department of General Practice and Primary Health Care  <b>The University of Auckland</b>  6012 Wellington  <b>New Zealand</b></p>
<p><b>Professor Fredrick Were</b>  Dean  School of Medicine  <b>University of Nairobi</b>  Nairobi  <b>Kenya</b></p>
<p><b>Dr Charles Shey Wiysonge</b>  Professor &amp; Deputy Director  Centre for Evidence-based Health Care  <b>Stellenbosch University</b>  Ruyterwacht  <b>South Africa</b></p>

## **Strategic Advisory Group of Experts (SAGE) Terms of reference**

### **Functions**

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

SAGE advises the WHO Director-General specifically on the:

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

### **Membership**

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

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

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

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

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

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

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

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

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

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

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

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

### **Meetings and operational procedures**

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

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

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

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

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

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

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

### **Roles and responsibilities of SAGE members**

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

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

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

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

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

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

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

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

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

([http://www.who.int/immunization/sage/Guidelines\\_development\\_recommendations.pdf?ua=1](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/](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:
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**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)

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

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

#### Terms of Reference

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

#### Composition

##### SAGE Members

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

##### Experts

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

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

### Terms of Reference

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

### Composition

#### *SAGE Members*

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

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

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

### Terms of Reference

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

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

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

### Composition

#### *SAGE Members*

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

#### *Experts*

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

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

##### **Terms of Reference**

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

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

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

##### **Composition**

#### *SAGE Members*

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

#### *Experts*

- Nick Andrews: Public Health England, United Kingdom.
- George Bonsu: Ministry of Health, Ghana.
- David Durrheim: Hunter New England Area Health Service, Australia. (SAGE member until April 2012)
- Ann Kelly: University of Exeter, United Kingdom.
- Jesse Goodman: Georgetown University, United States of America (resigned from Working Group in January 2017).
- Jean-Paul Jemmy: Médecins Sans Frontières, Belgium.
- Keymanthri Moodley: Stellenbosch University, South Africa.
- Cesar Velasco Muñoz: Hospital Clínico Lozano Blesa, Spain.

- Diop Ndack: University Cheikh Anta Diop, Senegal.
- Chris Ockenhouse: PATH, United States of America.
- Helen Rees: University of Witwatersrand, South Africa. (Co-Chair of the Working Group and former SAGE Chair 2010 - 2013)
- Oyewale Tomori: Redeemer's University, Nigeria. (Co-Chair of the Working Group until March 2016 and SAGE member until April 2015)

#### *Ex-Officio members*

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

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

### **Terms of reference**

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

Specifically, the Working Group will review evidence on:

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

### **Composition**

#### *SAGE Members*

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

#### *Experts*

- Narendra Arora: International Clinical Epidemiology Network, India. (SAGE member until April 2016)
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- Mark Miller: National Institutes of Health, United States of America.
- Christopher Parry: London School of Hygiene and Tropical Medicine, United Kingdom.
- Richard Strugnell: University of Melbourne, Australia.
- Dipika Sur: retired (former National Institute of Cholera and Enteric Diseases, India).

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

### **Terms of reference**

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

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

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

## Composition

### *SAGE Members*

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

### *Experts*

- Ahmed Be-Nazir: National Institute of Preventative and Social Medicine, Bangladesh.
- Arnaud Tarantola: Institut Pasteur, Cambodia.
- Deborah Briggs: Kansas State University, United States of America.
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- Mary Warrell: University of Oxford, United Kingdom.
- Mathurin Cyrille Tejiokem: Centre Pasteur, Cameroon.
- Naseem Salahuddin: The Indus Hospital, Pakistan.

## 7. SAGE Working Group on the use of bacille Calmette-Guérin vaccine (established October 2016)

### Terms of Reference

The Working Group will be requested to review the scientific evidence and relevant programmatic considerations to formulate proposed recommendations on the use of bacille Calmette-Guérin (BCG) vaccines for consideration by SAGE to inform a revision of the global policy on the use of BCG, and for subsequent updating of the WHO Position Paper on BCG and related materials.

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

1. Country practices in the use of BCG including that of targeted vaccination in low tuberculosis (TB) prevalence countries as well as the threshold applied to decide on stopping vaccination;
2. TB epidemiology as well as the epidemiology of leprosy;
3. Trends in antibiotic resistance and their implications for BCG use;
4. The safety, effectiveness, and duration of protection afforded by administration of BCG (in a strain specific analysis) in different age groups and according to HIV status and for different outcomes (i.e. death, pulmonary disease and infection);
5. Assessment of the duration of protection and need for revaccination (including a comparison of the effect of revaccination with that of alternative protective approaches e.g. isoniazid preventive therapy);
6. The effect of BCG co-administration with other vaccines administered at birth (OPV, hepatitis B) or later (e.g. co-administration with DTP containing and specifically pentavalent vaccine);
7. The economic burden of TB and cost-effectiveness of vaccination as well as modelling data to inform BCG vaccination strategies (including vaccination in the context of other control strategies);
8. The potential role of BCG in the control of leprosy.

In addition the Working Group will be briefed on the TB vaccine candidates development status, including BCG improvement strategies that may have implications for beneficial non-specific vaccine effects of the current BCG. The vaccine has several non-specific effects (NSE) which should be discussed but which should not be the immediate focus of the Working Group since this issue of NSE is being address by the Immunization and Vaccines-Related Implementation Research Advisory Committee (IVIR-AC).

## Composition

### *SAGE Members*

- Charles Shey Wiysonge: South African Medical Research Council, South Africa (Chair of the Working Group)
- Kari Johansen: European Centre for Disease Prevention and Control, Sweden



#### *Experts*

- Safaa Al-Khawaja: Ministry of Health, Bahrain
- Pamela Bakkabulindi: Ministry of Health, Uganda
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- Guangxue He: Chinese Center for Disease Control and Prevention, China
- Helen McShane: University of Oxford, England
- Elizabeth Obimbo: University of Nairobi, Kenya
- Jeffrey Starke: Baylor College of Medicine, USA

### **8. SAGE Working Group on pneumococcal conjugate vaccine (established December 2016)**

#### **Terms of Reference**

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

#### **Composition**

##### *SAGE Members*

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

##### *Experts*

- Narendra Arora: The INCLEN Trust International, New Delhi
- Stefan Flasche: London School of Hygiene & Tropical Medicine, United Kingdom
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- Tamara Plishvili: Centers for Disease Control and Prevention, United States of America
- Betuel Sigauque: Manhica Health Research Centre, Mozambique
- Cristiana Toscano: Federal University of Goiás, Brazil

### **9. SAGE Working Group on Quality and Use of Global Immunization and Surveillance Data**

#### **Terms of Reference**

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

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

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

### **Composition**

#### *SAGE Members*

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

#### *Experts*

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- Michael Edelstein: Public Health England, United Kingdom
- Hashim Ali Elzein Elmousaad: Independent Consultant, Pakistan
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**Strategic Advisory Group of Experts (SAGE) on Immunization  
17 - 19 October 2017  
Executive Board Room, WHO/HQ, Geneva, Switzerland**

**Provisional list of participants as of 26 September 2017**

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

The Strategic Advisory Group of Experts on immunization (SAGE)<sup>1</sup> met on 25–27 April 2017. This report summarizes the discussions, conclusions and recommendations.<sup>2</sup>

### Report from the WHO Department of Immunization, Vaccines and Biologicals

The report focused on acceleration of global and regional implementation of the Global Vaccine Action Plan (GVAP), the positioning of immunization in global health agendas, and the way forward.

The October 2016 midterm review of the GVAP acknowledged the progress made, but noted that it was too slow to achieve the goals of the Decade of Vaccines.<sup>3</sup> In 2015, 86% of infants worldwide (116.1 million) received 3 doses of diphtheria, tetanus and pertussis containing vaccine (DTP). However, to achieve universal coverage, 13.5 million unvaccinated children must be reached annually and an additional 6 million incompletely vaccinated children must complete the schedule. Access and missed opportunities for vaccination remain challenging in low, middle and high income countries.

Led by the WHO African Regional Office (AFRO), the Reaching Every District (RED)

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

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination<sup>1</sup> s'est réuni du 25 au 27 avril 2017. Le présent rapport résume les discussions, conclusions et recommandations auxquelles il est parvenu.<sup>2</sup>

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

Ce rapport porte sur l'accélération de la mise en œuvre à l'échelle mondiale et régionale du Plan d'action mondial pour les vaccins (GVAP), le positionnement de la vaccination dans les programmes mondiaux d'action sanitaire et les prochaines étapes.

L'évaluation à mi-parcours du GVAP, réalisée en octobre 2016, a reconnu les progrès accomplis tout en soulignant que la réalisation des objectifs de la Décennie de la vaccination demeurait trop lente.<sup>3</sup> En 2015, 86% des nourrissons dans le monde (116,1 millions) ont reçu 3 doses du vaccin contre la diphtérie, le tétanos et la coqueluche (DTC). Néanmoins, pour parvenir à une couverture universelle, 13,5 millions d'enfants non vaccinés doivent recevoir leurs doses de vaccin chaque année et les 6 millions d'enfants partiellement vaccinés doivent recevoir les doses manquantes afin de respecter le calendrier vaccinal. L'accès à la vaccination et les occasions manquées restent problématiques dans les pays à revenu faible, intermédiaire et élevé.

La stratégie «Atteindre chaque district», menée par le Bureau régional OMS de l'Afrique

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<sup>1</sup> See <http://www.who.int/immunization/sage/en/index.html>, accessed April 2017.

<sup>2</sup> Presentations and background materials used for the SAGE meeting together with the list of SAGE members and summarized declarations of interests are available at <http://www.who.int/immunization/sage/meetings/2017/april/en/index.html>, accessed April 2017.

<sup>3</sup> See 2016 midterm review of the Global vaccine action plan. Available at [http://www.who.int/immunization/global\\_vaccine\\_action\\_plan/SAGE\\_GVAP\\_Assessment\\_Report\\_2016\\_EN.pdf?ua=1](http://www.who.int/immunization/global_vaccine_action_plan/SAGE_GVAP_Assessment_Report_2016_EN.pdf?ua=1), accessed April 2017.

<sup>1</sup> Voir <http://www.who.int/immunization/sage/en/index.html>, consulté en avril 2017.

<sup>2</sup> 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 <http://www.who.int/immunization/sage/meetings/2017/april/en/index.html>, consulté en avril 2017.

<sup>3</sup> Voir l'évaluation à mi-parcours 2016 du Plan d'action mondial pour les vaccins. Disponible à l'adresse [http://www.who.int/immunization/global\\_vaccine\\_action\\_plan/SAGE\\_GVAP\\_Assessment\\_Report\\_2016\\_EN.pdf?ua=1](http://www.who.int/immunization/global_vaccine_action_plan/SAGE_GVAP_Assessment_Report_2016_EN.pdf?ua=1), consulté en avril 2017.

strategy is being updated to emphasize equity in immunization, life course vaccination, integration of health services, and health facility and community level focus. WHO is working on reducing missed opportunities for vaccination in 20 priority countries representing 30% (5.9 million) of the unvaccinated or partially-vaccinated global birth cohort.

Vaccine supply chain management constraints were the subject of a “call to action” in 2014 to national programmes and global partners to review the status of and investment in the vaccine supply chain and logistic systems. Several regional and global initiatives have been launched; WHO, UNICEF, the Bill and Melinda Gates Foundation (BMGF) and the GAVI Alliance launched the Cold Chain Equipment Optimization Platform, aiming to move towards deployment of safer and more cost-effective technologies in 55 focus countries.

WHO is also working on increasing vaccine price transparency and on pre-empting and managing vaccine shortages.

Data quality remains problematic in many countries, due to incomplete or inconsistent data from all administrative levels. To address these constraints, WHO is developing normative guidance and supports capacity building and strengthening.

Vaccines play an important role in combatting antimicrobial resistance (AMR). By preventing infections, vaccines reduce the use of antibiotics. With the emergence of multidrug resistant pathogens, vaccines may become the only available intervention against them. WHO now includes in its prioritization process the evaluation of the impact of vaccination on AMR.

The report stressed the importance of vaccines as a critical and strategic tool in the context of global health security, with vaccines currently in development against new and emerging epidemic diseases.

Sustained high level support for implementation of the GVAP remains essential. At a recent meeting, the heads of the GVAP lead agencies (BMGF, GAVI, US National Institute of Health, UNICEF, WHO) expressed satisfaction with progress in some areas, but deep concern regarding challenges in coverage and equity. They agreed to provide urgent oversight, drawing on experience gained during polio eradication and other successful immunization initiatives.

Member States expressed continued interest in the GVAP at the WHO Executive Board meeting in January 2017. The GVAP midterm report will be presented to the World Health Assembly in May together with a draft resolution.

In the African Region, the declaration on “Universal Access to Immunization as a Cornerstone for Health and Development in Africa” was endorsed by Heads of State at the African Union Summit in January 2017. The African and Eastern Mediterranean Regional Offices

(AFRO), est actuellement mise à jour pour mettre l'accent sur l'équité en matière de vaccination, la vaccination tout au long de la vie, l'intégration des services sanitaires et une action centrée sur les établissements de santé et les communautés. L'OMS s'emploie à réduire les occasions manquées de vaccination dans 20 pays prioritaires, qui représentent 30% (5,9 millions) des nouveau-nés non vaccinés ou partiellement vaccinés dans le monde.

Les difficultés liées à la gestion de la chaîne d'approvisionnement en vaccins ont fait l'objet d'un «appel à l'action» en 2014 adressé aux programmes nationaux et aux partenaires mondiaux afin d'examiner l'état des systèmes logistiques et de la chaîne d'approvisionnement en vaccins et de revoir les investissements correspondants. Plusieurs initiatives régionales et mondiales ont vu le jour; l'OMS, l'UNICEF, la Fondation Bill & Melinda Gates et l'Alliance GAVI ont lancé la plateforme d'optimisation de l'équipement de la chaîne du froid qui vise à déployer des technologies plus sûres et rentables dans 55 pays cibles.

L'OMS s'attache également à améliorer la transparence des prix des vaccins et à anticiper et gérer les pénuries de vaccins.

La qualité des données reste problématique dans de nombreux pays en raison des données incomplètes ou incohérentes provenant de tous les niveaux administratifs. Pour pallier ces difficultés, l'OMS élabore des orientations normatives et apporte son soutien au développement et au renforcement des capacités.

Les vaccins jouent un rôle important dans le combat contre la résistance aux antimicrobiens. En prévenant les infections, les vaccins réduisent l'usage des antibiotiques. Avec l'émergence d'agents pathogènes multirésistants, les vaccins pourraient devenir la seule arme disponible pour les combattre. Désormais, l'OMS inclut dans son processus d'établissement des priorités l'évaluation de l'impact de la vaccination sur la résistance aux antimicrobiens.

Ce rapport souligne l'importance des vaccins en tant qu'outils indispensables et stratégiques pour la sécurité sanitaire mondiale; des vaccins contre des maladies épidémiques nouvelles ou émergentes sont d'ailleurs actuellement à l'étude.

Un appui durable de haut niveau pour la mise en œuvre du GVAP demeure essentiel. Lors d'une récente réunion, les dirigeants des principaux organismes du GVAP (Fondation Bill & Melinda Gates, Alliance GAVI, instituts nationaux de la santé des États-Unis d'Amérique, UNICEF, OMS) ont exprimé leur satisfaction devant les progrès accomplis dans certains domaines, mais aussi leur profonde inquiétude concernant les problèmes de couverture et d'équité. Ils sont convenus de mettre en place une surveillance sans délai, en tirant parti de l'expérience acquise lors de l'éradication de la poliomyélite et d'autres initiatives de vaccination réussies.

Les États Membres ont réaffirmé leur intérêt dans le GVAP lors du Conseil exécutif de l'OMS en janvier 2017. Le rapport à mi-parcours du GVAP, accompagné d'un projet de résolution, sera présenté à l'Assemblée mondiale de la Santé en mai.

Dans la Région africaine, la déclaration sur l'«accès universel à la vaccination comme pierre angulaire de la santé et du développement en Afrique» a été adoptée par les chefs d'État lors du Sommet de l'Union africaine en janvier 2017. Les bureaux régionaux de l'Afrique et de la Méditerranée orientale (AFRO

(AFRO and EMRO) are developing a “Business Case for Immunization” on the African continent.

AFRO emphasized concerns with the impact of the “polio transition” as the polio programme is wound down. The immunization infrastructure in many countries is largely dependent on funding for the polio eradication effort. AFRO is working closely with countries to minimize the negative impact of the transition and stressed that reaching high vaccination coverage in fragile and insecure areas remains challenging.

In the Region of the Americas, the Regional Vaccine Action Plan (RVAP) coverage targets of 95% for DTP3 vaccination equity are still off track. Microplanning guides and manuals to reduce missed opportunities for vaccination are being developed and updated, and training is being provided to countries on data monitoring and analysis. Effective Vaccine Management assessments were conducted in 5 countries. In March 2017, the Regional Technical Advisory Group (RTAG) met to discuss the inactivated polio vaccine (IPV) supply situation; countries which administer >100 000 doses of IPV annually were recommended to use fractional IPV (fIPV) if they have the capacity to adequately train and supervise health-care workers in intradermal injection.

In the Eastern Mediterranean Region, crisis and humanitarian emergency situations continue to impact vaccination coverage. The importance of collaboration with partners in the field of immunization was stressed, including with non-governmental organizations and other United Nations agencies, to reach populations in crisis. Efforts to improve data quality in the Region are in progress. New vaccine introductions have proved challenging in middle income countries (MICs), although some progress has been noted with the help of the WHO MIC strategy.

In the European Region there is high level political support for immunization programmes. Of great concern in the Region is the reported increase in measles cases in the spring of 2017 and the importance of prompt response involving the highest political level was stressed. With more evidence becoming available, MICs were found to be lagging behind in the management of immunization programmes and the introduction of new vaccines. Activities are ongoing to address immunization safety concerns, strengthen knowledge of service providers, implement pharmacovigilance systems, and sustain demand for and acceptance of vaccination.

In the South-East Asia Region measles elimination and rubella/congenital rubella syndrome control are now flagship programmes. India and Indonesia are rolling out large-scale vaccination campaigns with measles-rubella (MR) vaccine, targeting >450 million children during the next 18 months. Initiatives have been launched to improve DTP3 coverage and to reach unvaccinated populations in all priority countries. The focus is on immunization system strengthening, mobilization

et EMRO) préparent une «analyse de rentabilité de la vaccination» sur le continent africain.

Le Bureau régional de l’Afrique a mis l’accent sur les préoccupations concernant l’impact de la «transition poliomyélite» au moment où le programme d’éradication de la poliomyélite touche à son but. Dans de nombreux pays, en effet, l’infrastructure utilisée pour la vaccination dépend en grande partie du financement des activités liées à l’éradication de la poliomyélite. AFRO travaille étroitement avec les pays pour réduire au minimum l’impact négatif de la transition; il a également souligné le fait qu’il demeure difficile de parvenir à une couverture vaccinale élevée dans les zones fragiles et touchées par l’insécurité.

Dans la Région des Amériques, les objectifs de couverture du plan d’action régional pour les vaccins (RVAP) qui fixaient à 95% le taux de vaccination par le DTC3 ne sont toujours pas atteints. Des guides et manuels de microplanification visant à réduire les occasions manquées de vaccination sont en cours d’élaboration et d’actualisation, et une formation à la surveillance et à l’analyse des données est dispensée aux pays. La gestion efficace des vaccins a été évaluée dans 5 pays. En mars 2017, le groupe consultatif technique régional s’est réuni pour discuter de l’approvisionnement en vaccins antipoliomyélitiques inactivés (VPI); il a été recommandé aux pays qui administrent plus de 100 000 doses annuelles de VPI d’utiliser le vaccin fractionné (VPIf) s’ils sont en mesure de former correctement les agents de santé à l’injection intradermique et de les superviser.

Dans la Région de la Méditerranée orientale, les crises et les urgences humanitaires continuent de nuire à la couverture vaccinale. L’importance de la collaboration avec les partenaires dans le domaine de la vaccination a été soulignée, notamment avec les organisations non gouvernementales et autres organismes des Nations Unies, pour pouvoir atteindre les populations en crise. Les efforts visant à améliorer la qualité des données dans la Région se poursuivent. Les nouvelles introductions de vaccins se sont révélées difficiles dans les pays à revenu intermédiaire (PRI), même si des progrès ont été réalisés avec l’appui de la stratégie de l’OMS pour les PRI.

La Région européenne jouit d’un appui politique de haut niveau pour les programmes de vaccination. L’augmentation des cas de rougeole au printemps 2017 génère cependant une forte inquiétude, et l’importance d’agir rapidement au plus haut niveau politique a été soulignée. Les données plus nombreuses dont on dispose aujourd’hui montrent que les PRI accusent un certain retard dans la gestion des programmes de vaccination et l’introduction de nouveaux vaccins. Des activités sont actuellement menées pour dissiper les inquiétudes concernant la sécurité de la vaccination, renforcer les connaissances des prestataires de services, mettre en œuvre des systèmes de pharmacovigilance et soutenir la demande de vaccination et son acceptation.

Dans la Région de l’Asie du Sud-Est, les programmes d’élimination de la rougeole et de lutte contre la rubéole/le syndrome de rubéole congénitale sont désormais emblématiques. L’Inde et l’Indonésie lancent actuellement des campagnes de vaccination à grande échelle avec le vaccin antirougeoleux et antirubéoleux, ciblant plus de 450 millions d’enfants au cours des 18 prochains mois. Des initiatives ont été déployées pour améliorer la couverture par le DTC3 et atteindre les populations non vaccinées dans tous les pays prioritaires. Elles sont axées



of resources, revitalization of multisectoral coordination, better programme management and enhanced monitoring. Fractional IPV is being administered in India and Sri Lanka, and being introduced in Bangladesh and Nepal. To mitigate risks to the immunization programmes associated with the “polio transition”, planning has been initiated in 5 priority countries with involvement of the Ministry of Health (MoH) and identification of alternative funding sources.

In the Western Pacific Region good progress in achieving and maintaining high vaccination coverage was noted, despite coverage disparities. Work is ongoing in relation to measles elimination and a consultation is being convened to discuss a new measles and rubella elimination work plan. Hepatitis B control is well on track, with evidence suggesting overall hepatitis B prevalence among young children to be <1% in 2017. Concerns were raised regarding the sustainability of immunization programmes, particularly for countries transitioning from GAVI support. Support from WHO and partners is critical and strategies for sustaining financial sustainability for countries will be discussed at the next RTAG meeting.

SAGE applauded the work on missed opportunities for vaccination, though stressed that additional efforts were needed, in particular in neglected and difficult-to-access groups.

SAGE encouraged the rapid finalization of tools and guidance under development on vaccination in humanitarian emergencies.

SAGE stressed the need for action plans for “polio transition” in order to reach the GVAP goals.

SAGE expressed its deep concern regarding the uncertainty of global health funding, in view of the needs in countries transitioning out of support from GAVI, the Global Fund and other such global resources.

### Report from GAVI, the Vaccine Alliance

In December 2016, the GAVI Board approved a set of principles to strengthen the emergency vaccine stockpiles across 3 areas: strategic design, effective implementation, and accountability. The Board also approved a funding increment up to US\$ 150 million to the existing yellow fever vaccine support over the period 2017–2020, US\$ 25 million for vaccines and procurement of cold chain equipment in Syria, and support for human papillomavirus (HPV) vaccine introduction. Based on the SAGE recommendations, countries can now apply directly for a national roll out, with an option of phased introduction.

To align with the Global Polio Eradication Initiative, the Board has requested an interim review of GAVI's IPV support policy post-2018 with a Board decision expected later in 2017.

sur le renforcement des systèmes de vaccination, la mobilisation des ressources, la relance de la coordination multisectorielle, une meilleure gestion des programmes et une surveillance accrue. Le VPI fractionné est actuellement administré en Inde et à Sri Lanka et il est en voie d'introduction au Bangladesh et au Népal. Pour atténuer les risques associés à la «transition poliomyélite» pesant sur les programmes de vaccination, des activités de planification ont démarré dans 5 pays prioritaires, avec le concours du ministère de la santé et l'identification d'autres sources de financement.

Dans la Région du Pacifique occidental, de nets progrès ont été accomplis vers la réalisation et le maintien d'une couverture vaccinale élevée, malgré certaines disparités. Les activités liées à l'élimination de la rougeole se poursuivent et une consultation a été convoquée pour discuter d'un nouveau plan d'élimination de la rougeole et de la rubéole. La lutte contre l'hépatite B est en bonne voie; les données indiquent que la prévalence globale de l'hépatite B chez le jeune enfant est inférieure à 1% en 2017. Des préoccupations concernant la pérennité des programmes de vaccination ont été exprimées, en particulier pour les pays qui ne bénéficieront plus du soutien de l'Alliance GAVI. L'appui de l'OMS et des partenaires est essentiel et les stratégies visant à maintenir une pérennité financière en faveur de ces pays seront discutées lors de la prochaine réunion du groupe consultatif technique régional.

Le SAGE a salué les activités liées aux occasions manquées de vaccination, tout en soulignant que des efforts supplémentaires seront nécessaires, en particulier en direction des groupes négligés et difficiles à atteindre.

Le SAGE a encouragé la finalisation rapide des outils et des orientations en préparation relatifs à la vaccination en situation d'urgence humanitaire.

Le SAGE a souligné la nécessité d'élaborer des plans d'action pour la «transition poliomyélite» afin de réaliser les objectifs du GVAP.

Le SAGE a exprimé une profonde préoccupation concernant l'incertitude des financements pour la santé dans le monde au regard des besoins des pays qui ne bénéficieront plus du soutien de l'Alliance GAVI, du Fonds mondial et d'autres ressources mondiales de même type.

### Rapport de l'Alliance GAVI

En décembre 2016, le Conseil d'administration de l'Alliance GAVI a fixé un ensemble de principes pour renforcer les stocks de vaccins d'urgence qui s'applique à 3 domaines: plan stratégique, mise en œuvre efficace et responsabilisation. Le Conseil a également approuvé une augmentation du financement à hauteur de US\$ 150 millions qui s'ajoute au financement pour la vaccination contre la fièvre jaune sur la période 2017-2020, un financement de US\$ 25 millions pour les vaccins et l'achat de matériel pour la chaîne du froid en Syrie, et un soutien pour l'introduction du vaccin contre le papillomavirus humain (PVH). Selon les recommandations du SAGE, les pays peuvent désormais déposer une demande directement pour un déploiement national, avec la possibilité d'opter pour une introduction par étapes.

Pour s'aligner sur l'Initiative mondiale pour l'éradication de la poliomyélite, le Conseil a demandé un examen intérimaire de la politique de financement du VPI par l'Alliance GAVI après 2018; une décision du Conseil à ce sujet est prévue dans le courant de l'année 2017.

In 2018, the GAVI Board will take strategic decisions on future funding for new vaccines and vaccination approaches and will rely on guidance from SAGE on potential vaccine candidates for the GAVI future Vaccine Investment Strategy.

Vaccine hesitancy and the need to mitigate the risks and impact of anti-vaccination messages to the public were highlighted. Other programme updates include the ongoing engagement with India and Nigeria to accelerate new vaccine introductions, improve vaccination coverage and equity, and cold chain equipment optimization. Through the INFUSE project (Innovation for Uptake, Scale and Equity), GAVI issues an annual call for innovation to find the best ways to improve vaccine delivery systems in developing countries.

GAVI has launched the Leadership, Management and Coordination approach to strengthen the management capacity of national immunization teams and the functionality of the Inter-agency Coordinating Committees at country level.

### **Report from the Global Advisory Committee on Vaccine Safety (GACVS)**

GACVS met in December 2016<sup>4</sup> and examined new safety data on: pandemic influenza (pH1N1 2009) vaccines; conjugate typhoid vaccines; and use of fractional dose yellow fever (fYF) vaccine during a mass vaccination campaign in the Democratic Republic of the Congo. GACVS also discussed recommendations from a review of the committee's first 15 years and expansion of the Vaccine Safety Net.<sup>5</sup>

For pH1N1 2009 vaccines, new data found no new safety issues beyond those already known for AS03 adjuvanted Pandemrix. SAGE noted that these new data do not change the previous information about pH1N1 2009 vaccines, and that several hypotheses regarding the pathophysiological mechanism triggering narcolepsy with Pandemrix were supported with limited evidence. SAGE highlighted the importance of best practices in effective safety monitoring for the introduction of typhoid conjugate vaccines and fYF vaccines in new settings. GACVS expects that additional safety data on these issues will be forthcoming.

SAGE welcomed the revitalized Vaccine Safety Net, and encouraged member sites to increase their efforts to share accurate information on vaccines through this system.

En 2018, le Conseil d'administration de l'Alliance GAVI prendra des décisions stratégiques sur le financement futur de nouveaux vaccins et approches de vaccination, et s'appuiera sur les orientations du SAGE concernant les vaccins candidats potentiels pour définir la future stratégie d'investissement de l'Alliance en faveur de la vaccination.

L'hésitation face à la vaccination et la nécessité d'atténuer les risques et l'impact des messages antivaccination adressés au public ont été soulignées. Les autres nouvelles concernant les programmes évoquaient la poursuite de l'engagement avec l'Inde et le Nigéria pour accélérer l'introduction de nouveaux vaccins, l'amélioration de la couverture vaccinale et de l'équité, et l'optimisation de l'équipement de la chaîne du froid. À travers le projet INFUSE (Innovations en faveur de l'utilisation, de l'expansion et de l'équité de la vaccination), l'Alliance GAVI lance un appel annuel à candidatures pour l'innovation afin de trouver les meilleures solutions pour améliorer les systèmes de distribution des vaccins dans les pays en développement.

L'Alliance GAVI a lancé l'approche Leadership, gestion et coordination pour renforcer les capacités de gestion des équipes nationales de vaccination et la fonction des comités de coordination interinstitutions au niveau national.

### **Rapport du Comité consultatif mondial pour la sécurité des vaccins (GACVS)**

Le GACVS s'est réuni en décembre 2016<sup>4</sup> et a examiné de nouvelles données d'innocuité relatives aux vaccins contre la grippe pandémique (H1N1p 2009), aux vaccins conjugués contre la fièvre typhoïde et à l'utilisation de doses fractionnées de vaccin anti-typhoïde lors de la campagne de vaccination de masse menée en République démocratique du Congo. Le GACVS a également discuté des recommandations issues de l'examen des 15 premières années de fonctionnement et de l'extension du Réseau pour la sécurité des vaccins mis en place par ses soins.<sup>5</sup>

Concernant les vaccins anti-H1N1p 2009, les nouvelles données n'ont mis en évidence aucun nouveau problème de sécurité en dehors de ceux déjà connus pour le Pandemrix adjuvanté avec de l'AS03. Le SAGE a fait remarquer que ces nouvelles données ne changeaient pas les précédentes informations relatives aux vaccins anti-H1N1p 2009, et que plusieurs hypothèses sur le mécanisme physiopathologique déclenchant la narcolepsie avec le Pandemrix reposaient sur des données limitées. Le SAGE a souligné l'importance d'appliquer les meilleures pratiques pour une surveillance efficace de la sécurité des vaccins conjugués contre la fièvre typhoïde et des doses fractionnées de vaccin anti-typhoïde lors de leur introduction dans de nouveaux contextes. Le GACVS prévoit que des données d'innocuité supplémentaires seront disponibles prochainement dans ce domaine.

Le SAGE a salué le Réseau pour la sécurité des vaccins, revitalisé et encouragé les sites membres à accroître leurs efforts pour partager des informations précises sur les vaccins au travers de ce système.

<sup>4</sup> See No. 28/29, 2016, pp. 341–348.

<sup>5</sup> See No. 2, 2017, pp.13–20.

<sup>4</sup> Voir N° 28/29, 2016, pp. 341-348.

<sup>5</sup> Voir N° 2, 2017, pp.13-20.

## Report from the Expert Committee on Biological Standardization (ECBS)

At its October 2016 meeting, ECBS established 3 written standards of particular relevance to SAGE:

- (i) A guideline on labelling information for inactivated influenza vaccines (IIV) for use in pregnant women provides a clear statement that, on the basis of current evidence, the use of IIV in pregnant women is not contraindicated. The guideline is intended to facilitate maternal immunization programmes by raising awareness of the convergence of regulatory positions despite differing approaches to labelling and regulatory language regarding the use of IIV in pregnant women worldwide.<sup>6</sup>
- (ii) A guideline on regulatory approaches for marketing authorization of pandemic influenza vaccines and on arrangements for lot release of these vaccines in public health emergency conditions, targeting in particular non-vaccine-producing countries; it emphasizes the need for, and gives practical guidance on, preparedness by regulatory authorities.<sup>7</sup>
- (iii) A guideline on clinical evaluation of vaccines providing a revision of the WHO specifications for the clinical evaluation of all vaccine types.<sup>8</sup> A supplementary document on regulatory considerations for human challenge trials for vaccine development has also been produced.

ECBS established 4 new reference materials (for Zika, Ebola, Dengue and hepatitis B) relevant to vaccine-preventable disease surveillance. These reagents serve as internationally validated calibrants for diagnostic tests and assays for clinical trials.

## Report of the Immunization Practices Advisory Committee (IPAC)

IPAC met in February 2017<sup>9</sup> and provided advice on:

- (i) The WHO Data Reference Manual, and guidance to address the increasing demands for data and monitoring imposed by more complex programmes; this highlights the need to prioritize and streamline indicators, improve data quality, consider new technologies, and promote local usage for improving services

<sup>6</sup> Labelling information of inactivated influenza vaccines for use in pregnant women: Addendum to Annex 3 of WHO Technical Report Series, No. 927. Available [http://www.who.int/entity/biologicals/expert\\_committee/Label\\_after\\_ECBS\\_HK\\_28\\_Oct\\_2016.clean.pdf?ua=1](http://www.who.int/entity/biologicals/expert_committee/Label_after_ECBS_HK_28_Oct_2016.clean.pdf?ua=1), accessed April 2017.

<sup>7</sup> Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries. Available at [http://www.who.int/entity/biologicals/expert\\_committee/PIP\\_Non-producer\\_guide\\_BS\\_final-working\\_version-19102016-clean.pdf?ua=1](http://www.who.int/entity/biologicals/expert_committee/PIP_Non-producer_guide_BS_final-working_version-19102016-clean.pdf?ua=1), accessed April 2017.

<sup>8</sup> Guidelines on clinical evaluation of vaccines; regulatory expectations. Available [http://www.who.int/entity/biologicals/expert\\_committee/Clinical\\_changes\\_IK\\_final.pdf?ua=1](http://www.who.int/entity/biologicals/expert_committee/Clinical_changes_IK_final.pdf?ua=1), accessed April 2017.

<sup>9</sup> IPAC February 2017 meeting report: [http://www.who.int/immunization/programmes\\_systems/policies\\_strategies/IPAC\\_Report\\_2017-02.pdf?ua=1](http://www.who.int/immunization/programmes_systems/policies_strategies/IPAC_Report_2017-02.pdf?ua=1), accessed April 2017

## Rapport du Comité d'experts de la standardisation biologique

Lors de sa réunion en octobre 2016, le Comité d'experts de la standardisation biologique a établi 3 normes écrites particulièrement pertinentes pour le SAGE:

- i) des lignes directrices sur les informations d'étiquetage des vaccins antigrippaux inactivés relatives à l'utilisation du vaccin chez la femme enceinte qui indiquent clairement que, sur la base des données actuelles, l'administration du vaccin à la femme enceinte n'est pas contre indiquée. Ces lignes directrices visent à faciliter les programmes de vaccination maternelle en sensibilisant au fait que les avis réglementaires convergent malgré les différentes approches adoptées pour l'étiquetage et le langage réglementaire concernant l'utilisation de ces vaccins chez la femme enceinte dans le monde;<sup>6</sup>
- ii) des lignes directrices sur les approches réglementaires pour l'autorisation de mise sur le marché des vaccins contre la grippe pandémique et sur les dispositions concernant la libération de lots de vaccins antigrippaux lors d'une urgence de santé publique, ciblant en particulier les pays non producteurs de vaccins; elles soulignent la nécessité d'une préparation des autorités de réglementation et fournit des conseils pratiques à cet égard;<sup>7</sup>
- iii) des lignes directrices sur l'évaluation clinique des vaccins qui incluent une révision des spécifications de l'OMS pour l'évaluation clinique de tous les types de vaccins.<sup>8</sup> Un document supplémentaire présentant des considérations réglementaires pour les épreuves infectantes chez l'homme dans le cadre du développement des vaccins a également été produit.

Le Comité d'experts de la standardisation biologique a établi 4 nouveaux produits de référence (pour Zika, Ebola, la dengue et l'hépatite B) pour la surveillance des maladies à prévention vaccinale. Ces réactifs servent d'étalons validés au plan international pour les tests diagnostiques et les dosages dans le cadre d'essais cliniques.

## Rapport du comité consultatif sur les pratiques vaccinales (IPAC)

L'IPAC s'est réuni en février 2017<sup>9</sup> et a donné un avis sur les points suivants:

- i) le manuel de référence de l'OMS relatif aux données et des orientations pour répondre aux demandes croissantes de données et de surveillance imposées par des programmes plus complexes; le comité souligne la nécessité d'établir des priorités et de rationaliser les indicateurs, d'améliorer la qualité des données, d'envisager de nouvelles technologies et de promouvoir leur usage au niveau local pour améliorer les services;

<sup>6</sup> Informations d'étiquetage des vaccins antigrippaux inactivés concernant l'utilisation du produit chez la femme enceinte: OMS, Série de rapports techniques, N° 927, addendum à l'annexe 3. Disponible à l'adresse [http://www.who.int/entity/biologicals/expert\\_committee/Label\\_after\\_ECBS\\_HK\\_28\\_Oct\\_2016.clean.pdf?ua=1](http://www.who.int/entity/biologicals/expert_committee/Label_after_ECBS_HK_28_Oct_2016.clean.pdf?ua=1), consulté en avril 2017.

<sup>7</sup> Lignes directrices relatives à la préparation réglementaire pour l'octroi d'une autorisation de mise sur le marché de vaccins contre la grippe pandémique humaine dans les pays non producteurs de vaccins. Disponible à l'adresse [http://www.who.int/entity/biologicals/expert\\_committee/PIP\\_Non-producer\\_guide\\_BS\\_final-working\\_version-19102016-clean.pdf?ua=1](http://www.who.int/entity/biologicals/expert_committee/PIP_Non-producer_guide_BS_final-working_version-19102016-clean.pdf?ua=1), consulté en avril 2017.

<sup>8</sup> Lignes directrices relatives à l'évaluation clinique des vaccins: exigences réglementaires. Disponible à l'adresse [http://www.who.int/entity/biologicals/expert\\_committee/Clinical\\_changes\\_IK\\_final.pdf?ua=1](http://www.who.int/entity/biologicals/expert_committee/Clinical_changes_IK_final.pdf?ua=1), consulté en avril 2017.

<sup>9</sup> Rapport de l'IPAC à l'issue de la réunion de février 2017, [http://www.who.int/immunization/programmes\\_systems/policies\\_strategies/IPAC\\_Report\\_2017-02.pdf?ua=1](http://www.who.int/immunization/programmes_systems/policies_strategies/IPAC_Report_2017-02.pdf?ua=1), consulté en avril 2017.



- (ii) WHO's operational guidance on vaccination in the second year of life; anchored by the second dose of measles vaccine, the guidance considers other vaccines, catch-up vaccination, integration with other preventive health care, and aims for a life-course approach.
- (iii) The Controlled Temperature Chain (CTC) roadmap for the next vaccines to prioritize for on-label single excursions beyond the cold chain; IPAC endorsed the prioritization of HPV, cholera, tetanus and birth dose hepatitis B vaccines.
- (iv) The Delivery Technology Working Group mapping of innovations in vaccine delivery and product presentation; this includes the final target product profile for measles and rubella-containing micro-array patches.

SAGE was also updated on new terms of reference for IPAC.<sup>2</sup>

SAGE highlighted the need to address service delivery in marginalized urban populations, the need for increased clarity and guidance on integrated service delivery, the potential to consider the environmental impact of immunization programmes, and the need to continue to identify priorities for service innovation. SAGE recommended that IPAC should continue to prioritize work on data improvement, addressing missed opportunities, total system effectiveness, new guidance on integration, CTC, and delivery technologies.

### Report from the Implementation Research Advisory Committee (IVIR-AC)

In February 2017,<sup>10</sup> IVIR-AC discussed: a model to estimate measles mortality; a protocol to compare models aiming at estimating hepatitis B vaccine impact and to compare the methodological approaches used to estimate hepatitis B surface antigen (HBsAg) prevalence in children; a model to estimate impact and economic benefits of typhoid vaccine; a reporting guide for improved and standardized reporting of data from observational studies of influenza vaccine effectiveness; tools to operationalize the WHO recommendations on the licensed dengue vaccine including seroprevalence survey guidelines, modelling using age-specific incidence data, transmission intensity map tools, and ways to maximize the efficiency of implementation of seroprevalence surveys.

Following a review of almost 50 potential research questions, SAGE was presented with 2 proposed questions and outlines of study protocols to further evaluate the hypotheses that have been proposed regarding the nonspecific effects (NSE) of vaccines. The protocols focus on issues that expert consultations and IVIR-AC deliberations identified as most pressing and policy relevant with respect to timing and sequencing of infant

- ii) les orientations opérationnelles de l'OMS sur la vaccination pendant la deuxième année de vie; partant de la seconde dose de vaccin antirougeoleux, ces orientations envisagent d'autres vaccins, la vaccination de rattrapage, l'intégration avec d'autres soins de santé préventifs, et elles visent une approche de vaccination tout au long de la vie;
- iii) la feuille de route de la chaîne à température contrôlée (CTC) concernant les prochains vaccins prioritaires pour une indication d'utilisation hors de la chaîne du froid; l'IPAC a approuvé la priorité donnée aux vaccins contre le PVH, le choléra, le tétanos et à la dose de vaccin contre l'hépatite B administrée à la naissance;
- iv) la cartographie des innovations en matière d'administration de vaccins et de présentation des produits, élaborée par le groupe de travail sur les technologies d'administration; elle inclut le profil de produit cible des timbres à micro-aiguilles contenant le vaccin contre la rougeole et la rubéole.

Le nouveau mandat de l'IPAC a également été présenté au SAGE.<sup>2</sup>

Le SAGE a souligné la nécessité de résoudre les problèmes liés à l'offre de services aux populations urbaines marginalisées, le besoin de clarté et d'orientations supplémentaires en matière d'offre de services intégrés, les possibilités de prendre en compte l'impact environnemental des programmes de vaccination, et la nécessité de continuer à définir des priorités en matière d'innovation dans le domaine des services. Le SAGE a recommandé à l'IPAC de continuer de donner la priorité aux travaux sur l'amélioration des données, les solutions pour éviter les occasions manquées de vaccination, l'efficacité des systèmes, les nouvelles orientations sur l'intégration, la CTC et les technologies d'administration.

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

En février 2017,<sup>10</sup> l'IVIR-AC s'est réuni pour discuter des points suivants: un modèle pour estimer la mortalité due à la rougeole; un protocole pour comparer les modèles visant à estimer l'impact du vaccin contre l'hépatite B et les méthodes employées pour estimer la prévalence de l'antigène de surface du virus de l'hépatite B (AgHBs) chez l'enfant; un modèle pour estimer l'impact et les avantages économiques du vaccin antityphoïdique; un guide visant à améliorer et à standardiser la présentation des données issues des études observationnelles sur l'efficacité des vaccins antigrippaux; des outils de mise en pratique des recommandations de l'OMS sur le vaccin homologué contre la dengue, notamment des lignes directrices pour les enquêtes de séroprévalence, une modélisation utilisant des données d'incidence par âge, des cartes d'intensité de la transmission et des moyens pour maximiser l'efficacité de la mise en œuvre des enquêtes de séroprévalence.

Après avoir examiné près de 50 questions potentielles de recherche, 2 questions et descriptifs de protocoles d'étude visant à évaluer plus avant les hypothèses concernant les effets non spécifiques des vaccins ont été proposés au SAGE. Ces protocoles portaient sur des questions que les consultations d'experts et les délibérations de l'IVIR-AC ont jugé particulièrement pressantes et pertinentes au niveau politique par rapport au calendrier et à la séquence des vaccins administrés aux nour-

<sup>10</sup> See No 15, 2017, pp. 181–188.

<sup>10</sup> Voir N° 15. 2017, pp. 181-188.

vaccines: (i) an individually randomized placebo-controlled trial of early versus later vaccination with Bacille Calmette-Guérin (BCG) to estimate its impact on all-cause mortality in infancy and; (ii) a 2x2 factorial double blind randomized placebo-controlled trial to assess the impact of an additional early dose of measles-containing vaccine at 12–16 weeks of age on all-cause mortality.<sup>2</sup> The agreed next steps include seeking inputs from other experts on the protocols and their formal publication by the end of 2017.

SAGE noted the careful methodological effort to review the potential questions, applying the principles outlined in its previous recommendation.<sup>11</sup>

SAGE reiterated the value of definitive evidence to confirm or refute the existence and magnitude of the impact of vaccine NSE on susceptibility to severe childhood infection, particularly attributable mortality, and the potential implications for national vaccination schedules.

SAGE encouraged WHO to complete the public consultation and the publication and dissemination of the protocols.

SAGE highlighted the need to implement these studies quickly as a step to obtaining robust evidence on the potential NSE of vaccines but also recognized the high cost involved, given the very large numbers needed.

### Polio eradication

SAGE acknowledged the progress towards eliminating wild poliovirus (WPV) transmission. There were 8 reported cases of poliomyelitis due to WPV during the last 6 months (as of 18 April 2017) in Afghanistan and Pakistan, compared with 32 cases during the comparable period one year ago. The overall situation in Afghanistan and Pakistan has significantly improved in common corridors of transmission (i.e. Nangarhar/Kunar – Khyber/Peshawar, Paktika – Federally Administered Tribal Areas (FATA)/Khyber Pakhtunkhwa (KP), Kandahar/Helmand – Balochistan). A recent serosurvey in Pakistan in children aged 6–11 months indicated >95% seroprotection in all districts, except for Pishin and Quetta. The programme is addressing the remaining risks (e.g. potential outbreak outside high-risk areas and among high-risk mobile populations). Nigeria has not reported any WPV case since August 2016. However, large areas in Borno remain inaccessible and up to 500 000 children aged <5 years remain unreached by vaccination programmes.

After the synchronized global switch from trivalent to bivalent oral polio vaccine (bOPV) in April 2016, Sabin type 2 virus is no longer detected from the environmental and acute flaccid paralysis (AFP) samples outside countries using monovalent type 2 OPV (mOPV2). However, Nigeria detected several type 2 vaccine-derived polioviruses (VDPV2) from the environment in Bauchi, Gombe and Sokoto in 2017. SAGE expressed

rissons: i) un essai contrôlé par placebo, individuellement randomisé, visant à évaluer la vaccination précoce versus tardive par le Bacille de Calmette-Guérin (BCG) afin d'estimer son impact sur la mortalité infantile toutes causes confondues; ii) un essai en plan factoriel 2x2, contrôlé par placebo, randomisé, à double insu visant à évaluer l'impact sur la mortalité toutes causes confondues d'une dose supplémentaire précoce de vaccin à valence rougeole administré entre 12 et 16 semaines de vie.<sup>2</sup> Les prochaines étapes qui ont été convenues consistent à recueillir les contributions d'autres experts concernant ces protocoles et à les publier officiellement d'ici la fin 2017.

Le SAGE a pris note du travail méthodologique rigoureux qui a été fourni pour examiner les questions potentielles, respectant les principes énoncés dans sa précédente recommandation.<sup>11</sup>

Le SAGE a réitéré la valeur des données probantes pour confirmer ou réfuter l'existence et l'ampleur de l'impact des effets non spécifiques des vaccins sur la sensibilité aux infections graves de l'enfant, en particulier sur la mortalité associée, et les implications potentielles pour les calendriers nationaux de vaccination.

Le SAGE a encouragé l'OMS à porter la consultation publique à son terme et à publier et diffuser les protocoles.

Le SAGE a souligné la nécessité de lancer rapidement ces études qui permettront d'obtenir des données fiables sur les effets non spécifiques potentiels des vaccins, tout en reconnaissant le coût élevé que cela implique en raison de leur ampleur.

### Éradication de la poliomyélite

Le SAGE a salué les progrès accomplis vers l'élimination de la transmission des poliovirus sauvages (PVS). Huit cas de poliomyélite due aux PVS ont été notifiés au cours des 6 derniers mois (données au 18 avril 2017) en Afghanistan et au Pakistan, contre 32 cas notifiés pendant la même période l'année précédente. La situation globale en Afghanistan et au Pakistan s'est nettement améliorée dans les corridors communs de transmission (Nangarhar/Kunar – Khyber/Peshawar, Paktika – zones tribales sous administration fédérale (FATA)/Khyber Pakhtunkhwa (KP), Kandahar/Helmand – Balouchistan). Une récente enquête sérologique menée au Pakistan chez des enfants âgés de 3 à 11 mois a indiqué un taux de séroprotection >95% dans tous les districts, sauf Pishin et Quetta. Le programme s'attache à éliminer les risques restants (par exemple une flambée épidémique potentielle hors des zones à haut risque et parmi les populations mobiles à haut risque). Le Nigéria n'a notifié aucun cas de PVS depuis août 2016. Cependant, de vastes zones dans l'État de Borno demeurent inaccessibles et 500 000 enfants âgés de <5 ans n'ont pas pu être couverts par les programmes de vaccination.

Après la transition mondiale synchronisée du vaccin antipoliomyélique oral trivalent à sa forme bivalente (VPOb) en avril 2016, les virus Sabin de type 2 ne sont plus détectés dans les échantillons environnementaux ni dans les échantillons de patients atteints de paralysie flasque aiguë (PFA) en-dehors des pays qui utilisent le VPO monovalent de type 2 (VPOm2). Cependant, le Nigéria a détecté plusieurs poliovirus dérivés d'une souche vaccinale de type 2 (PVDV2) dans l'environnement à Bauchi, Gombe et Sokoto

<sup>11</sup> See No. 21, 2014, pp. 221–236.

<sup>11</sup> Voir N° 21, 2014, pp. 221-236.

concern over the ongoing circulation of VDPV2 in Nigeria. Given that the risk of a significant outbreak increases with waning immunity levels, SAGE recommended that countries with co-circulation of WPV and cVDPV2 should administer at least 2 doses of mOPV2 before the next bOPV round, to prevent the transmission of circulating vaccine-derived poliovirus (cVDPV) and the risk of outbreaks due to cVDPV2.

In recognition of ongoing global IPV supply constraints, SAGE discussed the evidence on the role of IPV. While IPV may offer primarily a complementary benefit in stopping WPV/cVDPV transmission, the primary vaccine of choice to eliminate WPVs and respond to cVDPVs is OPV (bOPV and mOPV2, depending on the virus type). However, IPV has a significant role in routine immunization by protecting children against poliomyelitis caused by cVDPV2 in countries which no longer use type 2 containing OPV. The use of IPV in routine immunization is especially important as population immunity to type 2 poliovirus will otherwise continue to decrease following the switch from tOPV to bOPV.

In the short-term, given the ongoing global IPV shortage, SAGE recommended that:

1. Regional and national immunization technical advisory groups should recommend 2 fractional IPV doses in national routine immunization schedules, where feasible, provided that countries have access to appropriate IPV presentations (e.g. single-dose or 5-dose vials), the capacity to administer intradermal injections, and a good advocacy and communication plan for parents and health-care providers;
2. Available IPV supply should be prioritized for use in routine immunization (especially in Tier 1 and 2 countries);

SAGE requested that WHO review its tier classification of countries with respect to prioritization of IPV to take into account the size of the population with no IPV protection and the recent VDPV2 events.

SAGE discussed polio immunization policy after global OPV withdrawal. Studies indicated that 2 fractional or 2 full IPV doses (for prime and boost) are required to achieve 90% or more seroconversion (individual protection) to poliovirus types 1, 2 and 3, with the first dose at or after 14 weeks of age and an interval of  $\geq 4$  months between the first and second doses. SAGE also reviewed the risk of reintroduction of polioviruses after global OPV cessation. The modelling and epidemiology suggest that VDPV may emerge 0–4 years after the global cessation of OPV use. The WHO immunodeficiency-associated vaccine-derived poliovirus (iVDPV) registry indicated that iVDPVs could be excreted for  $< 5$  years in middle income countries and for  $\geq 10$  years in high income countries. In addition, the risk of containment failure or deliberate release of poliovirus may continue even after 10 years.

en 2017. Le SAGE a exprimé son inquiétude face à cette circulation persistante des PVDV2 au Nigéria. Sachant que le risque d'une flambée épidémique importante augmente quand les niveaux d'immunité baissent, le SAGE recommande aux pays dans lesquels circulent à la fois les PVS et les PVDVc2 d'administrer au moins 2 doses de VPOM2 avant la prochaine tournée de vaccination par le VPOb, afin de prévenir la transmission des poliovirus circulants dérivés d'une souche vaccinale (PVDVc) et le risque de flambées épidémiques dues aux PVDVc2.

Reconnaissant les difficultés persistantes de l'approvisionnement en vaccins antipoliomyélitiques inactivés (VPI) à l'échelle mondiale, le SAGE a examiné les données disponibles sur le rôle du VPI. Si le VPI peut offrir un avantage complémentaire pour arrêter la transmission des PVS/PVDVc, le vaccin de choix à privilégier pour éliminer les PVS et lutter contre les PVDVc est le VPO (VPOb et VPOM2, selon le type de virus). Néanmoins, le VPI joue un rôle notable dans la vaccination systématique en protégeant les enfants contre la poliomyélite due aux PVDVc2 dans les pays qui n'utilisent plus le VPO2. L'utilisation du VPI pour la vaccination systématique est particulièrement importante car l'immunité de la population contre les poliovirus de type 2 continuera à diminuer après la transition du VPOt au VPOb.

À court terme, face à la pénurie mondiale de VPI, le SAGE recommande les mesures suivantes:

1. les groupes consultatifs techniques nationaux et régionaux sur la vaccination devraient recommander 2 doses fractionnées de VPI dans les calendriers nationaux de vaccination systématique, quand il est possible de le faire, à condition que les pays aient accès à des présentations appropriées de VPI (par exemple en dose unique ou en flacons 5 doses), la capacité de faire des injections intradermiques et un plan efficace de promotion et de communication auprès des parents et des prestataires de soins;
2. les stocks de VPI disponibles devraient être utilisés en priorité pour la vaccination systématique (en particulier dans les pays de niveaux 1 et 2).

Le SAGE a demandé à l'OMS de revoir la classification des niveaux des pays par rapport à la priorité donnée au VPI afin de tenir compte de la taille de la population non protégée par le VPI et des récents événements liés aux PVDV2.

Le SAGE a discuté de la politique de vaccination antipoliomyélitique après le retrait mondial du VPO. Des études montrent que 2 doses fractionnées ou 2 doses complètes de VPI (primovaccination et rappel) sont nécessaires pour obtenir une séroconversion (protection individuelle) de 90% ou plus contre les poliovirus de types 1, 2 et 3, la première dose étant administrée à partir de 14 semaines de vie et l'intervalle entre la première et la seconde dose étant  $\geq 4$  mois. Le SAGE s'est également penché sur le risque de réintroduction des poliovirus après l'abandon du VPO à l'échelle mondiale. Les données de modélisation et d'épidémiologie suggèrent que les PVDV peuvent émerger 0 à 4 ans après l'arrêt de l'utilisation du VPO dans le monde. Le registre OMS des poliovirus dérivés d'une souche vaccinale associés à une immunodéficience (PVDVi) indique que les PVDVi pourraient être excrétés pendant  $< 5$  ans dans les pays à revenu intermédiaire et pendant  $\geq 10$  ans dans les pays à revenu élevé. En outre, le risque d'accident de confinement ou de libération délibérée de poliovirus pourrait persister même après 10 ans.



With the available evidence, SAGE recommended that after global OPV withdrawal:

1. Countries should include at least 2 doses of IPV in their routine immunization schedule, the first at or after 14 weeks (e.g. with the 2nd or 3rd dose of DTP-containing vaccine) and the second dose  $\geq 4$  months after the first dose, administered either as full or fractional doses.
2. Countries without Poliovirus Essential Facilities (PEFs) should maintain IPV in their routine immunization schedule for at least 10 years after global OPV withdrawal, to address: immediate (VDPVs), intermediate (iVDPVs) and longer term (e.g. containment failure) risks of poliovirus reintroduction;
3. Countries with PEFs should continue to use IPV as long as mandated by the Global Action Plan in order to minimize poliovirus facility-associated risk (GAP III).

SAGE noted the progress in the implementation of biocontainment of poliovirus and the development of the post-certification strategy, which aims at defining the essential functions that need to be sustained to maintain a polio-free world post-certification; these include containment, detection and response to outbreak, protection of population (e.g. bOPV withdrawal), management and monitoring of the essential functions.

### Cholera vaccination

Cholera remains endemic in many settings across Africa, Asia and in Haiti. There are 1.3–4 million cases annually worldwide, with 21 000–143 000 deaths. With increased urbanization and climate change, cholera incidence is expected to increase over the next decade.

Although access to safe water, hygiene promotion and sanitation are the mainstay for cholera control, there is mounting evidence over the last 3 years that high coverage with oral cholera vaccine (OCV) results in significant reduction of cholera transmission in various settings.

Three killed whole-cell OCVs are currently pre-qualified by WHO – Dukoral®, Shanchol™ and Euvichol®. All 3 vaccines have good safety profiles and  $>60\%$  effectiveness against disease for at least 3 years after 2 doses. A single dose gives protection of 63% against severe disease over a 6-month period. Protection is lower among children aged  $<5$  years.

In 2013, WHO formally established an OCV stockpile which currently comprises Shanchol™ and Euvichol®. Production of Dukoral® is limited and it is primarily marketed for travellers. As of April 2017, almost 8 million doses of OCV have been provided from the stockpile for more than 40 mass campaigns in 14 countries in various settings (e.g. for outbreaks, highly endemic areas, or in humanitarian crises).

The SAGE Cholera Working Group presented its review of data available since publication of the 2010 WHO

Au vu des données disponibles, après le retrait du VPO à l'échelle mondiale, le SAGE formule les recommandations suivantes:

1. les pays devraient inscrire au moins 2 doses de VPI dans leur calendrier de vaccination systématique, la première à administrer à partir de 14 semaines de vie (par exemple avec la 2<sup>e</sup> ou la 3<sup>e</sup> dose de vaccin DTC), la seconde dose  $\geq 4$  mois après la première dose, qu'il s'agisse de doses entières ou fractionnées;
2. les pays ne disposant pas d'établissements autorisés à détenir des stocks essentiels de poliovirus devraient maintenir le VPI dans leur calendrier de vaccination systématique pendant au moins 10 ans après le retrait mondial du VPO afin d'éviter les risques immédiats (PVDV), intermédiaires (PVDVi) et à long terme (accident de confinement) de réintroduction des poliovirus;
3. les pays disposant d'établissements autorisés à détenir des stocks essentiels de poliovirus devraient continuer à utiliser le VPI aussi longtemps que le préconise le Plan d'action mondial afin de minimiser les risques associés aux établissements détenant des poliovirus (GAPIII).

Le SAGE a constaté les progrès réalisés dans la mise en œuvre du confinement biologique des poliovirus et dans l'élaboration de la stratégie postcertification visant à définir les fonctions essentielles à maintenir pour conserver un monde sans poliomyélite après la certification; ces fonctions couvrent le confinement, la détection et la riposte aux flambées épidémiques, la protection de la population (par exemple le retrait du VPOb), la gestion et la surveillance des fonctions essentielles.

### Vaccination contre le choléra

Le choléra demeure endémique dans de nombreux endroits en Afrique, en Asie et en Haïti. On dénombre 1,3 à 4 millions de cas chaque année dans le monde, et 21 000 à 143 000 décès. Avec l'urbanisation croissante et le changement climatique, on s'attend à une augmentation de l'incidence du choléra au cours de la décennie à venir.

Même si l'accès à l'eau potable, la promotion de l'hygiène et l'assainissement constituent les piliers de la lutte contre le choléra, les données accumulées au cours des 3 dernières années montrent que la couverture par le vaccin anticholérique oral (VCO) se traduit par une réduction notable de la transmission du choléra dans divers contextes.

Trois VCO à germes entiers tués sont actuellement préqualifiés par l'OMS – Dukoral®, Shanchol™ et Euvichol®. Les 3 vaccins présentent un profil de sécurité satisfaisant et une efficacité  $>60\%$  contre la maladie pendant au moins 3 ans après 2 doses de vaccin. Une dose unique protège à hauteur de 63% contre la forme sévère de la maladie pendant 6 mois. La protection est moindre chez les enfants âgés  $<5$  ans.

En 2013, l'OMS a officiellement constitué un stock de VCO actuellement composé de Shanchol™ et d'Euvichol®. La production de Dukoral® est limitée et essentiellement commercialisée pour les voyageurs. En avril 2017, près de 8 millions de doses de VCO provenant de ce stock ont été distribuées pour mener plus de 40 campagnes de vaccination de masse dans 14 pays faisant face à différentes situations (par exemple flambées épidémiques, zones de forte endémie ou crises humanitaires).

Le groupe de travail sur le choléra du SAGE a présenté une revue des données disponibles depuis la publication de la note

position paper on OCV and proposed updated recommendations. The report included the results of a systematic review of the effectiveness and duration of protection afforded by OCVs and their safety profile, with particular focus on pregnant women.

SAGE recommended the following:

### General recommendations

1. Given the current availability of pre-qualified killed whole-cell OCVs and data on their safety, efficacy, field effectiveness, feasibility, impact and acceptability in cholera-affected populations, these vaccines should be used in areas with endemic cholera, in humanitarian crises with high risk of cholera and during cholera outbreaks, in conjunction with other cholera prevention and control strategies.
2. Appropriate case management, Water, Sanitation, and Hygiene (WaSH) interventions, surveillance and community mobilization remain cornerstones of cholera control. Vaccination is synergistic with these activities and should be implemented in relevant settings as part of comprehensive control strategies or while they are developed.
3. Mass vaccination campaigns are usually the most practical option for delivering OCV. Schools, religious institutions and other community settings can be appropriate venues for vaccination campaigns using fixed sites. Outreach activities can also be organized. Incorporating cholera vaccination with other vaccination activities can be an alternative or complementary strategy to mass campaigns.
4. Equitable access to the OCV stockpile should be ensured for populations exposed to the risk of cholera. In all settings requests should follow the established mechanisms of stockpile management.<sup>12</sup>
5. In all settings, the following criteria should be considered to guide the decision to vaccinate:
  - The risk of cholera among targeted populations and the risk of spatial extension.
  - The programmatic capacity to cover as many persons as possible, eligible to receive the vaccine and living in the targeted area (e.g. those aged  $\geq 1$  or 2 years, depending on the vaccine used).
  - Implementation of previous OCV campaigns. Cholera vaccination should generally not be conducted if a campaign has been conducted in the previous 3 years in the same population (unless justified by inadequate vaccine coverage during the previous campaign and/or substantial population movements).
6. Countries and agencies accessing the OCV stockpile should systematically implement monitoring and evaluation and provide accompanying data to the WHO Global Task Force on Cholera Control. Guidelines have been developed for this purpose.<sup>12</sup>

<sup>12</sup> Oral cholera vaccine stockpile for cholera emergency response. Available at [http://www.who.int/cholera/vaccines/Briefing\\_OCV\\_stockpile.pdf?ua=1&ua=1](http://www.who.int/cholera/vaccines/Briefing_OCV_stockpile.pdf?ua=1&ua=1), accessed April 2017.

de synthèse 2010 de l’OMS sur les VCO, et proposé des recommandations actualisées. Ce rapport présentait les résultats d’une revue systématique de l’efficacité et de la durée de la protection conférée par les VCO et leur profil d’innocuité, particulièrement pour les femmes enceintes.

Le SAGE a émis les recommandations suivantes:

### Recommandations générales

1. Étant donné la disponibilité actuelle des VCO à germes entiers tués préqualifiés et les données d’innocuité, d’efficacité, d’efficacité réelle sur le terrain, de faisabilité, d’impact et d’acceptabilité au sein des populations touchées par le choléra, ces vaccins devraient être utilisés dans les zones où le choléra est endémique, lors de crises humanitaires associées à un risque élevé de choléra et pendant les flambées épidémiques de choléra, parallèlement aux autres stratégies de prévention et de lutte contre le choléra.
2. La prise en charge appropriée des patients, les interventions en faveur de l’eau, l’assainissement et l’hygiène (groupe WaSH), la surveillance et la mobilisation des communautés demeurent les pierres angulaires de la lutte contre le choléra. La vaccination crée une synergie avec ces activités et devrait être mise en place là où elle est utile, dans le cadre de stratégies globales de lutte contre la maladie ou pendant leur élaboration.
3. Les campagnes de vaccination de masse constituent généralement le moyen le plus pratique d’administrer le VCO. Les écoles, les institutions religieuses et d’autres structures communautaires peuvent convenir pour les campagnes de vaccination qui utilisent des structures fixes. Il est également possible d’organiser des activités de vaccination de proximité. En remplacement ou en complément des campagnes de masse, on peut envisager d’incorporer la vaccination anticholérique dans d’autres activités de vaccination.
4. Il convient de garantir un accès équitable aux stocks de VCO pour les populations exposées au risque de choléra. Quel que soit le contexte, les demandes doivent suivre les mécanismes établis de gestion des stocks.<sup>12</sup>
5. Dans tous les cas, la décision de vacciner devrait reposer sur les critères suivants:
  - le risque de choléra parmi les populations ciblées et le risque de propagation spatiale;
  - les capacités programmatiques pour couvrir autant de personnes que possible, répondant aux critères pour recevoir le vaccin et vivant dans la zone ciblée (par exemple, la population âgée de  $\geq 1$  ou 2 ans, selon le vaccin utilisé);
  - la mise en œuvre de précédentes campagnes de vaccination par le VCO. De manière générale, la vaccination anticholérique ne doit pas être proposée si une campagne a été menée au cours des 3 précédentes années dans la même population (sauf si la couverture vaccinale de la précédente campagne était insuffisante et/ou en cas de mouvements notables de populations).
6. Les pays et les organismes qui ont accès aux stocks de VCO devraient systématiquement effectuer une surveillance et une évaluation, et fournir les données correspondantes au groupe spécial mondial de lutte contre le choléra de l’OMS. Des lignes directrices ont été élaborées à cet effet.<sup>12</sup>

<sup>12</sup> Oral cholera vaccine stockpile for cholera emergency response. Disponible à l’adresse [http://www.who.int/cholera/vaccines/Briefing\\_OCV\\_stockpile.pdf?ua=1&ua=1](http://www.who.int/cholera/vaccines/Briefing_OCV_stockpile.pdf?ua=1&ua=1), consulté en avril 2017.

7. Pregnant women should be included in OCV campaigns. Evidence indicates high potential benefit and minimal risks.
8. Vaccination is not generally recommended for long or short term travellers to cholera-affected countries because most are at very low risk of cholera. However, OCV should be considered for travellers whose activities may involve exposure to cholera, including humanitarian, emergency, or relief workers who are likely to be directly exposed to cholera patients or to contaminated food or water, particularly those staying in areas with poor access to health-care facilities.

### Control of endemic cholera

1. Cholera vaccination should be prioritized and targeted to cholera hotspots. A cholera hotspot is defined as a geographically limited area where environmental and contextual conditions facilitate the dissemination of the disease and where cholera persists or re-emerges periodically. Campaign planning should be carried out to ensure that vaccination takes place prior to known cholera seasons.
2. Cholera vaccination in endemic areas should be contingent on multisectoral interventions as part of a long-term plan for cholera prevention and control endorsed at the local and national levels by the relevant ministries and should be budgeted.
3. Universal vaccination (throughout a country regardless of risk) is generally not recommended. This may be considered in small countries or islands.
4. Strategies targeting specific age groups at higher risk of disease may be considered.

### Humanitarian emergencies

1. During humanitarian emergencies with a risk of cholera, but without a current cholera outbreak, vaccination with OCV should be considered to help prevent outbreaks, as an additional preparedness measure, depending on the local infrastructure (i.e. capacity to organize a vaccination campaign).
2. The decision to vaccinate should be guided by a thorough investigation of the current and historical epidemiological situation, an assessment of the actual risk of cholera, and a clear identification of geographical areas and populations to be targeted, applying the framework on the use of vaccinations in humanitarian emergencies.<sup>13</sup>
3. Campaign planning should be carried out to ensure that vaccination takes place prior to any known cholera season. Campaign preparation should be conducted early to ensure that vaccination starts immediately once the vaccines become available in country.

<sup>13</sup> See <http://apps.who.int/iris/bitstream/10665/255575/1/WHO-IVB-17.03-eng.pdf>, accessed May 2017.

7. Les femmes enceintes doivent être incluses dans les campagnes de vaccination par le VCO. Les données montrent que le bénéfice potentiel est élevé et que les risques sont minimes.
8. La vaccination n'est pas recommandée, en général, pour les voyageurs qui se rendent dans des pays touchés par le choléra, que leur séjour soit court ou long, car la plupart ont un très faible risque de contracter le choléra. Néanmoins, la vaccination par le VCO doit être envisagée pour les voyageurs dont les activités peuvent comporter une exposition au choléra, notamment les travailleurs humanitaires, les personnes intervenant lors de situations d'urgence ou les secouristes qui seront vraisemblablement directement exposés aux patients atteints de choléra ou à des aliments ou de l'eau contaminés, en particulier les personnes qui se trouvent dans des zones où l'accès aux établissements de santé est problématique.

### Lutte contre le choléra endémique

1. La vaccination anticholérique doit cibler prioritairement les «points chauds» du choléra. Un point chaud est défini comme une zone géographiquement limitée où les conditions environnementales et le contexte facilitent la propagation de la maladie et où celle-ci persiste ou réémerge périodiquement. La planification des campagnes de vaccination doit se faire de manière à ce que la vaccination ait lieu avant les saisons propices au choléra.
2. La vaccination anticholérique dans les zones d'endémie doit se faire en fonction des interventions multisectorielles prévues dans le cadre d'un plan à long terme de prévention et de lutte contre le choléra approuvé aux niveaux local et national par les ministères compétents, et elle doit être budgétisée.
3. La vaccination universelle (dans tout un pays, quel que soit le risque) n'est généralement pas recommandée. Elle peut néanmoins être envisagée dans des pays ou îles de petite dimension.
4. Des stratégies ciblant certains groupes d'âges davantage exposés au risque de contracter la maladie peuvent être envisagées.

### Urgences humanitaires

1. Lors d'urgences humanitaires associées à un risque de choléra, mais sans flambée épidémique en cours, la vaccination par le VCO devrait être envisagée pour aider à prévenir des flambées, en tant que mesure de préparation supplémentaire, en fonction de l'infrastructure locale (c'est-à-dire des capacités pour organiser une campagne de vaccination).
2. La décision de vacciner doit reposer sur une étude approfondie de la situation épidémiologique actuelle et passée, sur une évaluation du risque réel de choléra et sur une identification claire des zones géographiques et des populations à cibler, en appliquant le cadre pour la vaccination dans les situations d'urgence humanitaire.<sup>13</sup>
3. La planification des campagnes de vaccination doit se faire de manière à ce que la vaccination ait lieu avant les saisons propices au choléra. Les campagnes doivent être préparées à l'avance de manière à commencer les activités de vaccination dès que les vaccins sont disponibles dans le pays.

<sup>13</sup> Voir <http://apps.who.int/iris/bitstream/10665/255575/1/WHO-IVB-17.03-eng.pdf> consulté en mai 2017.



### Control of cholera outbreaks

1. Cholera vaccination should systematically be considered to help prevent the spread of current outbreaks to new areas. The decision to vaccinate should be guided by a thorough investigation of the current and historical epidemiological situation and a clear identification of geographical areas and populations to be targeted.
2. Campaign preparation should be conducted early to ensure that vaccination starts immediately once the vaccines become available in country.
3. Based on available evidence regarding short term protection, a single dose strategy could be considered in areas experiencing cholera outbreaks. Considering the limited evidence about the duration of protection, additional doses might be needed to ensure longer-term protection.

SAGE endorsed the areas flagged by the Working Group for additional research and evaluation. SAGE also stressed the importance of continuing the development of improved vaccines and in particular those for use in infants and children aged <5 years.

### Ebola vaccines

Ebola outbreaks of the past were reviewed, noting that they often started in remote rural areas, generally resulted in fewer than 300 cases with very low attack rates in the general population, and lasted less than 6 months. Health-care worker infections in the early phases of these outbreaks, before initial cases were laboratory-confirmed, contributed to the initial amplification of Ebola virus transmission. Ebola outbreaks can be controlled through well-defined interventions: (i) early isolation of patients to prevent transmission at home and in the community; (ii) early detection of new Ebola cases through close monitoring of contacts and isolation of contacts when they show symptoms and; (iii) safe burial of the deceased to reduce transmission through contact with cadavers. In the 2013–2016 outbreak in West Africa, these measures were not fully implemented initially, resulting in unprecedented geographical spread, a large number of cases, urban spread of disease, and high mortality.

Twelve candidate vaccines (including monovalent, bivalent and multivalent candidates) have undergone or are currently undergoing clinical development at different trial phases. The Phase 3 trial for an rVSV-vectored candidate vaccine (rVSVΔG-ZEBOV-GP), undertaken in Guinea, is the only study that has reported clinical efficacy and effectiveness for any candidate Ebola vaccine.

The rVSVΔG-ZEBOV-GP candidate vaccine was granted access to the Priority Medicine (PRIME) scheme by the European Medicine Agency, and Breakthrough Therapy designation by the US Food and Drug Administration.

The rVSVΔG-ZEBOV-GP candidate vaccine and a prime/boost candidate vaccine based on Ad26- and MVA-vectored components (Ad26.ZEBOV/MVA-BN-Filo) have submitted WHO Emergency Use Assessment and Listing (EUAL)

### Lutte contre les flambées épidémiques de choléra

1. La vaccination anticholérique doit être systématiquement envisagée pour aider à prévenir la propagation des flambées en cours vers de nouvelles zones. La décision de vacciner doit reposer sur une étude approfondie de la situation épidémiologique actuelle et passée et sur une identification claire des zones géographiques et des populations à cibler.
2. Les campagnes doivent être préparées à l'avance de manière à commencer les activités de vaccination dès que les vaccins sont disponibles dans le pays.
3. D'après les données disponibles sur la protection à court terme, on peut envisager une stratégie de dose unique dans les zones touchées par des flambées épidémiques de choléra. Au vu des données limitées concernant la durée de la protection, des doses supplémentaires pourront être nécessaires pour garantir une protection à plus long terme.

Le SAGE a approuvé les zones identifiées par le groupe de travail pour conduire des recherches et des évaluations supplémentaires. Le SAGE a également souligné l'importance de poursuivre le développement de vaccins améliorés, en particulier ceux qui sont destinés aux nourrissons et aux enfants âgés <5 ans.

### Vaccins contre le virus Ebola

Les flambées épidémiques de maladie à virus Ebola survenues dans le passé ont fait l'objet d'un examen qui montre qu'elles ont souvent débuté dans des zones rurales reculées, qu'elles ont généralement engendré moins de 300 cas avec de très faibles taux d'atteinte dans la population générale, et qu'elles ont duré moins de 6 mois. La contamination des agents de santé lors des phases précoces de ces flambées, avant la confirmation en laboratoire des premiers cas, a contribué à l'amplification initiale de la transmission du virus Ebola. Les flambées de maladie à virus Ebola peuvent être endiguées à l'aide de mesures bien définies: i) l'isolement précoce des patients pour prévenir la transmission au domicile et dans la communauté; ii) la détection précoce des nouveaux cas de maladie à virus Ebola grâce à une surveillance attentive des contacts et à l'isolement des contacts symptomatiques; et iii) l'inhumation sécurisée des personnes décédées afin de réduire la transmission par contact avec les cadavres. Lors de la flambée épidémique de 2013-2016 en Afrique de l'Ouest, ces mesures n'ont pas été pleinement appliquées au départ, entraînant une propagation géographique sans précédent, un grand nombre de cas, une expansion urbaine de la maladie et une mortalité élevée.

Douze vaccins candidats (monovalents, bivalents ou multivalents) ont été mis au point ou sont en cours de développement clinique, et ont atteint différentes phases d'essais cliniques. L'essai de phase III du vaccin candidat à vecteur rVSV (rVSVΔG-ZEBOV-GP), entrepris en Guinée, est la seule étude à avoir démontré une efficacité clinique parmi tous les vaccins candidats anti-Ebola.

Le vaccin rVSVΔG-ZEBOV-GP s'est vu octroyer l'accès au régime de médicaments prioritaires (PRIME) par l'Agence européenne des médicaments et le statut de percée thérapeutique (Breakthrough Therapy Designation) par la Food and Drug Administration des États-Unis d'Amérique.

Les fabricants du vaccin candidat rVSVΔG-ZEBOV-GP et d'un vaccin candidat de type primovaccination/rappel à vecteurs Ad26 et MVA (Ad26.ZEBOV/MVA-BN-Filo) ont transmis à l'OMS la documentation requise aux fins de la procédure d'évaluation

documentation to WHO. To date, no Ebola vaccine has been prequalified by WHO or completed the EUAL procedure.

A prime/boost candidate vaccine based on rVSV- and Ad5-vectored components (GamEvac-Combi) is licensed in its country of origin based on Phase 2 data. However, the full dossier has not yet been made available to WHO for review.

SAGE noted that the information on duration of protection for candidate Ebola vaccines in the clinical phase is limited and that there is uncertainty on vaccine cross-protection for the different Ebola virus species for any of the candidate vaccines.

Should an Ebola disease outbreak occur before the candidate vaccine is licensed, SAGE recommended that the rVSVΔG-ZEBOV-GP vaccine be promptly deployed under the Expanded Access framework, with informed consent and in compliance with Good Clinical Practice. If the outbreak is caused by an Ebola virus species other than Zaire, consideration should be given to the use of other candidate vaccines that target the putative viral species.

Ring vaccination, as used in the Phase 3 study in Guinea, is the recommended delivery strategy. This should be adapted to the social and geographic conditions of the outbreak areas and include people at risk including but not limited to: (i) contacts and contacts of contacts; (ii) local and international health-care and front-line workers in the affected areas and (iii) health-care and front-line workers in areas at risk of expansion of the outbreak.

The Expanded Access study protocol, which is being discussed with Member States by Médecins Sans Frontières (MSF), the vaccine developer, and partners, should be implemented promptly after the confirmation of a case of Ebola, in coordination with the current control interventions. It should be used as an opportunity to accumulate additional information on vaccine safety, efficacy and effectiveness.

SAGE considered that available evidence on candidate Ebola vaccines, especially duration of protection, is insufficient to formulate conclusive recommendations regarding mass vaccination of the general population or vaccination of health-care workers in the absence of an outbreak.

GAVI has entered into an Advance Purchase Commitment for a licensed product, under which 300 000 doses of today's investigational vaccine will be available if an outbreak occurs. GAVI has also approved funding for procurement of vaccine for a global stockpile when one or more vaccines are licensed and recommended by WHO. SAGE recommended that mathematical modelling estimates be further refined to indicate the potential benefit of various immunization strategies, and future vaccine supply needs.

SAGE supported the WHO Secretariat efforts to facilitate regulatory convergence through supporting national regulatory authorities to develop consensus on regula-

et d'homologation pour les situations d'urgence (EUAL). À ce jour, aucun vaccin anti-Ebola n'a obtenu la préqualification de l'OMS ni complété la procédure EUAL.

Un vaccin candidat de type primovaccination/rappel à vecteurs rVSV et Ad5 (GamEvac-Combi) a été homologué dans son pays d'origine sur la base des données des essais de phase II. Cependant, le dossier complet n'a pas encore été soumis à l'OMS pour examen.

Le SAGE a fait remarquer que les informations sur la durée de la protection conférée par les vaccins candidats anti-Ebola en phase clinique étaient limitées et qu'il existait une incertitude quant à la protection croisée des vaccins candidats contre les différentes espèces de virus Ebola.

Dans le cas où une flambée épidémique de maladie à virus Ebola surviendrait avant l'homologation du vaccin candidat, le SAGE a recommandé de déployer rapidement le vaccin rVSVΔG-ZEBOV-GP en vertu du cadre de l'accès élargi, en veillant à recueillir le consentement éclairé et à respecter les bonnes pratiques cliniques. Si la flambée épidémique est causée par des espèces de virus Ebola autres que Zaire, il conviendra d'envisager l'utilisation d'autres vaccins candidats qui ciblent l'espèce virale présumée.

La vaccination en anneau, telle que celle mise en œuvre dans l'essai de phase III en Guinée, est la stratégie vaccinale recommandée. Elle doit être adaptée aux conditions sociales et géographiques des zones touchées par la flambée épidémique et inclure les personnes à risque, notamment: i) les contacts et leurs propres contacts, ii) les agents de santé et les agents de première ligne locaux et internationaux; et iii) les agents de santé et les agents de première ligne dans les zones où il existe un risque de propagation de la flambée épidémique.

Le protocole d'étude de l'accès élargi, qui fait l'objet de discussions entre les États Membres et Médecins sans frontières, le fabricant du vaccin et les partenaires, doit être rapidement mis en œuvre après la confirmation d'un cas de maladie à virus Ebola, en coordination avec les interventions actuelles de lutte contre la maladie. Ce protocole doit être envisagé comme une occasion d'accumuler des informations supplémentaires sur la sécurité et l'efficacité potentielle et réelle du vaccin.

Le SAGE a considéré que les données disponibles sur les vaccins candidats contre le virus Ebola, en particulier concernant la durée de la protection, étaient insuffisantes pour formuler des recommandations définitives sur la vaccination de masse de la population générale ou la vaccination des agents de santé en l'absence de flambée épidémique.

L'Alliance GAVI a conclu un engagement d'achat préalable de produit homologué, au titre duquel 300 000 doses du vaccin actuellement à l'étude seront disponibles si une flambée épidémique survient. L'Alliance GAVI a également approuvé le financement de l'achat de vaccins pour constituer un stock mondial quand un ou plusieurs vaccins seront homologués et recommandés par l'OMS. Le SAGE a recommandé d'affiner ultérieurement les estimations issues de la modélisation mathématique afin qu'elles donnent des indications sur l'avantage potentiel des différentes stratégies de vaccination et les besoins futurs en vaccins.

Le SAGE a appuyé les travaux du Secrétariat de l'OMS visant à faciliter la convergence réglementaire en aidant les autorités nationales de réglementation à parvenir à un consensus sur les



tory pathways for the development and registration of candidate Ebola vaccines.

SAGE encouraged manufacturers of candidate Ebola vaccines to proactively engage with relevant national regulatory authorities in Africa and regional regulatory structures (e.g. African Vaccine Regulatory Forum, AVAREF) regarding licensure requirements.

SAGE acknowledged the national licensure of the vaccine GamEvac-Combi and encouraged the manufacturer to submit additional data, including the required evidence necessary to apply for WHO prequalification status.

As different Ebola candidate vaccines may have characteristics suited to different scenarios and populations, SAGE supported the ongoing development of all candidate vaccines and recommends that vaccine developers submit data as they become available to the WHO Secretariat to inform policies.

SAGE noted that further research is required to establish the acceptability of vaccines for use in health-care workers, duration of protection conferred by various candidate vaccines, cross protection between virus species and number of doses required, including need for boosting doses.

### **National immunization programme management: functions and competencies**

In a rapidly changing environment, national immunization programme managers are expected to perform diverse functions requiring different and specialized competencies, and are faced with an ever-increasing workload. The GVAP states that the capacities of immunization managers should be strengthened in order to have in place strong immunization programmes as part of well-functioning health systems. Currently there are no standard functions and competencies to assist countries with immunization programme workforce planning. An initial list of functions and competencies, intended for planning, training and managing the immunization technical workforce, was presented to SAGE. The core functions and competencies outlined in this list were encompassed in 7 main technical and management areas: (1) Policy, planning and financing, (2) Advocacy and communication, (3) Human resources and performance management, (4) Vaccine supplies and logistics, (5) Immunization and injection safety, (6) Disease surveillance, investigation and response and (7) Monitoring, evaluation and data use. Country experiences from Pakistan and Armenia were shared with SAGE.

WHO seeks to engage key partners and country staff in the development and implementation of 2 main outputs: a guidance document and a workforce mapping tool.

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

voies réglementaires en matière de développement et d'homologation des vaccins candidats contre le virus Ebola.

Le SAGE a encouragé les fabricants de vaccins candidats anti-Ebola à collaborer proactivement avec les autorités nationales de réglementation concernées en Afrique et avec les structures réglementaires régionales (par exemple le Forum africain pour la réglementation des vaccins, AVAREF) sur les critères d'homologation.

Le SAGE a pris acte de l'homologation nationale du vaccin GamEvac-Combi et a encouragé le fabricant à fournir des données supplémentaires, notamment les éléments probants requis pour déposer une demande de préqualification auprès de l'OMS.

Sachant que les vaccins candidats contre le virus Ebola présentent des caractéristiques adaptées à différents scénarios et populations, le SAGE a salué le développement de tous les vaccins candidats et recommande aux fabricants de vaccins de soumettre leurs données au Secrétariat de l'OMS, quand elles seront disponibles, afin d'éclairer les politiques.

Le SAGE a fait remarquer que des travaux de recherche supplémentaires sont nécessaires pour établir l'acceptabilité de l'administration des vaccins aux agents de santé, la durée de la protection conférée par les différents vaccins candidats, la protection croisée contre les différentes espèces de virus et le nombre de doses requises, y compris les doses de rappel si nécessaire.

### **Gestion des programmes nationaux de vaccination: fonctions et compétences**

Dans un environnement qui évolue rapidement, les gestionnaires de programmes de vaccination sont supposés assumer différentes fonctions nécessitant des compétences variées et spécialisées, et sont confrontés à une charge de travail en constante augmentation. Le GVAP estime que les capacités des gestionnaires des programmes de vaccination doivent être développées afin de renforcer ces programmes dans le cadre de systèmes de santé performants. Aujourd'hui, il n'existe pas de fonctions et compétences standard pour aider les pays à organiser les effectifs des programmes de vaccination. Une liste initiale de fonctions et de compétences, conçue aux fins de l'organisation, de la formation et de la gestion des effectifs techniques des programmes de vaccination, a été présentée au SAGE. Ces fonctions et compétences fondamentales ont été réparties en 7 domaines techniques et de gestion: 1) politique, planification et financement; 2) promotion et communication; 3) ressources humaines et gestion de la performance; 4) approvisionnement en vaccins et logistique; 5) sécurité de la vaccination et des injections; 6) surveillance de la maladie, investigation et riposte; et 7) suivi, évaluation et exploitation des données. Les expériences du Pakistan et de l'Arménie ont été partagées avec le SAGE.

L'OMS cherche à impliquer les partenaires clés et les personnels nationaux dans l'élaboration et la mise en œuvre de 2 éléments fondamentaux: un document d'orientation et un outil de cartographie des effectifs.

Le SAGE a salué cette initiative et souligné l'importance et l'urgence d'élaborer des orientations adaptables à la structure et aux besoins propres à chaque pays. Le SAGE a mis l'accent sur le fait que les fonctions et les compétences doivent être envisagées du point de vue du système de santé, c'est-à-dire de manière à ce que toutes les fonctions liées à la vaccination soient correctement

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.

### **National Immunization Technical Advisory Groups (NITAGs)**

For more than 9 years, WHO has been recommending its Member States to establish NITAGs as a way to improve evidence-informed decision making and country ownership of national immunization programmes. The GVAP recommends that each Member State establish and/or strengthen a NITAG that can guide country policies and strategies based on local epidemiology and cost-effectiveness. Data on the existence of functional NITAGs are collected in the WHO-UNICEF joint reporting form (JRF).

In 2015, 124 of 194 Member States reported the existence of a NITAG. Of these, 116 (60%) have a NITAG with an administrative and legislative basis and 41%, including 49 low and middle income countries (LMICs), reported that their NITAG complies with the 6 basic JRF process indicators of functionality. This represents an 88% increase from 2010. In 2016, as part of the GVAP midterm review, SAGE noted that good progress had been made in this area, though the achievement of the GVAP 2020 target would need additional efforts from countries and the partners.

SAGE was presented with a NITAG literature review. Main issues addressed in NITAG-related publications were frameworks, processes and evidence to issue recommendations, availability of expertise and human resources, integration within the national decision-making process, independence of the NITAG and recommendations and the need for collaboration between NITAGs.

NITAGs from Senegal, Sri Lanka, and the United Kingdom presented their experience to illustrate achievements and challenges as well as country differences in structure and functioning.

Main issues that countries are facing in establishing, strengthening and sustaining NITAGs include funding challenges, lack of work plans and agendas, lack of assessments of conflicts of interest, lack of human resources, insufficient training on evidence-based review processes, language and limited access to critical literature and publications, and recognition of the NITAG by the respective MoH.

In light of their contribution to the improvement of national immunization programmes, SAGE stressed the importance of NITAGs as a core institution of well-functioning immunization programmes and urged that countries, WHO, partners and the donor community continue to provide support and facilitate the work of

assumées par des personnels compétents, quelle que soit la structure du système de santé dans le pays. Le SAGE a recommandé aux pays et régions de partager leurs expériences en matière d'organisation des effectifs des programmes de vaccination. Le SAGE a suggéré de créer des outils pour aider les pays dans différents domaines relevant de la gestion des ressources humaines pour la vaccination, notamment les politiques de relève et de rotation des personnels, les évaluations de la performance et le plan de formation. Le SAGE a recommandé que ces travaux soient guidés dans un certain nombre de pays.

### **Groupes consultatifs techniques nationaux sur la vaccination (NITAG)**

Depuis plus de 9 ans, l'OMS recommande à ses États Membres de constituer des NITAG de manière à améliorer la prise de décisions fondée sur des faits probants et l'appropriation des programmes nationaux de vaccination par les pays. Le GVAP recommande à chaque État Membre de constituer et/ou de renforcer un NITAG qui soit en mesure de guider les politiques et stratégies nationales en fonction de l'épidémiologie locale et de leur rapport coût/efficacité. Les données sur l'existence de NITAG fonctionnels sont consignées dans le formulaire conjoint de déclaration OMS/UNICEF.

En 2015, 124 des 194 États Membres ont notifié l'existence d'un NITAG. Parmi ceux-ci, 116 (60%) disposent d'un NITAG doté d'une base administrative et juridique et 41%, dont 49 pays à revenu faible ou intermédiaire, ont déclaré que leur NITAG respectait les 6 indicateurs de processus fondamentaux relatifs à la fonctionnalité contenus dans le formulaire conjoint de déclaration OMS/UNICEF. Cela représente une augmentation de 88% par rapport à 2010. En 2016, dans le cadre de l'évaluation à mi-parcours du GVAP, le SAGE a constaté les progrès notables accomplis dans ce domaine, même si des efforts supplémentaires de la part des pays et des partenaires seront nécessaires pour atteindre la cible du GVAP pour 2020.

Une revue des publications traitant des NITAG a été présentée au SAGE. Les principaux points soulevés dans ces publications étaient les cadres, processus et données nécessaires pour émettre des recommandations, la disponibilité d'experts et de ressources humaines, l'intégration dans le processus décisionnaire national, l'indépendance des NITAG et des recommandations, et la nécessité d'une collaboration entre les NITAG.

Les NITAG du Sénégal, du Sri Lanka et du Royaume-Uni ont présenté leurs expériences pour illustrer les réalisations et les difficultés, ainsi que les différences structurelles et fonctionnelles entre les pays.

Parmi les principaux problèmes auxquels les pays sont confrontés pour créer, renforcer et pérenniser les NITAG figurent: les difficultés de financement, le manque de plans et de programmes de travail, d'évaluations des conflits d'intérêts, de ressources humaines, et de formation aux processus d'examen fondé sur des preuves, la langue de la littérature et des publications essentielles et l'accès limité à ces ressources, et la reconnaissance du NITAG par le ministère de la santé du pays.

Étant donné la contribution des NITAG à l'amélioration des programmes nationaux de vaccination, le SAGE a souligné leur importance en tant qu'institutions centrales pour des programmes de vaccination performants, et a enjoint les pays, l'OMS, les partenaires et les donateurs à poursuivre leurs efforts pour soutenir et faciliter le travail des NITAG et de leurs secré-

NITAGs and their secretariats in order to meet the GVAP 2020 goal. SAGE noted that fostering collaborations between countries and at regional and global level was essential for success.

SAGE emphasized the status of NITAGs as independent advisory bodies, and reiterated that transparency and adequate reporting and disclosure and management of relevant interests were important concepts to ensure the credibility of NITAGs and their recommendations.

Solutions are required for the establishment of advisory bodies in countries with small populations for which the establishment of a separate NITAG is not feasible. The important role of RTAGs was underscored in the establishment and strengthening of existing 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.

### **Private sector engagement with national immunization programmes**

The private sector, comprising all health-care providers outside the public sector, whether for philanthropic or commercial purposes, encompasses individuals and institutions. The degree of engagement of private sector entities with national immunization programmes (NIPs) varies between and within countries. Improvements in vaccine coverage to support GVAP goals require the optimization of this involvement. SAGE was presented with 2 systematic literature reviews which outlined the complexity of models of private providers' engagement with NIPs. Private sector contributions to coverage generally remain poorly documented and there is limited information on successful models of private-public collaboration. Information exchange between public and private sectors, particularly for-profit providers, is weak in many countries; in many cases, the private system is not integrated or may be non-compliant with reporting. In LMICs, mechanisms to enforce quality standards for vaccine storage and administration in the private sector are limited by human and financial resource constraints. The experience of Uganda and India was presented with respect to the contributions, risks, challenges and strengths of NIP engagement with the private sector.

Taxonomy of the term "private provider" was discussed; it is not a single group, but encompasses a range of different not-for-profit and for-profit providers in different settings, including primary care organizations and hospitals, civil society organizations (CSOs), non-governmental organizations (NGOs), faith-based organizations (FBOs), community-based organizations (CBOs), and private companies providing health care to

tariats afin de réaliser l'objectif 2020 du GVAP. Le SAGE a fait remarquer que promouvoir les collaborations entre pays aux niveaux régional et mondial était essentiel.

Le SAGE a insisté sur le statut d'organe consultatif indépendant des NITAG et a rappelé que la transparence, la communication adéquate des informations, la déclaration et la gestion des intérêts en jeu étaient des concepts importants pour garantir la crédibilité des NITAG et de leurs recommandations.

Il convient de trouver des solutions pour la création d'organes consultatifs dans les pays peu peuplés où la constitution d'un NITAG séparé n'est pas envisageable. Le rôle important des RTAG dans l'établissement et le renforcement des NITAG existants a été souligné.

Le SAGE a recommandé l'élaboration d'orientations, d'outils, de programmes de formation et d'encadrement sur mesure pour aider les NITAG. Il a insisté sur le rôle essentiel d'initiatives telles que le réseau mondial des NITAG et le centre de ressources pour les NITAG, qui nécessitent des moyens financiers et humains dédiés. Le SAGE a également indiqué que les évaluations des NITAG étaient importantes, au-delà des indicateurs de processus actuels, et qu'elles devaient être poursuivies et appuyées par les pays et les institutions partenaires. Les évaluations des NITAG doivent porter sur la fonction, la qualité et l'intégration.

### **Participation du secteur privé aux programmes nationaux de vaccination**

Le secteur privé, qui comprend tous les prestataires de santé hors du secteur public, que ce soit à des fins philanthropiques ou commerciales, englobe des personnes et des institutions. Le degré de participation des entités du secteur privé aux programmes nationaux de vaccination varient selon les pays et à l'intérieur même des pays. Pour améliorer la couverture vaccinale aux fins des objectifs du GVAP, il est nécessaire d'optimiser la participation du secteur privé. Deux revues systématiques de publications décrivant la complexité des modèles de participation des prestataires privés aux programmes nationaux de vaccination ont été présentées au SAGE. Les contributions du secteur privé à la couverture vaccinale restent généralement peu documentées et l'on manque d'informations sur les modèles réussis de collaboration public-privé. L'échange d'informations entre les secteurs public et privé, en particulier les prestataires à but lucratif, est médiocre dans de nombreux pays; souvent, le système privé n'est pas intégré ou ne communique pas les informations comme il se doit. Dans les pays à revenu faible ou intermédiaire, les mécanismes pour imposer des normes de qualité pour le stockage et l'administration des vaccins dans le secteur privé sont limités par le manque de ressources humaines et financières. L'expérience de l'Ouganda et de l'Inde en matière de contributions, risques, difficultés et forces de la collaboration des programmes nationaux de vaccination avec le secteur privé a été présentée.

La taxonomie du terme «prestataire privé» a été discutée; il ne s'agit pas d'un groupe unique, mais d'un ensemble de prestataires à but lucratif et sans but lucratif intervenant dans différents contextes, notamment des organisations de soins primaires et des hôpitaux, des organisations de la société civile, des organisations non gouvernementales, des organisations confessionnelles, des organisations communautaires, et des entreprises privées qui offrent une couverture sanitaire à leurs employés



their employees and families. SAGE recognized the complexity of the topic and called for global, regional and country efforts to encourage further private sector involvement with NIPs. A single standard approach for all countries is not realistic or appropriate. It was noted that it is important to distinguish between private providers' engagement in routine immunization versus humanitarian emergency response.

SAGE was requested to provide input to draft guidance for countries to optimize engagement between private providers and NIPs in order to support improvement in coverage and quality of vaccine delivery and reduce equity gaps. Specific recommendations were proposed in 6 broad areas: assessment; optimization of service delivery; facilitation of dialogue and decision-making; ensuring adequate data management and reporting; provision of adequate training and capacity building; and facilitation of accountability and performance oversight.

Potential mechanisms for supporting private sector engagement include clinical franchising and the use of incentive packages. Regional support could assist with development of a menu of good practice models to be shared. Priorities for addressing gaps in research need to be identified.

SAGE recommended that all NIPs should increase collaboration and communication with private providers regardless of the latter's relative contribution to the delivery of vaccination. SAGE urged that all countries should, as a first step, conduct an assessment of the current role of private providers in immunization service delivery including contribution to coverage, immunization advocacy, adverse events surveillance and vaccine-preventable disease surveillance. An inventory of key players/stakeholders, distinguishing private for-profit, CSOs, FBOs and international NGOs, should be undertaken to identify problems, strengths and challenges, and solutions to address the issues identified. SAGE stressed that it would be particularly important that private providers ensure adequate reporting to the NIP. Each country should determine the optimal model for engaging the private sector tailored to the country immunization system and in a managed programme. Countries are encouraged to include private providers in NITAGs as core members and/or as liaison members for various private provider constituencies.

Existing tools, such as Expanded Programme for Immunization reviews, Multiple Indicator Cluster Surveys, and Joint Appraisals could initially be used to assess the engagement of the private sector.

SAGE applauded the development of the draft guidance as an initial step in tackling this area of work and urged WHO to finalize a common framework starting with a set of core principles.

et leurs familles. Le SAGE a reconnu la complexité du sujet et a appelé à consentir des efforts aux niveaux mondial, régional et national pour encourager une plus grande participation du secteur privé aux programmes nationaux de vaccination. Une approche standard unique pour tous les pays n'est pas réaliste ni appropriée. Par ailleurs, l'importance de faire la distinction entre une participation des prestataires privés dans le cadre de la vaccination systématique et leur participation dans le cadre d'une action d'urgence humanitaire a été soulignée.

Il a été demandé au SAGE d'apporter des éléments afin de préparer des orientations à l'intention des pays pour optimiser l'engagement entre prestataires privées et programmes nationaux de vaccination en vue d'améliorer la couverture et la qualité de la vaccination et de réduire les inégalités. Des recommandations spécifiques ont été proposées dans 6 grands domaines: l'évaluation, l'optimisation de la prestation de services, la facilitation du dialogue et de la prise de décisions, la gestion et la communication adéquates des données, l'offre d'une formation appropriée et le développement des capacités, et la facilitation de la responsabilisation et de la surveillance de la performance.

Les mécanismes possibles pour encourager la participation du secteur privé comprennent le franchisage clinique et l'offre de bouquets incitatifs. Un appui au niveau régional pourrait aider à l'élaboration d'un ensemble de modèles de bonnes pratiques à partager. Il est nécessaire d'identifier les priorités pour combler les lacunes de la recherche.

Le SAGE a recommandé à tous les programmes nationaux de vaccination de développer la collaboration et la communication avec les prestataires privés quelle que soit la contribution de ces derniers aux activités de vaccination. Le SAGE a vivement encouragé tous les pays à réaliser, dans un premier temps, une évaluation du rôle actuel des prestataires privés dans la fourniture de services de vaccination, notamment leur contribution à la couverture, à la promotion de la vaccination, à la surveillance des manifestations indésirables et à la surveillance des maladies à prévention vaccinale. Il convient de dresser une liste des acteurs/parties prenantes clé, en faisant la distinction entre les entreprises privées à but lucratif, les organisations de la société civile, les organisations confessionnelles et les organisations non gouvernementales internationales, afin d'identifier les problèmes, les forces et les difficultés, ainsi que les solutions pour remédier aux questions soulevées. Le SAGE a souligné qu'il était particulièrement important que les prestataires privés fassent dûment rapport aux programmes nationaux de vaccination. Chaque pays devrait déterminer le modèle optimal de participation du secteur privé adapté au système national de vaccination et dans le cadre d'un programme dirigé. Les pays sont encouragés à inclure les prestataires privés dans les NITAG en tant que membres à part entière et/ou en tant que membres de liaison avec diverses parties prenantes privées.

Les outils existants, comme les revues du Programme élargi de vaccination, les enquêtes en grappes à indicateurs multiples et les évaluations conjointes, pourraient être initialement utilisés pour évaluer l'engagement du secteur privé.

Le SAGE a salué l'élaboration du projet d'orientations comme une première étape pour s'attaquer à ce domaine de travail et a appelé l'OMS à finaliser un cadre commun qui pose un ensemble de principes fondamentaux.

## Diphtheria

SAGE was presented with an analysis of recent diphtheria outbreaks and a systematic review of vaccine effectiveness and serological studies on the duration of protection conferred by diphtheria vaccination. Based on this evidence, SAGE was asked to decide whether there was sufficient evidence to revisit the recommendation on the administration of decennial diphtheria booster doses to adults and synchronization of immunization schedules in light of the recently revised recommendations on the use of the pertussis and tetanus containing vaccines.<sup>14, 15</sup>

In view of reports of diphtheria antitoxin (DAT) supply shortages in the context of increasing reports of diphtheria outbreaks, and sporadic cases in settings with no diphtheria for decades and very low vaccine coverage, SAGE had also requested a review of the DAT supply situation.

The analysis of JRF data revealed that progress in decreasing diphtheria incidence has stalled in the last 5 years, with approximately 5000 cases reported per year. The South-East Asia Region, particularly India, accounts for the majority of the global reported diphtheria incidence but cases were reported in all 6 Regions.

It was noted that a significant proportion of countries, particularly in the African and Eastern Mediterranean Regions, were not submitting reports on diphtheria. Outbreaks have occurred in countries not reporting cases through the JRF, providing further evidence of under-reporting of cases. Thus, reported cases are likely to represent only a fraction of the total number of cases.

Analysis of data from 58 sources on 10919 cases occurring in outbreaks in 33 countries showed that a lower proportion of diphtheria cases with recorded age were aged >15 years in countries with higher case counts ( $\geq 10$  cases in 3 years during 2000–2016), than in countries with sporadic incidence (40% versus 66%). Among cases with known vaccination status most were unvaccinated, and a lower proportion were incompletely vaccinated, underlining the need for the full primary immunization series plus booster doses. This also indicates that failure to vaccinate, rather than waning immunity, was the main predisposing factor.

SAGE further stressed that diphtheria is a forgotten disease in large parts of the world and needs global attention. SAGE highlighted the need for strengthening surveillance systems to enhance the capacity to detect and investigate diphtheria cases, to generate better data to inform recommendations on optimal vaccination schedules, and to prevent outbreaks and respond promptly when outbreaks occur. Countries should be

## Diphthérie

Une analyse des récentes flambées épidémiques de diphtérie et une revue systématique des études d'efficacité des vaccins et des études sérologiques sur la durée de protection conférée par la vaccination antidiphthérique ont été présentées au SAGE. Sur la base de ces informations, il a été demandé au SAGE de décider si les données étaient suffisantes pour revoir la recommandation concernant l'administration de doses de rappel tous les 10 ans aux adultes et la synchronisation des calendriers de vaccination à la lumière des recommandations récemment révisées relatives à l'administration des vaccins anticoquelucheux et antitétanique.<sup>14, 15</sup>

Face aux pénuries d'antitoxine diphtérique dans un contexte d'augmentation des flambées épidémiques de diphtérie et en présence de cas sporadiques dans des milieux exempts de diphtérie depuis des décennies et bénéficiant d'une très faible couverture vaccinale, le SAGE a également demandé une revue de la situation de l'approvisionnement en antitoxine diphtérique.

L'analyse des données des formulaires conjoints de déclaration OMS/UNICEF a révélé que les progrès réalisés pour diminuer l'incidence de la diphtérie stagnaient depuis 5 ans, avec environ 5000 cas notifiés chaque année. La Région de l'Asie du Sud-Est, en particulier l'Inde, concentre une grande part de l'incidence mondiale de la diphtérie, mais des cas ont été notifiés dans les 6 Régions.

Il a été mentionné qu'une proportion notable de pays, notamment dans la Région africaine et la Région de la Méditerranée orientale, ne communiquaient pas de données sur la diphtérie. Il s'avère que les flambées épidémiques se sont produites dans des pays qui ne rapportent pas les cas de diphtérie au moyen du formulaire conjoint de déclaration OMS/UNICEF, ce qui confirme un phénomène de sous-notification. Les cas notifiés représentent donc vraisemblablement seulement une fraction du nombre total de cas.

L'analyse des données issues de 58 sources sur 10919 cas survenus lors de flambées épidémiques dans 33 pays, a montré que, parmi les cas de diphtérie dont l'âge a été précisé, la proportion de cas chez les >15 ans était inférieure dans les pays comptant le plus grand nombre de cas ( $\geq 10$  cas en 3 ans entre 2000 et 2016), par rapport aux pays ne comptant que des cas sporadiques (40% versus 66%). Parmi les cas dont on connaît le statut vaccinal, la plupart n'était pas vaccinée et une moindre proportion était partiellement vaccinée, ce qui souligne la nécessité d'administrer une série complète de primovaccination plus des doses de rappel. Cela indique aussi que le principal facteur prédisposant à la maladie n'est pas la diminution de l'immunité dans le temps mais l'absence de vaccination.

Le SAGE a aussi insisté sur le fait que la diphtérie était une maladie oubliée dans de nombreuses parties du monde qui nécessitait une attention à l'échelle mondiale. Il a souligné la nécessité de renforcer les systèmes de surveillance pour améliorer la capacité à détecter et à étudier les cas de diphtérie, pour générer de meilleures données afin d'éclairer les recommandations pour des calendriers vaccinaux optimaux et pour prévenir les flambées épidémiques et riposter rapi-

<sup>14</sup> See No. 35, 2015, pp. 433–460.

<sup>15</sup> See No. 6, 2017, pp. 53–76.

<sup>14</sup> Voir N° 35, 2015, pp. 433-460.

<sup>15</sup> Voir N° 6, 2017, pp. 53-76.

encouraged to report diphtheria cases caused by *Corynebacterium diphtheriae* and *C. ulcerans* where laboratory capability for confirmation is available. 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.

SAGE also concluded that coverage with diphtheria-containing vaccines in paediatric immunization programmes needs to be increased, and that vaccination schedules for diphtheria, tetanus and, when appropriate, pertussis, should be harmonized as these antigens are often provided in combination vaccines. SAGE reiterated its previous recommendation that combination vaccines containing tetanus and diphtheria toxoids should also be administered for catch-up vaccination of older children and adults, maternal and neonatal tetanus prevention, and prevention of tetanus among those with an injury if indicated.

Available data from non-endemic countries and the findings from the systematic review on the duration of diphtheria vaccine protection currently do not support the need for decennial booster doses, though further sero-epidemiological studies will be required to assess the duration of protection throughout the life course. It is clear that some boosting is needed and that if the schedule of 3 booster doses recommended for lifelong protection for tetanus are given in an age appropriate combination with diphtheria toxoid, long term protection against diphtheria will be maintained.

SAGE also proposed that the availability of data on transmission of cutaneous diphtheria possibly leading to respiratory diphtheria should be assessed.

SAGE expressed its grave concern about the limited DAT supplies worldwide, and stressed that DAT is urgently needed for managing suspected cases of diphtheria. SAGE therefore advised that WHO collaborate closely with partners to establish and manage a global procurement mechanism and a physical or virtual DAT 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.

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. ■

dement le cas échéant. Les pays doivent être encouragés à notifier les cas de diphtérie causée par *Corynebacterium diphtheriae* et *C. ulcerans* quand les laboratoires sont en mesure de les confirmer. Le SAGE recommande de mettre à jour les critères de surveillance, les lignes directrices pour l'investigation, notamment concernant le diagnostic et la notification des cas de diphtérie et des flambées épidémiques, afin d'améliorer la qualité des données et de faciliter la méta-analyse. Ces lignes directrices doivent inclure des formats standard pour indiquer l'âge avec plus de précision et le statut vaccinal.

Le SAGE a également conclu que la couverture par les vaccins à valence diphtérie dans les programmes de vaccination pédiatrique devait augmenter et que les calendriers vaccinaux pour la diphtérie, le tétanos et, le cas échéant, la coqueluche, devaient être harmonisés, car ces antigènes sont souvent administrés dans des vaccins associés. Le SAGE a réitéré sa précédente recommandation selon laquelle les vaccins associés contenant les anatoxines diphtérique et tétanique devraient aussi être administrés dans le cadre d'une vaccination de rattrapage chez les enfants plus âgés et les adultes, pour la prévention du tétanos maternel et néonatal et pour la prévention du tétanos chez les personnes présentant une plaie, s'il est indiqué de le faire.

Les données disponibles issues des pays où la diphtérie n'est pas endémique et les conclusions de la revue systématique sur la durée de la protection conférée par le vaccin antidiphtérique ne plaident pas en faveur de l'administration de doses de rappel tous les 10 ans, même si d'autres études séro-épidémiologiques seront nécessaires pour évaluer la durée de la protection tout au long de la vie. Il est clair que des rappels sont nécessaires et que si les 3 doses de rappel recommandées pour une protection à vie contre le tétanos sont administrées avec l'anatoxine diphtérique dans un vaccin associé adapté à l'âge du receveur, cela permettra de maintenir une protection à long terme contre la diphtérie.

Le SAGE a également proposé que la disponibilité des données sur la transmission de la diphtérie cutanée susceptible d'entraîner une diphtérie respiratoire soit évaluée.

Le SAGE a exprimé une profonde préoccupation concernant les stocks limités d'anatoxine diphtérique dans le monde et a souligné le besoin urgent de disposer de cette anatoxine pour prendre en charge les cas suspects de diphtérie. Le SAGE a donc conseillé à l'OMS de collaborer étroitement avec les partenaires pour mettre en place et gérer un mécanisme d'achat mondial et pour constituer un stock physique ou virtuel d'anatoxine diphtérique à la disposition de tous les pays. Le SAGE a aussi insisté sur la nécessité de mettre en place des voies réglementaires pour garantir un déploiement rapide de l'anatoxine diphtérique. À long terme, le SAGE a conseillé à l'OMS d'identifier des mécanismes pour soutenir le développement d'un anticorps monoclonal susceptible de remplacer l'anatoxine diphtérique d'origine équine.

Le SAGE a exprimé sa préoccupation face à la pénurie de vaccins Td (anatoxine tétanique + teneur réduite en anatoxine diphtérique) pour la vaccination systématique des enfants et des adolescents, pour la vaccination de rattrapage des adultes et pour la prévention du tétanos après une blessure, et il a recommandé l'évaluation de scénarios de demande et d'offre de vaccins Td. ■

## SAGE TRACKING RECORD OF RECOMMENDATIONS AND ACTION POINTS

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

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

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

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
General	SAGE recommended that ways to improve curricula for medical personnel should be explored.	Nov 2008	Ongoing	The Regional Office for Africa (AFRO) has published the pre-service curriculum and efforts are being made to disseminate the findings and ensure that medical and nursing schools change their outdated curriculum. This is a long process but few steps have started in that direction.
General	SAGE stressed that additional disaggregation was needed in the analysis of the progress achieved on the ground, and in identifying bottlenecks for progress, and recommended that reports display disparities observed at sub-national levels.	Apr 2015	Ongoing	WHO headquarters (HQ) is working closely with regional offices to obtain subnational level data. Surveillance data for measles and rubella as well as for new vaccines is collected at the district level on regular basis and there are efforts to collect sub-national level coverage data. Currently this is happening in the African Region on monthly as well as annual basis; and in the South East Asian Region and the European Region it is done on annual basis. In October 2016, at the Global Monitoring Meeting all regions agreed to collect and submit to HQ district level coverage data (numerator, denominator and coverage from DTP1, DTP3 and MCV1) as part of annual data collection exercise. Out of 194 member states, 125 countries reported subnational coverage, 36 at the 1st subnational level and 89 at the 2nd subnational administrative level (often corresponding to districts). The 20,000 districts for which data were received are home to 88 million children, two-thirds of the surviving infants worldwide. An initial analysis shows large differences in the size of these districts and the coverage they report. A large proportion report coverage over 100%, revealing the challenges to accurately measure coverage at subnational level. Detailed analysis and reported data will be made available by October 2017.
AEFI reporting	SAGE urged that efforts be pursued to enhance Adverse Events Following Immunization (AEFI) reporting worldwide.	Apr 2016	Ongoing	With Gavi support, 30 African countries have established work plans. A first analysis of the new Global Vaccine Action Plan (GVAP) indicator for adverse events following immunization (AEFI) monitoring has identified 84 member states that meet the recommended level of at least 10 AEFI cases reported per 100,000 surviving infants per year. A manuscript is currently submitted that describes the AEFI reporting ratio through Joint Reporting Form (JRF). 2016 data are currently analyzed and indicate an increase in the number of member states that fulfill the indicator requirement.



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AEFI reporting	SAGE commented on the passive surveillance data from the Uppsala Monitoring Centre (UMC) and raised concerns that the safety signal detection was not undergoing appropriate peer review. SAGE concurred with GACVS on the need to increase collaboration and to implement a strong review process.	Apr 2016	Ongoing	The Global Advisory Committee on Vaccine Safety (GACVS) concluded that signals documented by the Uppsala Monitoring Centre (UMC) provide useful information in monitoring the safety of vaccines from worldwide sources. It was proposed that a strengthened process of collaboration with UMC would allow use of the expertise on vaccine safety available within the GACVS and partner agencies for the review of this information before it is communicated to the network of pharmacovigilance centres and to vaccine manufacturers. This review should take into account the limitations of signal detection methods along with the reviews performed routinely by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), given their extensive experience and access to more complete information with the Individual Case Safety Reports (ICSRs) they receive and that may not all be shared with UMC. The GACVS Secretariat will liaise with UMC to identify mechanisms for such collaboration. UMC revised its signal assessment guideline in April 2015. In March 2016, UMC was recommended to establish a review group for the vaccine signals. So far this has not happened though and new signals are being generated. The WHO Essential Medicines and Health Products (EMP) Department has examined the issue and requested a reply from UMC Director to the WHO Safety and Vigilance team.
Data quality	SAGE requested the establishment of a Working Group on Quality and Use of Global Immunization and Surveillance Data.	Apr 2017	Completed	The call for nominations was issued in June 2017. The selection panel met on 14 July 2017 to decide on the composition of the group. The group has now been established and has taken up its work during an initial teleconference in August 2017.
Decade of vaccines/GVAP	The SAGE working group should continuously review the need for reformulation of the indicators or mechanisms for collection and reporting of data.	Nov 2012	Ongoing	The SAGE Decade of Vaccines (DoV) Working Group (WG) continues to review the need for reformulation of the indicators and mechanisms for data collection. In 2016 the WG has specifically discussed safety and demand side indicators as well as discussed indicators to be used as part of the Sustainable Development Goals (SDGs). The SAGE report of progress with the Global Vaccine Action Plan (GVAP) for 2016 i.e. the midterm progress report was published online and is available at: <a href="http://www.who.int/immunization/global_vaccine_action_plan/en/">http://www.who.int/immunization/global_vaccine_action_plan/en/</a> This report was tabled at the Executive Board in Jan 2017 together with a draft GVAP resolution sponsored by Australia, Brazil and Colombia. A series of calls the SAGE WG took place in Q2 2017 with specific focus on the selection of the SDGs indicator for Immunization (3.8 and 3.b.1), on discussing data quality and on selecting priority countries for the 2017 GVAP Secretariat report. The SAGE DOV WG calls started on 18 July to revise the different sections of the draft secretariat report 2017. The SAGE DOV WG will meet in person from 29-31 August for the yearly revision of progress in the implementation of GVAP for the year 2016, with a focus on the regional and country reports, the acceleration of pace, the Gavi and Polio transition and the post 2020. SAGE will be informed on these issues during the GVAP session at the October 2017 meeting.
Diphtheria	SAGE expressed concern with the shortage of Td vaccine (tetanus toxoid + reduced diphtheria toxoid content) for routine immunization of children and adolescents, catch-up vaccination of adults and tetanus prevention after injury, and recommended that the demand and supply scenarios for Td vaccines should be assessed.	Apr 2017	Ongoing	An assessment of global demand and supply for Diphtheria and Tetanus containing vaccines is being finalized. The assessment was conducted with support from Linksbridge and MMGH consulting group. A temporary Advisory Group of expert was convened to guide this work advising on methodology, assess current and future supply risks and advice on policy implications. A final meeting of the Advisory Group was held on September 13th concluding that: i) shortages of D&T containing vaccines in Europe); global supply is more than sufficient to meet demand over the next 15 years even assuming global switch from TT to Td vaccines and global introduction of 3 booster doses as per recommendations; nevertheless, Td and aP vaccines require careful management as they can become (Td) or are (aP) in tight supply. The final assessment will be available mid October 2017.



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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	Manufacturers have been contacted to provide information on feasibility, time-lines and cost. Current products/volumes inadequate for global stockpile. WHO is working with DAT monoclonal developers to review timelines, costs, and overcoming barriers to regulatory approval (existing plans are for expanded access use rather than formal approval).
Diphtheria	SAGE recommended that surveillance standards, guidelines for the investigation including diagnostics and reporting of diphtheria cases and outbreaks, be updated to improve the quality of data and to facilitate pooled analysis. The guidelines should include standard formats for reporting age with increased granularity and immunization status categorization.	Apr 2017	Ongoing	Work is ongoing to update the global vaccine-preventable disease (VPD) surveillance standards and will include a new and improved chapter on diphtheria surveillance. It will address the points recommended by SAGE and should be ready by early 2018.
Diphtheria	SAGE expressed its deep concern over the reported lack of diphtheria antitoxin and encouraged WHO to take on a strong leadership role in resolving this shortage globally.	Oct 2016	Completed	A session was held at the April 2017 SAGE meeting which tackled the issue of diphtheria antitoxin supply shortages.
Ebola vaccines	Noting WHO's unique position to coordinate the development of Ebola vaccines, SAGE stressed the importance of transparent and prompt sharing of information on the trial protocols and data from the phase 3 clinical trials, and the need for a greater role for WHO in facilitating the sharing of information so that results between studies will generate the greatest benefit for policy decision-making.	Apr 2015	Ongoing	SAGE established an Ebola working group (WG) in Nov 2014 which met regularly via teleconference as well as during a face-to-face meeting on the 9-10 Mar 2015. The WG reviewed the epidemiological data on Ebola Virus Disease (EVD), the preliminary results of the phase 1 trials, the status of the phase 2 and 3 trials, and the preparations for the large scale deployment of vaccines. They also identified the scope of the recommendations and the key questions and data for formulating recommendations. The framework was presented to SAGE at the Apr 2015 meeting. The WG met again on 19-20 Aug 2015 to review the available information and to start framing recommendations, based on the framework approved by SAGE in Apr 2015. The WG input was presented to SAGE at the Oct 2015 meeting. Now, that the final results of the Ring trial have been published in the Lancet in Dec 2016, a WG meeting took place 14-15 Mar 2017 to discuss the results. Regulatory evaluation of the vaccine is currently ongoing. There is information regarding a Russian developed vaccine that was licensed in Russia, but despite WHO requests no detailed data are available. The emerging data and draft recommendations were discussed during the face to face meeting of the WG which took place Mar 2017. The evidence was presented during the April 2017 SAGE meeting.

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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 &gt;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 &gt; 14 years of age in the post vaccination period. Most of these represent non-vaccinated adolescents or adults that escaped HAV-infection in previous outbreaks.</p> <p>Both Colombia and Paraguay also introduced a single dose national immunization schedule for 1 year old children. Yearly review of the Argentinian surveillance data will continue as Argentina was the front runner country to introduce a 1 dose schedule with the inactivated vaccine.</p> <p>A third phase immunogenicity study is ongoing in Argentina, to assess long term protective antibodies in children more than 9 years following single dose vaccination. The results of the phase 2 study conducted in 2013 with a median post-vaccination interval of 7.7 years were quite reassuring with a prevalence of protective antibodies of 97.4% (95% CI: 96.3-98.3) still protected. More recent analysis (phase 3) indicates that the prevalence of protective antibodies in children &gt; 9 years following a single dose of hepatitis A vaccine was still 87.6% but a decrease was observed in all centers with decreased GMCs. It is still unclear if different samples or differences in methodology or recall bias in seronegative individuals could actually account for the difference, but this requires continued follow up. For the time being epidemiologic surveillance continues to show very low infection rates in all regions and age groups with sporadic cases occurring mainly in frontier regions and non-vaccinated adolescents.</p>

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Hepatitis B	SAGE recommended that the timely delivery of a birth dose of hepatitis B vaccine (that is, within 24 hours of birth) should be used as a performance measure for all immunization programmes. Reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose.	Apr 2009	Ongoing	<p>A new indicator for Hepatitis B birth dose has been added to the WHO /UNICEF Joint Reporting Form (JRF) 2017 - this new indicator will allow the distinction between timely (24 hours) and late birth dose administration.</p> <p>In Nov 2016, AFRO held consultation on hepatitis B control and included discussing barriers, actions and support needed towards hepatitis B birth dose introduction. This was part of joint meeting held with viral hepatitis counterparts.</p> <p>A consultation on implementation of a new universal birth dose recommendation was conducted in Dec 2010 with special focus on countries with a high percentage of home births. Outputs include a monograph documenting the systematic review and best practices from the consultation. Immunization Practices Advisory Committee (IPAC) reviewed this work in early 2011 and again in Apr 2012, and endorsed the 2013 publication of 'Practices to Improve Coverage of the Hepatitis B birth dose vaccine.' From this, work is ongoing to develop field guidelines for scaling up Hepatitis B birth dose. The JRF and associated materials have been revised to improve reporting of birth dose with a particular focus in Western Pacific Regional Office (WPRO). The WHO/UNICEF estimate process was piloted in 2012 in WPRO and was applied globally for the first time to the 2013 JRF birth dose data. Analysis of timely birth dose data for 2008 shows no significant changes from 2006 analysis and the major issue is lack of data quality. A study of the cost of scaling up the birth dose by country has been completed, based upon previously published methodology estimating the cost of implementing the Global Immunization Vision and Strategy (GIVS) goals. In 2012, WPRO convened Expanded Program on Immunization (EPI) and Maternal and Child Health (MCH) managers from the five priority countries to jointly propose actions towards improving birth dose uptake.</p> <p>In Jan 2015 the African Regional Office (AFRO), and in Mar 2015 WPRO, held Hepatitis B birth dose consultations to improve birth dose coverage. In Feb 2015, an AFRO workshop on birth dose introduction was conducted in Brazzaville; this workshop included guidance on birth dose monitoring. An assessment of birth dose implementation has taken place in Sao Tome Principe in July 2015 and Nigeria in September 2015 and in the Gambia in Dec 2015. Senegal held a Hepatitis B birth dose training workshop in Dec and introduced birth dose in Jan 2016.</p> <p>Guidance for hepatitis B birth dose introduction was published on June 2016 ('Preventing Perinatal Hepatitis B Virus Transmission: A Guide for Introducing Hepatitis B Birth Dose Vaccination', available from: <a href="http://www.who.int/immunization/documents/general/SBN9789241509831/en/">http://www.who.int/immunization/documents/general/SBN9789241509831/en/</a> in English, French and Spanish. An Arabic version is under development). The guidance includes a chapter on reporting and monitoring birth dose vaccination.</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	To date, WHO has not received any application from hepatitis B vaccine manufacturers to support the label change of prequalified hepatitis B vaccine.

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Hepatitis B	All regions and associated countries should develop goals for hepatitis B control appropriate to their epidemiologic situations. Serologic surveys of hepatitis B surface antigen (HBsAg) prevalence, representative of the target population, will serve as the primary tool to measure the impact of immunization and achievement of the control goals.	Nov 2008	Ongoing	<p>In 2017, it was approved to collect an additional variable on hepatitis B birth dose to distinguish birth dose vaccine administered within 24 hours (TIMELY) and any birth dose administered (TOTAL) as part of the WHO/UNICEF Joint Reporting Form (JRF). Previously only timely birth dose was requested.</p> <p>As of August 2017, all regions have had the regional committees (RCs) on immunization endorse hepatitis B control goals, except for the South East Asian Regional Office (SEARO) which as noted below had a 2016 ITAG recommendation to establish a goal. Regional goals slightly differ in target dates, threshold prevalence and specific ages in which to measure prevalence - but are largely similar nonetheless.</p> <p>In Sept 2016, the European Regional Office (EURO) held a consultation to discuss establishing a regional verification mechanism.</p> <p>In June 2016, the SEARO's ITAG recommended to establish a Regional control goal of less than or equal to 1% HBsAg sero prevalence by 2020 among children aged 5 years. In August 2015, an HQ mission took place to discuss HepB control targets.</p> <p>In August 2016, the The African Regional Office (AFRO) Regional Committee discussed adopting a viral hepatitis strategy in line with the Global Health Sector Strategy (GHSS) for viral hepatitis which includes a hepatitis B control target in-line (although more ambitious) with the target endorsed as part of the immunization strategy at the 2014 RC meeting.</p> <p>In April 2016, WHA Endorsed the GHSS for viral hepatitis that includes immunization-related 'elimination targets'; specifically to reduce chronic HBV infection rates (HBsAg prevalence) in children to at least 1% by 2020 and to at least 0.1% by 2030.</p> <p>In 2014, the AFRO RC meeting adopted resolution to reduce Hep B infection to &lt;2% among children under 5 years of age by 2020 and adopted hepatitis B activities as part of the RVAP that was also endorsed at the same RC meeting.</p> <p>The Eastern Mediterranean Region (EMR) has a RC goal of reducing childhood hepatitis B prevalence to &lt;1% among children &lt;5 years by 2015. Its regional office, EMRO is working with Member States to ensure achievement of this goal.</p> <p>The Western Pacific Region (WPR) established a RC goal to reduce hepatitis B infection to &lt;1% among children at least 5 years of age by 2017.</p> <p>The EURO will consider a regional hepatitis B control goal as proposed by ETAGE.</p> <p>The Pan American Health Organization (PAHO) has resolved to eliminate hepatitis B virus transmission and is formulating a regional strategy.</p> <p>Documenting the "Impact of Hepatitis B Immunization: best practices for conducting a serosurvey" (WHO/IVB/11.08) was published in 2011 by the department of immunization, Vaccines and Biologicals.</p> <p>In 2012, WHO HQ has published a framework for global action to control viral hepatitis (<a href="http://www.who.int/csr/disease/hepatitis/Framework/en/index.html">http://www.who.int/csr/disease/hepatitis/Framework/en/index.html</a>).</p>
HIV	SAGE requested regular updates on the progress of HIV-vaccine research.	Apr 2010	Ongoing	<p>The recent start of a phase 2b efficacy trial in South Africa constitutes an important progress in the HIV vaccine research and development area, building on the promising results from 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), and favorable results from a preparatory study in South Africa. The vaccination regimen in the upcoming HVTN 702 trial in South Africa will, like RV144, be based on a canarypox-based vaccine called ALVAC-HIV and a bivalent gp120 protein subunit vaccine, but will also include a new adjuvant, target HIV subtype C and include the addition of booster doses. Other live-attenuated candidate vaccine constructs are under evaluation in early clinical development. Finally there are major, and promising, vaccine science initiatives underway to attempt to induce broadly neutralising antibodies through re-engineered antigens. These have a longer time frame, but raise the prospect of cross-clade protection. WHO IVR is preparing for the organizing of a consultation on preparation for success, downstream access and use.</p>
Immunization schedules	SAGE requested that IVIR-AC assess optimal immunization schedules based on both direct and indirect effects and not only direct effects.	Oct 2015	Ongoing	<p>As part of any vaccine impact evaluation, IVIR-AC reviews and encourages studies of optimal schedules on both direct and indirect effects. Study projects and meetings have been held and are planned on HPV, Hep B vaccines, rotavirus vaccines among others.</p>

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Immunization schedules	SAGE requested a critical appraisal of alternative schedules for pneumococcal conjugate vaccine, rotavirus vaccine and Hib vaccine in 2011.	Nov 2010	Ongoing	<p>The funding grant from Bill &amp; Melinda Gates Foundation (BMGF) for schedules-related work to inform SAGE discussions on immunization schedules is now over. All delays in regard to this work were due to the Ebola outbreak and the R&amp;D Blueprint on staff responsibilities.</p> <ul style="list-style-type: none"> <li>- Pneumococcal Conjugate Vaccine (PCV): evidence was reviewed by SAGE in November 2011. A new position paper was published in 2012.</li> <li>- Rotavirus: evidence was reviewed by an ad-hoc group of experts in February 2012 and presented to SAGE in April 2012. An updated vaccine position paper was published in February 2013. A new review of evidence is ongoing.</li> <li>- Haemophilus influenzae type b (Hib): The issue was revised during the April SAGE 2013 meeting. A new position paper was issued.</li> <li>- Pertussis: evidence was reviewed by SAGE in 2015. A new position paper was published in August 2015.</li> <li>- Hepatitis B: evidence was reviewed by SAGE in Oct 2016. A new position paper was published in July 2017.</li> <li>- HPV: evidence was reviewed by SAGE in Oct 2016. A new position paper was published in May 2017.</li> <li>- TT vaccine: evidence was reviewed by SAGE in Oct 2016. A new position paper was published in February 2017.</li> <li>- Diphtheria: evidence was reviewed by SAGE in Apr 2017. A new position paper was published in August 2017.</li> </ul> <p>A consultation to develop analytic tools to support countries with the selection and/or adjustment of vaccine schedules in different epidemiological and operational scenarios took place in December 2016.</p> <p>With support from the BMGF we are updating the review of the evidence (epidemiology, vaccine efficacy and effectiveness, safety, risk benefit, impact). A consultation will take place in the fall of 2017. The review will include the two new vaccines.</p>
Implementation	SAGE recommended that WHO promote further progress in the area of implementation more actively, and that a preparatory team continue the dialogue and develop a more targeted agenda.	Apr 2016	Ongoing	<p>The WHO is currently implementing multiple World Health Assembly (WHA) resolutions that mandate integration of disease-specific programs, using a Health Systems Strengthening (HSS) framework to achieve Universal Immunization coverage as part of Universal health Coverage (UHC). This fits well with the Sage proposal to make integration a 'third pillar' of immunization service provision. Within the Gavi sphere, the Alliance has committed to having HSS underpin the Country Engagement Framework (CEF), under which all Gavi grants will be aligned and managed as a single package of results-focused investments. WHO Health Systems and Innovation (HIS)/Health Sys Governance, Policy &amp; Aid Effectiveness (HGS) has assisted the Gavi Alliance Partners and Gavi Secretariat in developing CEF. The WHO's Regional and Country Office HGS/HSS Focal Points are the organizational drivers for CEF engagement, providing technical Assistance on strategic, financial and operational integration of core immunization functions and systems.</p>
Implementation research	The implementation research agenda should define equity beyond traditional economic money metrics such as social economic status gradients, to include other measures of inequity such as the multidimensional poverty index or impacts on marginalized populations. SAGE suggested that studies to examine the integration of immunization with other health interventions should be included in the implementation research agenda.	Nov 2013	Closed	<p>This recommendation is part of the new Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) agenda under research to minimize barriers and improve coverage of vaccines currently in use. Since 2014 research topics on the non-specific effects of vaccines, missed opportunities and community vaccine acceptance have been part of the agenda of IVIR-AC.</p>

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Implementation Research	SAGE identified the conditions necessary for pertussis resurgence and the effective strategies for prevention of resurgence as important topics for modelling research.	Apr 2014	Ongoing	<p>The June 2015 meeting of the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) meeting agreed on the plan for phase 1 of the comparison of pertussis models from Australia, England &amp; Wales and the United States of America, which is meant to be a rapid assessment on the relative contributions of vaccine formulations, waning immunity, vaccine coverage and schedule to the observed pertussis resurgence in these countries. If successful, phase 2 offers further opportunities to test whether existing models are sufficiently robust to changes in factors such as demographics, spatial heterogeneity, immunity and contact matrices across multiple settings. In many countries using aP vaccine in the national immunization programme, aP vaccine is used in the private sector which represents a variable proportion of infant immunizations, so these complexities will need to be reflected when the models are extended to low and middle income settings.</p> <p>Phase 1 has been implemented and preparations are under development for Phase 2 and implementation will depend on funds being made available.</p> <p>Pertussis surveillance and laboratory capacity are still extremely poor in LMICs (particularly in Africa), and beyond the scope of the model comparison exercise to address. The committee noted that data are expected to be forthcoming through ongoing studies and follow-on analysis of maternal influenza trials, and strongly endorses the identification of further opportunities to add pertussis markers (primarily PCR on respiratory specimens) to studies such as Gavi- or the BMGF-supported vaccine impact studies.</p> <p>There were concerns that the opportunistic process by which the 3 models were identified may not have included all relevant parameters or modelling approaches. The feasibility of taking into account other models and parameters identified through a literature review and/or open call should be assessed, focusing on the main results of the different models for phase 1, and if they are interested to include them in phase 2.</p> <p>The work under Phase 1 has recently been completed by the modelers and will be shared with SAGE Chair soon for further follow up. Meanwhile the WHO burden of pertussis disease estimates have been updated by the WHO secretariat in collaboration with Hong Kong University. The global pertussis estimates for age under 5 have been published in Lancet Infect Dis. 2017 Jun 13. pii: S1473-3099(17)30390-0.</p>
Implementation Research	SAGE outlined some considerations for IVIR-AC to include in their deliberations – assessment of the use of high quality randomized controlled trials where feasible (noting the substantial ethical and methodological challenges involved), with sufficient power to explore sex differences, and a priori defined and standardized immunological endpoints designed to answer the specific question of non-specific effects– and emphasized that future research should draw on a broad investigator pool and from a wide range of geographic locations using a standardized protocol.	Apr 2014	Closed	<p>During the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) June 2015 meeting, IVIR-AC endorsed the designing of one or more protocols to assess the prospective non-specific effects (NSE) of immunization on mortality. The work of the WHO Secretariat needs to be completed in preparing the protocols for the questions identified and trials outlined during the ad-hoc expert consultation of Feb 2016. These generic protocols would enable harmonized implementation of the trials across multiple settings. While further development of all the proposed trial designs is important, IVIR-AC recognizes that full evaluation necessitates a complete protocol. IVIR-AC will help inform decisions on feasibility and the selection of designs, and formulate questions.</p> <p>At the February 2017 meeting, IVIR-AC reviewed the final proposals for 2 trial designs suggested by the ad-hoc Working Group on NSE. It was presented at the SAGE April 2017 meeting as part of the briefing of IVIR-AC by chair Rob Breiman.</p>
Influenza	SAGE issued the recommendation to establish a Working Group on influenza vaccines.	Apr 2017	Ongoing	<p>A call for nominations will be issued in September/October 2017 to solicit candidates interested in serving on the Working Group.</p>

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Integration	WHO should discuss and develop guidelines on how to fully integrate vaccination (GVAP) into the operation of all aspects of the health-care system and to reduce missed opportunities to vaccinate.	Oct 2014	Ongoing	<p>During the April 2016 SAGE meeting, SAGE members were successfully updated on the ongoing work in AFRO, PAHO and SEARO on using the missed opportunities for vaccination (MOV) strategy to facilitate the integration of immunization with other health services. Following the SAGE session, WHO received multiple requests from countries for technical assistance to implement the MOV strategy in additional countries. Based on MOV assessments conducted in Chad and Malawi in 2015 (draft manuscripts prepared for peer reviewed journal submission) and Kenya in 2016, WHO has developed a set of updated guidance documents and field tools that will be finalized and published in Q4-2017. These include: a planning guide, the assessment methodology (including the MOV protocol, sample questionnaires and generic field tools) and an intervention guidebook. In the meantime, WHO has launched a web page with the draft materials for easy access.</p> <p>Having strengthened the capacity of AFRO to implement MOV assessments (Chad, Malawi, Burkina Faso (led by partner AMP), Kenya, DRC and Nigeria completed; Mozambique and Zimbabwe in planning stages for Q4), collaboration is ongoing with SEARO (MOV assessment completed in Timor Leste; interventions are ongoing) and WPRO (MOV workshop is being planned and supported in Cambodia, in collaboration with CDC). A network of partners engaged in MOV has been established since March 2016 to provide regular briefings 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 third partner coordination call took place on January 26, 2017, the next call will take place in Oct 2017.</p> <p>In May 2017, WHO held a training workshop in AFRO for partners and consultants on the MOV strategy with the objectives of training a pool of consultants to support countries in planning and conducting MOV assessments, to further strengthen the regional, subregional and country capacity for MOV work and to serve as a platform to discuss opportunities to address MOV and improve routine immunization coverage. The workshop was attended by 8 partner organizations (CDC, UNICEF, VillageReach, AMP, MSF, JSI, SA-MRC, CHAI), WHO-CO, partner and MOH staff from 8 countries (Cameroun, Ethiopia, Liberia, Mozambique, Nigeria, Uganda, South Sudan, Zimbabwe) and WHO colleagues from HQ, AFRO and IST-Eastern and Southern.</p>
IVIR-AC	SAGE noted that a sub-group of IVIR-AC members and external subject experts should make recommendations on the types of prospective studies to assess the non-specific effects of vaccines.	Oct 2014	Closed	<p>An ad-hoc consultation on clinical trials for non-specific effects of vaccines (NSE) was held on 16-17 February 2016. Eighteen experts (including 3 IVIR-AC members) contributed to this consultation, whose main objectives were to reach a consensus on priority trial questions and to propose trial designs for each of the priority questions. Protocol synopses for the six different trials that the experts proposed were prepared for review and discussion at June 2016's IVIR-AC meeting. At the February 2017 meeting IVIR-AC reviewed the final proposals for 2 trial designs suggested by the ad-hoc working group on NSE. It was presented at the SAGE April 2017 meeting as part of the briefing of IVIR-AC by the chair, Rob Breiman. Currently IVIR-AC will not further assess NSE.</p>
IVIR-AC	IVIR-AC should seek linkages with the WHO Alliance for Health Policy and Health Systems Research as they might be useful in priority setting and discussions.	Oct 2014	Ongoing	<p>The Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) secretariat have had initial discussions with WHO staff of the Alliance for Health Policy and Health Systems Research (HPHSR) to update on the IVIR-AC deliberations in September 2014. Discussions for concrete steps for their involvement in vaccine implementation research are ongoing. The WHO Alliance for HPHSR will have a seat in the WHO Secretariat of the IVIR-AC. In addition, Initiative for Vaccine Research (IVR) was involved in a call for proposals issued by the WHO Alliance with financial support from Gavi and UNICEF on implementation research studies in low and middle income countries (LMICs) in 2015. Seven proposals have been selected for funding and being implemented with a one year timeline until 2016. A new funding proposal was prepared for 2016-2017 with support from Gavi and UNICEF. New projects have been granted and a workshop on implementation research protocol development took place in August 2016.</p>

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
IVIR-AC	SAGE encouraged WHO to complete the public consultation and the publication and dissemination of the protocols on non-specific effects (NSE) of vaccines.	Apr 2017	Ongoing	WHO has solicited public comments on the draft protocol synopsis until 15 September 2017 and is currently finalizing these. Their formal publication is anticipated by the end of 2017. ( <a href="http://www.who.int/immunization/research/implementation/nse_protocol_comments/en/">www.who.int/immunization/research/implementation/nse_protocol_comments/en/</a> ).



Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
<p>Lower middle-income countries: sustainable adoption and financing for new vaccines</p>	<p>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.</p>	<p>Nov 2010</p>	<p>Ongoing</p>	<p>WHO set up a Middle Income Countries (MIC) Task Force in June 2014 with main immunization stakeholders (WHO, UNICEF, World Bank, Gavi Secretariat, BMGF, AMP, Sabin, Task Force for Global Health), which led to the creation of the "MIC strategy", presented at SAGE in April 2015. The strategy aims at improving sustainability of immunization programmes and access to vaccines in non-Gavi MICs. The MIC strategy is based on four pillars : i) Strengthening evidence-based decision-making; ii) Enhancing political commitment and ensuring financial sustainability of immunization programmes; iii) Enhancing demand for and equitable delivery of immunization services; and iv) Improving access to timely and affordable supply.</p> <p>The timeline for the strategy is up to 2020 to align with the GVAP timeframe and up to 2025 for a longer term horizon. In the longer term, the MIC strategy could provide a platform to ensure sustainability of Gavi's investments in fully self-financing countries.</p> <p>Following SAGE endorsement of the MIC Strategy in Apr 2015, the WHO-led MIC Task Force initiated a country engagement process: in collaboration with key immunization partners WHO started multi-partner dialogues with four countries struggling with raising or maintaining high immunization coverage and/or introducing new vaccines. With each of these countries, the MIC Task Force has identified obstacles to achieving and sustaining the immunization system performance and potential solutions to reaching GVAP targets through plans of action. The MIC Task Force selected four countries for the MIC strategy implementation based on potential for impact (birth cohort, coverage of traditional vaccines, status of new vaccines introduction) and feasibility of engagement. Selected countries are Romania, Swaziland, Jordan and Philippines. Countries are at different stages of implementation of their plan of actions, but concrete results are starting to show (e.g. Philippines formal decision to procure all vaccines through UNICEF in the mid term while strengthening procurement skills, and concrete steps towards creation of a functional NITAG, UNICEF-SD support to Jordan for procurement to PCV).</p> <p>Also, some efforts to support all MIC countries in the area of access to timely and affordable supply have been implemented. Notably, the creation of a mechanism for access to supply in humanitarian emergencies in MICs not supported by Gavi; set up of a peer platform and regional workshop to strengthen country procurement capacity; work on price transparency continues successfully with 85% of world (n. of countries) sharing vaccine product, price and procurement information since the beginning of WHO price transparency efforts. 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. As it close, the MIC TF made the following recommendations:</p> <p>1- The TF expressed important concerns regarding funding for implementation of the MIC Strategy and called for fundraising efforts by its member organisations or other appropriate coalition of partners. For these purposes it proposed continued awareness raising on the MIC issue through:</p> <p>A- Development of an advocacy tool to be developed starting from technical background documents prepared for the SAGE April 2015 meeting. A time limited and informal Steering Committee of some TF members (WHO, UNICEF, TFGH and other as interested) could be set up to follow work by external consultants. Due to human resource constraints this has not been developed.</p> <p>B- Regular monitoring &amp; reporting on MIC progress against GVAP as well as monitoring of implemented activities against intended activities under the MIC strategy (dashboard). For the first time the GVAP report this year includes a dedicated chapter for MICs to respond to this request.</p> <p>2-The TF agreed on the importance to ensure completion of pending tasks and enhance smooth transitioning as the TF sunsets.</p> <p>3- 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>

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Malaria Vaccine	SAGE requested continued review of the planning of the pilot implementations and to receive regular updates on the results.	Oct 2015	Ongoing	<p>Ghana, Kenya and Malawi were officially announced as the 3 pilot countries to participate in the Malaria Vaccine Implementation Programme (MVIP) by the WHO Regional Office for Africa on 24 April 2017. Progress has been made with the 3 funding agencies, Gavi, the Global Fund and Unitaid, to formalize the terms of the agreements expected to provide funding of up to US\$49.2 million for phase 1 of the MVIP for the period July 2017 to December 2020. Finalization of the bilateral agreements is expected in Q3 2017. Interim funding provided by PATH to WHO through a grant from the Bill and Melinda Gates Foundation, together with the PATH's existing grants from the Gates Foundation, has so far allowed critical activities to proceed.</p> <p>All pilot countries have initiated the development of vaccine introduction plans, preparatory activities to strengthen pharmacovigilance and planning for communications activities. First vaccine introduction is currently still anticipated for mid-2018. WHO developed a master protocol for the pilot evaluations which was reviewed by the WHO Research Ethics Review Committee (ERC) on August 3, 2017 and submitted to the European Medicines Agency as part of GSK's risk management plan. Feedback from the ERC and EMA reviews will be addressed in a revised version of the master protocol.</p> <p>On 18 May 2017, WHO released a Request for Proposals (RFP) to identify research partners to conduct the pilot evaluations in the 3 pilot countries. Bids were opened on 30 June 2017 and submissions are currently under review by a Proposal Review Committee. Selection in principle of research partners in September 2017 will enable in-depth discussion of their technical and financial proposals to proceed and contracts to be awarded in the final quarter of 2017.</p> <p>Updates on the MVIP were provided to the AFRO RITAG and the Global Advisory Committee on Vaccine Safety (GACVS) in June 2017. GACVS recommended a set of pharmacovigilance readiness criteria for the 3 participating countries and will continue to provide advice and support to the pilot countries and to the planned MVIP Data Safety and Monitoring Board.</p> <p>GSK has committed to re-start the RTS,S bulk manufacturing site (which has been idle since 2015) in order to meet the needs of the pilots and lay the foundation for vaccine supply in the longer term should the vaccine be recommended for broader use based on the experience from the MVIP. The formal collaboration agreement between WHO, PATH and GSK to define roles and responsibilities in the MVIP, including a quantification of the required vaccine supply and longer term access provisions, has not yet been finalised.</p>
Maternal immunization	SAGE recommended that WHO endorse the importance and ethical imperative of clinical trials in pregnant women for potentially life-saving interventions such as RSV vaccine (and future vaccines against other targets currently in development, such as group B streptococcal disease).	Apr 2016	Closed	<p>WHO is promoting vaccine trials be conducted in pregnant women. Updated TRS guidance for vaccines includes a section on trials in pregnant women. WHO Draft Preferred Product Characteristics for Next Generation Influenza Vaccines includes advocacy for clinical trials in pregnant women.</p> <p>Also, IVR has supported two efforts evaluating the ethics of maternal immunization:</p> <ol style="list-style-type: none"> <li>1) Beeler JA, Lambach P, Fulton TR, Narayanan D, Ortiz JR, Omer SB. A systematic review of ethical issues in vaccine studies involving pregnant women. Hum Vaccin Immunother. 2016 May 31:1-8. [Epub ahead of print] PubMed PMID: 27246403, and</li> <li>2) Verweij M, Lambach P, Ortiz JR, Reis A. Maternal Immunisation: Ethical Issues. In press at Lancet Infectious Diseases.</li> </ol> <p>Both publications advocate for the ethical imperative of clinical trials in pregnant women.</p>
Maternal Immunization	SAGE encouraged the Regional Office for the Americas to document the successful regional experience of delivering influenza vaccine to pregnant women.	Apr 2015	Ongoing	<p>Regarding the Pan-American Health Organization's (PAHO) documentation of the successful regional experience of delivering influenza vaccines to pregnant women, PAHO has progressed with its in-depth survey to develop case-studies with key countries that have acquired a lot of experience in maternal immunization (currently ongoing in three countries). Also, PAHO has published its field guide for maternal immunization (in English and Spanish). It is available from <a href="http://www.paho.org/hq/index.php?option=com_content&amp;view=article&amp;id=13445%3Amaternal-and-neo-natal-immunization-field-guide-for-latin-america-and-the-caribbean&amp;catid=6774%3Aslide-show&amp;Itemid=40557&amp;lang=en">http://www.paho.org/hq/index.php?option=com_content&amp;view=article&amp;id=13445%3Amaternal-and-neo-natal-immunization-field-guide-for-latin-america-and-the-caribbean&amp;catid=6774%3Aslide-show&amp;Itemid=40557&amp;lang=en</a>.</p>

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Maternal Immunization	SAGE concluded that the recommending bodies, including WHO, need to engage in a dialogue with regulators and manufacturers to review current regulatory practices against the evidence on risks and benefits and biological plausibility on product safety. SAGE requested WHO to develop a process and a plan to move this agenda forward in support of an increased alignment of data safety evidence, public health needs and regulatory processes.	Nov 2013	Ongoing	WHO has completed evaluations of product monograph language regarding safety and use during pregnancy, as well as a survey of health care provider's perceptions of the specific product monograph language regarding use in pregnancy. WHO has reviewed various regulatory approaches to labelling of the pregnancy and lactation sections of product inserts and has produced a document titled, "Labelling information of inactivated influenza vaccines for use in pregnant women." The document was reviewed and endorsed by Expert Committee on Biological Standardization (ECBS) in late 2016. Future vaccines intended for use by pregnant women will undergo phase III trials in pregnant women. Currently available vaccines recommended for use in pregnancy (influenza, tetanus, acellular pertussis) are unlikely to have phase III trials necessary for an indication for use during pregnancy, however, there is regulatory consensus that pregnant women are not contra-indicated from receiving vaccines merely because a product is not indicated for use in that group.
Maternal Immunization	SAGE encouraged WHO to promote more implementation research to generate generalizable data on the best ways to integrate maternal immunization into routine antenatal care in low resource settings	Apr 2015	Ongoing	WHO's Initiative for Vaccine Research (IVR) is in the process of producing many implementation research tools and guidance regarding: 1) assessment of vaccine confidence/hesitancy in pregnant women; 2) maternal influenza immunization program costing tool; 3) guidance document to estimate the influenza economic burden of a country (not pregnancy specific); 4) guidance document to estimate the cost effectiveness of influenza vaccines in a country (not pregnancy specific); 5) field guide for the evaluation of influenza vaccine effectiveness (not pregnancy specific); and 6) implementation guidance document. IVR is collaborating with several research and public health groups to pilot some of these tools in low and middle income countries.
Measles	SAGE recommended that the most expeditious clinical development and regulatory pathway to licensure of measles containing vaccines (MCV) micro-array patch (MAP) be determined, and that barriers to the development, licensure, and use of MAPs for measles and rubella vaccine delivery be identified and addressed urgently.	Oct 2016	Ongoing	Pending approval of financial support, a Measles and Rubella/ micro-array patch (MAP) Working Group (WG) will be set up in Q4 of 2017 to develop a clinical regulatory pathway. The outcomes and recommendations from this WG will be shared with SAGE in 2018.
Measles	SAGE supported the development by WHO of a standardized method to categorize countries based on their level of disease control and likelihood of achieving and sustaining measles and rubella elimination, and tailoring immunization and surveillance strategies to the country categorization.	Oct 2016	Ongoing	The categorization of countries was discussed by the Measles and Rubella SAGE Working Group as well as the regional verification commissions chairs and the measles and rubella regional focal points. The final categorization was agreed upon and will be reported on at the October 2017 SAGE meeting.
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. However, further analysis is needed before the current recommendations can be refined.
Measles	SAGE requested evidence on the need for measles revaccination of HIV-infected adolescents and adults. Further research is needed to monitor the long-term immune responses to measles vaccine in HIV-infected children revaccinated after starting HAART and in HIV-infected children starting HAART prior to receiving their first dose of MCV.	Oct 2015	Ongoing	A systematic review of the evidence on the need for measles revaccination of HIV-infected adolescents and adults was completed and will be presented at the October 2017 SAGE meeting.

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Measles	SAGE recommended further clinical, immunological, epidemiological and modelling studies regarding the impact of different measles vaccination schedules.	Oct 2015	Ongoing	The RIVM in the Netherlands conducted a systematic review on the safety and effectiveness of MCV prior to 6 months of age. The findings from this review will be presented at the October 2017 SAGE meeting.
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: <a href="http://www.who.int/wer/2015/wer9008/en/">http://www.who.int/wer/2015/wer9008/en/</a> . Ten of the 26 meningitis belt countries have received approval from Gavi, the Vaccine Alliance for introduction of the meningococcal A conjugate vaccine into their routine immunization programme, with a single dose at 9, 15 or 18 months of age concomitantly with the administration of the first or second dose of Measles/Rubella vaccine. Among them, 6 countries have launched their introduction at the age of 9 months (Sudan, July 2016; Mali, Feb 2017; Central African Republic, June 2017; Chad, July 2017); at the age of 18 months (Ghana, November 2016) and at the age of 15 months (Burkina Faso, Mar 2017), respectively. The remaining four countries intend to do so in 2017 (Niger and The Gambia) or in 2018 (Côte d'Ivoire, Nigeria). Another 3 countries (Guinea; Guinea Bissau; Togo) have applied to Gavi through its new country engagement framework for an introduction in 2019. Other meningitis belt countries intend to apply for the introduction of the vaccine into their routine programme at the next Gavi application windows in Sep 2017, Jan 2018 and May 2018.
MNTE	Where feasible, the use of serosurveys to validate assessment of risk identified from other data sources should be considered to guide vaccination strategies, especially in high-risk districts. Close attention should be paid to sampling strategies and laboratory methods to ensure that results are valid and interpretable. WHO should provide guidance on: sampling methods; sample collection and testing; and analysis, interpretation and use of serosurvey data for monitoring. WHO should consider establishing reference laboratories and reference serum panels to support standardization and quality assurance of the laboratory methods used in serosurveys.	Oct 2016	Ongoing	This recommendation has not yet progressed much. WHO has, however, initiated discussions with the US CDC on the feasibility of combining some of the MNTE validation surveys with serosurveys.
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	Efforts are currently going on to submit a proposal to the Gavi Alliance Policy and Programme Committee to request for financial assistance to support the production and availability of this critical pre-filled device aimed at markedly increasing access to the Tetanus Toxoid vaccine to very remote parts of some selected countries where currently access is seriously compromised as a result of insecurity, active conflicts and lack of human resources. A concept note is being finalized in the context of using this initiative as a test case to assess the Total System Effectiveness (TSE) to support the use of TT in the uniject presentation to achieve public health objectives. The TSE in the context of innovation and markets is new and BMGF is actively involved in this effort.
MNTE	UNICEF, UNFPA, and WHO should urgently develop an MNTE investment case and resource mobilization strategy to secure predictable and timely funding support for the remaining 18 countries, if the 2020 elimination timeline is to be met.	Oct 2016	Ongoing	There is currently a collaborative work by WHO, UNICEF and The United Nations Population Fund (UNFPA) that has led to contracting the University of North Carolina to conduct the work on the investment case for MNTE. Work is progressing in earnest, and the first phase of the work focusing on the attainment of elimination by the 16 remaining priority countries is expected to be completed by the end of 2017. Discussions on the second phase of the investment case work on sustaining MNTE have started.

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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	A stakeholder's meeting was convened at the end of Nov 2016 to follow up on this. Other efforts include the concept note produced to follow up on funding for Tetanus Toxoid Uniject from Gavi, the Vaccine Alliance, with active collaboration of the Bill and Melinda Gates Foundation and the work on the investment case that is anticipated to facilitate resource mobilization to help support countries to implement their elimination activities.
MNTE	UNICEF, UNFPA and WHO should work with countries to generate and sustain political commitment to maintaining elimination of MNT, in order to guard against complacency once a country has been declared to have achieved elimination.	Oct 2016	Ongoing	All opportunities including the Regional Immunization Technical Advisory Group (RITAG) meetings and Immunization Managers' meetings are being utilized to advocate for efforts by countries to sustain their Maternal and Neonatal Tetanus Elimination (MNTE) status. Update on the status of implementation of the AFR RITAG recommendations were presented at the annual meeting of the AFR RITAG in June. MNTE was one of the topics discussed at the SEAR and WPR TAG meetings in June 2017 as well. Additionally, efforts are being made to finalize the guidelines on sustaining MNTE to ensure that countries are guided through the appropriate steps to take to sustain their achievements.
Multiple injections	SAGE noted the need for further research on multiple injections during the same visit and recommended the following research topics and activities: (i) impact of multiple injections in the same visit on vaccine coverage, disease reduction, vaccine programme success and caregiver and provider experience; (ii) development of a standardized monitoring protocol for acceptance and acceptability by caregivers and providers and for prevalence of adverse events; (iii) development of optimal provider and infant caregiver communication approaches; (iv) optimal multiple injection administration techniques, and (v) development of new technologies, such as intradermal patches and new combination vaccines, which would decrease the number of vaccine injections in a single visit.	Apr 2015	Ongoing	Multiple injection studies have been conducted in collaboration with US CDC in South Africa, Gambia, and Albania, with studies ongoing in the Philippines, Sudan, and Columbia. Studies are primarily designed to evaluate healthcare provider and infant caregiver attitudes and practices regarding administration of multiple injectable vaccines in the same visit, in most cases following the introduction of IPV and PCV. A new time motion study is also being initiated in Uganda and another country in the African region. The findings of these studies will feed into the development of any further guidance required to address concerns related to multiple injections and pain.
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 is planned for September 2017 to discuss ways forward. The US CDC had drafted an article on this topic for a peer-reviewed journal, which should be published by end of this year.

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National Immunization Technical Advisory Groups (NITAGs)	SAGE recommended that tailored guidance, tools, training, mentoring programmes and sharing of information are needed to assist NITAGs. Therefore, SAGE stressed that initiatives such as the Global NITAG Network and the NITAG Resource Centre are essential and that these would require dedicated financial and human resources. SAGE further noted that NITAG evaluations are important beyond the current process indicators and should be continued and supported by countries and partner institutions. NITAG evaluations need to focus on function, quality and integration.	Apr 2017	Ongoing	The second Global NITAG Network (GNN) meeting was successfully held from the 28th to 29th of June 2017 in Berlin, Germany. The meeting was attended by 38 NITAG country representatives (NITAG Chair, member or secretariat) from a total of 26 countries. During this meeting the GNN was formally established and its strategic document endorsed. A next meeting in 2018 is envisaged, likely to take place outside Europe. WHO is creating a post to ensure the secretariat of GNN and the sustaining of further development of the NITAG Resource Centre.
Pain mitigation	SAGE recommends that WHO: 1) includes pain mitigation recommendations with WHO immunization practice guidance materials; 2) disseminates pain/distress mitigation recommendations through the usual dissemination channels, immunization managers, National Immunization Technical Advisory Group (NITAG) and partner organizations; 3) monitors and evaluates the implementation success of pain mitigation measures; 4) works with industry, ECBS and regulatory agencies to advocate that grading of pain experienced during the vaccine injection be included in data for licensing and in the product monograph.	Apr 2015	Ongoing	Internal discussions have taken place on how to move forward across relevant WHO departments. A brief position paper was drafted based on the SAGE recommendations and published in the Weekly Epidemiological Record on 25 September 2015. This formed the basis for additional proactive communication activities. As example of actions in response to points 1 and 2, WHO ensured that information in WHO guidance on multiple injections and IPV was consistent with the SAGE recommendations on reducing pain, specifically in two documents: Practical considerations for the successful introduction of IPV, and Multiple Injections: Acceptability and Safety, both available on this web page. The WHO position paper on reducing pain was also added on the same web page. In relation to the training aspects for IPV introduction, we updated training modules for health workers, also to reflect the recommendations from the latest WHO position paper. The Immunization in Practice recently published has in module 5 'Managing immunization sessions', recommendations on vaccine sequence (increasing pain- oral before injection, rota before OPV), positioning the recipient, no aspiration etc. IPV has been distributed to countries and the last edition was also translated into several local languages. Work is also ongoing to ensure appropriate incorporation of pain mitigation in WHO guidance documents when they get updated and to ensure that any recommendation posted on the web at odds with SAGE's guidance be adjusted/removed. The pain mitigation guidance has been included in the NITAG resource center. As a further example of use and integration in WHO documents, reference to the pain mitigation position paper has been made in the recently published updated tetanus position paper. PDVAC will consider pain mitigation within their preferred product characteristics to guide target product profiles. Steps have been taken and discussions started to also reflect the measurement of pain at time of injection in the updated Guidelines on clinical evaluation of vaccines were discussed and endorsed by ECBS in October 2016. They allude to pain mitigation. More specific activities still need to be implemented with respect to points 3 and 4.
Polio	SAGE requested that WHO review its tier classification of countries with respect to prioritization of IPV to take into account the size of the population with no IPV protection and the recent VDPV2 events.	Apr 2017	Ongoing	WHO, in collaboration with partners, is working on updating its tier classification of countries with respect to prioritization of IPV. It will be presented to the SAGE Working Group in September 2017 and to SAGE in October 2017.

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Polio	SAGE advised GPEI to accelerate implementation of the WHO Global Action Plan for containment (GAPII) including: a) all countries completing phase I; b) regional focal points closely monitoring country activities and ensuring each country completes its inventories of facilities that hold or handle polioviruses, and destroys or commits to destroying WPV2 by end 2015 and any other type 2 containing materials including Sabin poliovirus by July 2016.	Oct 2015	Ongoing	As of 27 Jul 2017, all 223 countries and territories have completed their reports on the first part of Phase I. However, the release of mOPV2 in 8 countries for post-switch cVDPV-outbreak response will require these countries to repeat their surveys and inventories and revise their reports. 94 countries or territories have reported that they no longer retain any OPV2/Sabin2 materials. The completion of this second part of Phase I will follow the publication of WHO's 'Guidance for non-polio facilities to minimize risk of sample collections potentially infectious for polioviruses', pending endorsement by the Containment Advisory Group (CAG) planned for end-November 2017. For Phase II, 31 countries reported the intention to retain PV2 materials (WPV2 or OPV2/Sabin2) in 90 designated poliovirus-essential facilities (PEFs). 18 of these countries have nominated a national authority for containment (NAC).
Polio	SAGE urged WHO to facilitate discussions and decision-making by National Immunization Technical Advisory Groups (NITAGs) to introduce IPV intradermal fractional dose use by providing necessary technical information.	Oct 2016	Ongoing	WHO prepared the communication and technical materials to National Immunization Technical Advisory Groups (NITAGs). The WHO secretariat is advocating for the use of fractional dose IPV at both regional and country technical advisory group meetings (TAGs).
Polio	SAGE noted that the IPV supply situation is further deteriorating. Therefore, the programme should explore the possible use of devices facilitating intradermal administration (e.g. jet injectors, intradermal adapters).	Oct 2016	Ongoing	WHO is working on pre-qualification of both jet injectors and intradermal adapters. In addition, WHO is conducting several pilots of the use of these devices in immunization campaigns (e.g. Karachi, Pakistan).
Polio	SAGE requested WHO to complete the guidance on identification of potentially infectious materials (including stool and respiratory specimens) into 3 groups based on likelihood of being contaminated with VDPV2 or WPV2.	Oct 2016	Ongoing	A revised draft of the 'Guidance for non-polio facilities to minimize risk of sample collections potentially infectious for polioviruses' has been submitted to the Containment Advisory Group (CAG) at their first meeting of 19-20 June 2017, with a request to reconsider the handling and storage conditions for poliovirus genetic materials, currently requiring full containment according to GAPII. The draft guidance is being revised based on CAG recommendations and comments from CAG meeting participants, and will then be posted on the web for a period of public comments and pilot testing. Feedback collected will be included in the final version that is planned to be submitted to CAG at their second meeting of 28-30 November 2017 for endorsement and publication.
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	Capturing this information is integrated into the country-level transition planning guidelines, and the work of the Transition Management Group of the Global Polio Eradication Initiative is emphasizing the importance of this. All Transition Planning consultants are briefed/ trained on the Transition Guidelines.
Polio	SAGE requested its Polio Working Group (WG) to provide urgent guidance on optimal management of IPV supply and mitigation of other risks in case the IPV supply is further reduced.	Oct 2015	Ongoing	The IPV supply situation is being closely monitored. An update from the September Polio Working Group meeting, including on discussions with vaccine producers, will be provided during the October 2017 SAGE meeting.



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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	Inter-Cluster Transition Steering Committees have been established in both WHO Regional Office for Africa (AFRO) and WHO Regional Office for the Eastern Mediterranean (EMRO). They are chaired by the Directors Programme Management of the respective Regions. The Regional Offices are also members of the WHO Global Polio Transition Steering Committee established by the Director-General's Office. Headquarters (HQ) and Regional Colleagues are members of the Global HR Working Group that is planning for the effective and efficient reduction in the Polio Staffing levels in countries, regions and HQ. Guidance on Transition Planning, and Budget Rampdown figures for 2017 - 2019 have been provided to AFRO, EMRO and Regional Office for South-East Asia (SEARO), and the 16 polio priority transition countries by the Global Polio Eradication Initiative (GPEI) through the Transition Management Group (TMG) and all three Regions are Members of the TMG. Financing has also been provided through the TMG to support Consultants, vetted by the Regional Offices, who are assisting priority countries in developing transition plans. Both AFRO and EMRO are also involved in the development of a Business case for Immunization in the African continent as a follow-up to the Addis Declaration on Immunization. Polio transition and its consequences will inform this business case. AFRO, EMRO and SEARO all decided to hold a specific session/side meeting on transition planning in their Regional Committee meetings in 2017. EMRO Inter-cluster Steering Committee decided to review the country plans of the countries in the EMRO Region by an interdepartmental regional team.
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	While a communications officer to focus on containment is currently being recruited and a communication plan is being finalized, articles providing details of global progress with containment have been published in June 2017 in MMWR and WER. The WHO Containment team is organizing advocacy in-country visits with NACs and PEFs to support the nomination of NACs and encourage the engagement of PEFs and NACs in containment certification activities, including the issuance of certificates of participation (CPs). Deadlines for CP applications and other containment measures will be discussed at the next GCC meeting of 23-25 Oct. WHO is training GAPIII auditors nominated by the NAC to assess PEFs against the implementation for GAPIII. Containment certificates will be delivered by NACs in consultation with GCC. So far however, GCC has not received any application yet.
Preferred Product Characteristics	SAGE noted the utility of Preferred Product Characteristics (PPCs) to developers and funders, and proposed that the opportunity for input into future PPCs at an early stage for any vaccine of public health importance could be included as part of SAGE's global public health mandate.	Apr 2013	Ongoing	Since this recommendation, the Product Development for Vaccines Advisory Committee (PDVAC) has been created, and identified as the WHO committee responsible for overseeing the PPC generation process and content. PDVAC has emphasized the need for several PPC documents to be developed by WHO IVR. PPCs for Group B streptococcus and RSV vaccines have been finalized. Target Product Profiles for emerging pathogens have been developed as part of the Blueprint initiative. PPCs for new tuberculosis vaccines, next-generation influenza vaccines influenza vaccines, Group A streptococcus, ETEC, Shigella and Herpes Simplex Virus 2 are under development. PPCs when finalized and ready for public circulation are posted on the WHO IVR website.
Private sector engagement with national immunization programmes	SAGE applauded the development of the draft guidance as an initial step in tackling this area of work and urged WHO to finalize a common framework starting with a set of core principles.	Apr 2017	Completed	As requested by SAGE the "WHO Guidance Note: Engagement of private providers in immunization service delivery. Considerations for National Immunization Programmes" has been revised and particularly shortened. The WHO Guidance Note was published in September 2017 and can be retrieved through the following link: <a href="http://www.who.int/immunization/programmes_systems/policies_programmes/Private_sector_immunization.pdf?ua=1">http://www.who.int/immunization/programmes_systems/policies_programmes/Private_sector_immunization.pdf?ua=1</a>

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Regulatory	SAGE recommended that the further development of the Emergency Use Assessment and Listing procedure being developed by WHO, which would allow use of a vaccine in the context of a Public Health Emergency of International Concern, be done in close consultation with relevant regulatory authorities, including those of the affected countries.	Apr 2015	Ongoing	Regarding the Emergency Use Assessment and Listing (EUAL) procedure, the WHO Prequalification Team took note of SAGE recommendation and further development of the EUAL will consider relevant regulatory authorities including those of impacted countries. Further, a document entitled, "Vaccine evaluation in public health emergencies – review of regulatory pathways in selected countries" was prepared and presented to SAGE working group (WG) on Ebola vaccines in Aug 2015. In Oct 2015, the document was submitted to the Expert Committee on Biological Standardization (ECBS) for review and advice. The Committee considered that a guidance document might be of value to National Regulatory Authorities (NRAs) and other public health organizations. However, it also recognized the complexity of emergency situations, each of which is essentially unique, and that decisions ultimately rest on a benefit/risk assessment. The ECBS reviewed the document's progress in 2016. Evaluation of vaccines for public health emergencies was discussed in the 3rd meeting of the WHO Collaborating Centers Network on Vaccines in Seoul, in July 2016. Lessons learned from the Ebola crisis in West Africa and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in Korea were discussed and several activities of the CC network were proposed. In addition, new initiative called the Coalition for Epidemic Product Innovation (CEPI) was discussed as a framework in which a number of partners will work together to assure better preparedness for public health emergencies in future. The ECBS was also briefed about the CEPI in Oct 2016. The CEPI initiative led to the establishment of a Regulatory Working Group in 2017 with the focus on data requirements for product development in the absence of an outbreak, regulatory issues related to stockpiling and the use of stockpiled products during the outbreaks.
Reports from other advisory committees on immunization	SAGE recommended appointment of appropriate programmatic and implementation expertise to IVIR-AC membership including representation of experts from low and middle-income countries.	Nov 2011	Ongoing	Since 2013, Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) includes 2 programmatic and implementation research members from the African Region (AFR) and the South East Asian Region (SEAR). Since 2014, IVIR-AC includes a mathematical modeler/economist from SEAR and a medical anthropologist from AFR. There was a call for new members in 2015. Three potential candidates were selected to attend the June 2015 meeting. The mathematical modeler was selected to become a member but the two health economists were not selected as they did not meet the expectations. A new call for Committee Members was issued in Q3-Q4/2016. Five new members have been recruited with expertise in vaccinology, epidemiology, vaccine economics, modeling and social science.
Reports from other advisory committees on immunization	WHO and NIBSC should develop with other stakeholders, a business plan to assure long-term security of the development of WHO reference preparations as a global public health resource and additional efforts should be undertaken to disseminate outcomes of the committees deliberations and to explain the relevance of its work to the broader immunization community.	Nov 2006	Pending	A network of WHO Collaborating Centres (CC) on the Standardization of Vaccines has been established. At its 3rd meeting, the network agreed to establish a "Core Expert Group (CEG)" to assist the Expert Committee on Biological Standardization (ECBS) to review selected proposals for measurements standards. Proposals for replacement measurement standards are usually straightforward, with few strategic or scientific issues, and they would be the initial focus of the CEG. The ECBS agreed that the CEG could pre-review selected measurement standards in the vaccines area and thus help to streamline the ECBS review process. A drafting group on Men B guidelines was established as a part of CEG activity on written standard and report will be submitted to ECBS for discussion. Review of measurement standards will be conducted in September and feedback from CEG will be submitted to the ECBS. Further discussion on the activities of the CEG is going to take place at the ECBS meeting from 17 to 20 October 2017.

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RSV	SAGE asked for preparations to be made to support global policy-making for respiratory syncytial virus (RSV) maternal immunization as well as passive immunization with long-acting mAb. SAGE emphasized the need to link maternal immunization platform strengthening with influenza, tetanus and pertussis vaccines along with preparations for potential country introductions of RSV vaccine.	Apr 2016	Ongoing	Further discussions have been held with the WHO Prequalifications (PQ) team with regard to prequalification processes for both respiratory syncytial virus (RSV) vaccines and monoclonal antibodies (mAbs). The ECBS Guidelines for RSV vaccines are planned for development and possible adoption at Expert Committee on Biological Standardization (ECBS) 2018, as these are a prerequisite for consideration for PQ. The Essential Medicines and Health Products (EMP) department is considering an approach to PQ of mAbs. Intensive discussions continue about the most appropriate way to prepare for policy-making in Low and Middle Income Countries (LMICs), without any results yet available for efficacy trials in these settings. A Phase 3 trial of the Novavax RSV F Vaccine in 11,856 older adults (60 years of age and older, enrolled in the USA), did not meet the pre-specified primary or the secondary efficacy objectives, and did not demonstrate vaccine efficacy. Efficacy may differ between elderly and healthy pregnant women target groups. The Novavax Phase 3 trial in late 2nd/early 3rd trimester pregnant women continues with endpoints accruing in neonates and young infants. Public release of available results from a Medimmune candidate vaccine tested in adults are awaited. The RSV vaccine pipeline remains very robust and can be accessed at the IVR Vaccine Pipeline Tracker: <a href="http://who.int/immunization/research/clinicaltrials_newvaccinepipeline/en/">http://who.int/immunization/research/clinicaltrials_newvaccinepipeline/en/</a> (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, soon to be made publically available on the WHO IVR website.
Second year of life (2YL)	A recommendation was made for consideration of a platform for immunization coverage in the 2nd year of life, in view of potential necessary booster doses and opportunities to catch up with incomplete vaccination, and removing the artificial barrier often experienced after the 1st birthday.	Apr 2014	Ongoing	Two country case studies (Zambia, presented to SAGE in April 2016, and Senegal) (WHO, JSI) and a global landscape analysis and literature review (UNICEF) have been conducted; learnings from these as well as country demonstration projects in Ghana and Malawi (CDC) have been used to inform the draft global guidance on Establishing and strengthening immunization in the second year of life. Practices for immunization beyond infancy. An advanced draft of the guidance document was shared reviewed by the Immunization Practices Advisory Committee (IPAC) in Feb 2017 and the document was circulated for a final round of review in September 2017. Advocacy and demand creation packages targeting decision makers, planners, health workers and caretakers are also under development and be ready by end of 2017. With the guidelines on track, WHO and UNICEF are moving ahead to develop training materials for country-level staff and for building a pool of consultants trained to identify gaps and facilitate actions needed to maximize coverage of vaccines scheduled in the second year of life.
Smallpox vaccines	SAGE recommended that WHO initiate discussions with countries in possession of smallpox vaccine to establish mechanisms for replenishment of the WHO stockpile in case of need.	Nov 2013	Ongoing	Discussion with the French Government is still ongoing to provide 5 million doses. WHO is waiting for the french regulatory authority to provide the technical information about the vaccine for evaluation. The negotiations with the Japanese Government for 10 000 doses have been put on hold until the Japanese NRA approve the manufacturer to restart production. WHO is working on smallpox vaccine prequalification for the emergency stockpile. WHO restarted the dialogue with the UK for the donation of 4 million doses. A WHO meeting took place in Geneva 7-8 Sep 2015 to discuss with the National Regulatory Authorities and vaccine manufacturers what would be the minimum criteria to pre-qualify smallpox vaccines in case of re-emergence of variola virus. The report is not yet published.
Strengthening of NITAGs	SAGE requested a regular update on the number of established National Immunization Technical Advisory Groups (NITAGs).	Apr 2016	Ongoing	This information is collected via the WHO/UNICEF joint reporting form and analyzed every year. The figures are included in the GVAP secretariat report, which is made available to the SAGE DoV working group and then to SAGE. By the end of 2016, 127 Member States reported the existence of a NITAG and 82 Member States (including 27 GAVI-eligible and 25 non GAVI supported Middle Income countries) the existence of a NITAG that meets all 6 basic process indicators included in the JRF and used as part of the GVAP indicator. These figures can also be included in the global report on a yearly basis. A specific NITAG session was held at the April 2017 SAGE meeting.

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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.</p> <p>WHO IVB Department, in collaboration with Essential medicines and health products (EMP) and with support from Linkbridge consulting funded by the Bill &amp; Melinda Gates Foundation and IMMIGH consulting, is leading a Vaccine Shortage Project. The aim of the project is 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 is 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&amp;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 will be developed. Draft Terms of Reference for the operating model -with related resource assumptions- will be made available by Q4 2017. In the interim, an assessment of the global BCG vaccine market has been completed and is available upon request.</p>

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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 2016, 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 has continued through the first half of 2017. Data management processes continue to be improved toward a more systematic approach in reporting, cleaning, analysing and interpreting data. The reference laboratories are appropriately supporting sites and network laboratory performance has been successfully monitored by the global external quality assessment program as well as quality control programmes. Sentinel site and laboratory assessments are ongoing at priority sites. The most recent complete year of data available is from 2016, and it reflects the strength of the data and the network. Network data has contributed to vaccine introduction decisions, such as choice of pneumococcal conjugate vaccine (PCV) formulation, and the surveillance networks have been used as platforms for vaccine impact evaluations, particularly for rotavirus vaccines (RV). The surveillance platform has also been leveraged to monitor other VPDs, such as typhoid using the IB-VPD surveillance sites and other enteric pathogens such as norovirus, Shigella, and ETEC using the rotavirus network. Moving forward, the rapid introduction of PCV and RV by Member States now requires the surveillance networks to focus on improving baseline data for sites for sites that meet inclusion criteria in vaccine-using Member States. A web-based data management tool is being rolled out in one Region (PAHO) and has great potential to improve data quality and sharing across the Network. We are discussing how to better integrate IB-VPD meningitis surveillance with existing meningococcal meningitis surveillance systems. We conducted a meeting in December 2016 to evaluate the cost of surveillance to help countries and funders develop sustainable surveillance plans, including other VPDs such as measles. 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. We have an ongoing evaluation of what sites to include in the Network and how to incorporate countries conducting surveillance outside of the Network. Finally, one of our main activities is to work with countries on making surveillance sustainable in the long term.</p>
Sustainable Development Goals	<p>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.</p>	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 &amp; vaccines goal (3.b).1. The choice of this indicator has been validated by the SAGE Decade of Vaccine Working Group. In November 2016, at the 4th meeting of the inter-agency and Expert Group on Sustainable Development Goal Indicators (IAEG-SDG), the new accepted immunization indicator was defined as 3.b.1 Proportion of the target population covered by all vaccines included in their national programme. WHO and UNICEF were identified as co-custodians for this indicator. The definition of the indicator and the proposed measurement needs to be developed and validated by SAGE Decade of Vaccine working group. Measles second dose was chosen as a proxy indicator by the SAGE working group. The indicator will be presented at the October 2017 SAGE meeting for final decision. The definition needs to be finalized or IAEG meeting scheduled for fall 2017 in order to include the indicator to 2018 SDG report.</p>

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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	Progress in TB vaccine development was reviewed by PDVAC in June 2016. Since the adolescent/adult population carry the heaviest disease burden, there is consensus within the TB vaccine community that prioritizing this target population will have the highest and most immediate public health impact from reduction in transmission. The most advanced vaccine candidates are GSK's M72/AS01E, the recombinant BCG VPM1002, M. vaccae TM. M. vaccae is a heat killed homogenized lysate developed by Anhui Zhifei Longcom, China, which has been evaluated in Phase 3 for prevention of tuberculosis in healthy adults with latent TB infection, as well as as adjunctive immunotherapy with the aim to shorten TB treatment. Results have not been communicated. VPM 1002 is a recombinant BCG, originally developed by the Max Planck Institute; now licensed to the Serum Institute of India (SIi) and being developed with Vakzine Projekt Management (VPM), Hannover, Germany. It is currently in Phase IIb/III trials, being compared to BCG in neonates in South Africa, as well as being tested for prevention of TB recurrence in adults in India. Discussions are ongoing about neonatal BCG comparison phase 3 study design to ensure appropriate data is generated, supporting robust policy decision on possible BCG replacement. M72/AS01E a GSK adjuvanted protein vaccine candidate in phase IIb evaluation in Southern Africa, being tested for prevention of pulmonary TB. Primary results are awaited in the coming months. Secondary endpoints include safety and immunogenicity. H4/IC31 is an adjuvanted recombinant protein under development by Sanofi Pasteur, SSI and Aeras, currently in a Phase II prevention of infection study in adolescents (Phase II) with data expected by the end of 2017. Upon PDVAC recommendation, WHO IVR is driving an effort to generate guidance on preferred product characteristics for TB vaccines targeted to adults and adolescents, with support from the Bill and Melinda Gates Foundation.
Typhoid	Establish a SAGE working group on typhoid conjugate vaccines in 2016 to prepare for a SAGE review of the evidence in 2017.	Oct 2015	Ongoing	The SAGE Working Group (WG) on Typhoid Vaccines was established in Mar 2016 and will report its evidence review and draft policy recommendations for typhoid vaccines to SAGE at the Oct 2017 meeting. Data on the safety of typhoid vaccines was reviewed by the Global Advisory Committee on Vaccine Safety (GACVS) in Dec 2016. New modelling data on the dynamics of diseases transmission and economic evaluation of typhoid burden and of vaccination strategies have also been reviewed by the Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC) in Feb and Sept 2017. Important new data have also been generated in recent and ongoing studies on areas such as the epidemiology and burden of typhoid fever, trends in antimicrobial resistance of S. Typhi and implications for typhoid control. These data have provided critical information to inform the SAGE Working Group's evidence review, or are anticipated to provide data in the next few years to support country level decisions on typhoid control. Currently, one licensed typhoid conjugate vaccine is undergoing WHO prequalification review.
Un/under-immunized children	SAGE requested that WHO quickly roll out tools so that other countries can address low coverage of vaccination.	Nov 2010	Ongoing	Work is ongoing on the tool to assess "Missed Opportunities for Vaccination" (see item 284). On a broader level, a companion document to the Global Vaccine Action Plan (GVAP) focusing on Routine Immunization entitled "Global Routine Immunization Strategies and Practices" (GRISP) has been presented to the SAGE WG on DoV twice, and in Aug 2016 was published. Additionally, a range of additional guidance materials are under development and close to finalization. These include a health worker knowledge, attitudes, and practices (KAP) tool, training materials for health workers on conversations with hesitant parents/caregivers, and addressing concerns regarding multiple injections and pain. A global field guide for 'Tailoring immunization programmes', based on the original guide from EURO, is being finalized. General guidance is also being developed to outline the range of interventions that may be considered when identifying and working to address hesitant populations.
Vaccination during humanitarian emergencies 22 September 2017	SAGE also suggested that the framework approach to vaccine decision-making could be considered for other health interventions in emergencies.	Apr 2012	Ongoing	Possibilities of using the SAGE framework in other public health areas and emergency settings are being explored.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccination during humanitarian emergencies	SAGE emphasized the need to advance work on refining guidance in delivering continuous immunization services during humanitarian conflicts. A session on human emergencies will tentatively be slotted at the April 2016 SAGE meeting.	Oct 2015	Ongoing	<p>A WHO meeting on implementation of vaccination during humanitarian emergency situations was convened in Cairo from 12-14 January 2016. The objectives were to:</p> <ul style="list-style-type: none"> <li>-reflect on the experience of EMR countries in implementing vaccination in humanitarian emergencies and the issues, challenges, best approaches and existing country guidance documents to ensure satisfactory vaccination of the target populations.</li> <li>-reflect on countries experience using vaccination in acute humanitarian emergencies: a framework for decision making.</li> <li>-build on countries experience to initiate development of a draft guidance document on the implementation of vaccination in humanitarian emergency situations.</li> </ul> <p>A draft guidance document on implementation issues was initially produced by EMRO, adjusted some as a result of limited preliminary peer-review, and then distributed for a much broader peer review.</p> <p>'Vaccination in acute humanitarian emergencies: a framework for decision making' has also been adjusted/updated based on the feedback received during the Cairo meeting and a draft operational manual is being developed. Finally, although there was no separate specific session during the Apr 2016 SAGE meeting an update was featured in the IVB Director's global report at this meeting. A meeting was jointly organized with MSF on 20 June to tackle the issue of supply and procurement obstacles in humanitarian emergencies:</p> <ol style="list-style-type: none"> <li>Discuss/map the obstacles to necessary access to affordable vaccines in a timely manner in emergency and humanitarian crisis situations.</li> <li>Discuss proposed solutions for addressing the key barriers to timely provision of affordable vaccines in humanitarian crisis situations.</li> <li>Agree upon a set of priority issues to be addressed by partners with a proposed plan of action/timeframe for follow up.</li> </ol> <p>A follow-up meeting took place on 10-11 Oct to develop consensus on the various guidance and priorities mentioned above and discuss how to best communicate and advocate for their implementation. Feedback from the meeting included that the envisaged operational manual missed important features while still being too long. Therefore the participants concluded that with having the revised and edited framework for decision-making along with the web-based tools, the operational manual was obsolete.</p> <p>The updated framework for decision-making has been published and is available at <a href="http://apps.who.int/iris/bitstream/10665/255575/1/WHO-IVB-17.03-eng.pdf">http://apps.who.int/iris/bitstream/10665/255575/1/WHO-IVB-17.03-eng.pdf</a> and implementation guide was finalized and is available at <a href="http://apps.who.int/iris/bitstream/10665/258719/1/WHO-IVB-17.13-eng.pdf">http://apps.who.int/iris/bitstream/10665/258719/1/WHO-IVB-17.13-eng.pdf</a>. Work is ongoing with UNICEF for the development of web based interactive tools to support its use and facilitate further updating. These tools should be available by Q3 2017. Attempts are currently being made to have a proactive dissemination and communication plan to ensure adequate distribution of the tools.</p>

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccine coverage	SAGE recommended that WHO explore alternative survey methods to improve the precision, reduce the cost and improve the usefulness of survey results to national and local immunization programmes.	Nov 2011	Ongoing	<p>To improve the quality, precision and usefulness of survey results and to reduce the cost of surveys, the Global Immunization Monitoring and Surveillance Group (GIMS) explored recent advances in sampling methodologies; new technologies for constructing sampling frames, supervision of field work, data collection, and analysis; and alternative content, collection, analysis, presentation and linkages. An initial meeting was convened of the Department of Immunization Vaccines and Biologicals (IVB) Informal Advisory Group on Monitoring Immunization Programme Performance through Household and Community Surveys. The first meeting addressed the need to modify Demographic and Health Surveys (DHS) implemented by ICF International; and the UNICEF Multiple Indicator Cluster Surveys (MICS) and the WHO Immunization Cluster Survey to accommodate changes in immunization system strategies. In 2012, following a meeting with representatives of ICF and the MICS team, WHO and UNICEF provided written recommendation to these agencies to propose modifications to their standard recommendations on data collection, analysis and presentation of immunization coverage data. An informal working group was created to review and revise WHO guidance on measuring immunization coverage through household and community surveys. In 2013, the working group met to agree on the scope of work, to identify initial products, and establish a plan of document production, review, pilot testing, and clearance. Draft guideline was circulated to external reviews in 2014-2015. The proposed methods were reviewed in September 2014 by Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC). IVIR-AC agreed that the revised method for coverage surveys is the proper way forward, but that statistical expertise will be required to implement the survey in the field and provided other considerations, including the importance of using GPS technology, the need for qualitative studies and piloting of surveys in hard-to-reach settings. IVIR also noted that difficulties in monitoring progress and comparing cross-sectional data across methods and time must be addressed.</p> <p>Protocol for pilot testing was used in Bangladesh. In mid-2015, a working draft of the WHO Vaccination Coverage Survey Reference Manual was distributed and posted on the departmental website. Between 2015 and 2016, all or some aspects of the recommendations included in the new Survey Manual were used in Burkina Faso, Lao PDR, and to a lesser extent in Lebanon and for surveys following supplementary immunization activities (SIA) in Kenya, Swaziland, to name a few. Nigeria combined a MICS with a vaccination coverage survey and Pakistan planed its 2017 Vaccination Coverage Survey using the new Manual. In Dec 2015, a briefing workshop on the methodology for regional focal points and consultants was conducted. In 2016, countries in the African and Eastern Mediterranean regions were briefed. Between 2016 and early 2017, WHO in collaboration with UNICEF and CDC conducted trainings that brought together statisticians from developing countries (one Anglophone and one Francophone training), along with immunization program officers and consultants were conducted for countries from all regions, except EUR. A separate training was done in China for all provinces. It is expected that the WHO Vaccination Coverage Survey Reference Manual will be finalized by the end of 2017, after experiences and lessons learned are shared and discussed. The revised recommendations will likely improve accuracy, by decreasing selection bias and reliance on maternal recall, and should also increase likelihood for adequate power, increase rigor and quality. The cost of the various trade-offs needs to be further explored.</p>
Vaccine coverage	WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage.	Nov 2011	Ongoing	<p>Currently, WHO is developing global guidelines on conducting serosurvey studies on measles and rubella to identify immunity gaps in the population. An expert working group has been assembled, based on the expertise in the various fields of each of the members needed to conduct such studies, including statisticians, epidemiologists, laboratory experts, and program experts, given sub-tasks in developing parts of these guidelines that pertain to their respective expertise. A working draft has been circulated for comments and was finished by the end of 2015. It was tested subsequently in pilot studies in two different settings (post campaign/post outbreak in Mongolia, and at elimination in Bhutan). The data collection part of a pilot study has been conducted in Mongolia in 2016; analysis of the survey results is underway. The data collection has been completed in Bhutan and laboratory testing is ongoing; this study was an integrated study alongside hepatitis B/C. Based on the field work, the working draft guidelines are being adjusted, amended and corrected where needed. The final document is planned to be ready and published by end of 2017 and to be rolled out as a tool to evaluate the immune status of the target or targeted population.</p>



Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccine coverage	SAGE recommended that WHO support new research for biological specimen collection including rapid on-site diagnostics that could improve coverage and susceptibility estimates. Improved serological surveillance techniques could be integrated with existing population-based surveys such as DHS or MICS. These research topics should be included on the QUIVER (now IVIR-AC) agenda.	Nov 2011	Ongoing	With the support from the Bill and Melinda Gates Foundation (BMGF), a point-of-care testing (POCT) prototype sample Oralight collection device and POCT test system based on lateral flow and a reader combined with mobile phone, has been developed for the detection of measles specific antibodies in serum and oral fluid. The prototype showed high sensitivity and specificity (91 and 94% respectively for serum and 90 and 96% for OF). On top of that, measles virus genome could be reliably detected in the POCT strips and used for genotyping, even after prolonged storage for more than a month at 20-25°C. The added advantage was that the POCT was highly thermostable and the results showed high concordance with gold standard assay used in the Global Measles Rubella Laboratory Network (GMLRN). The assay is particularly useful in endemic settings as well as in settings near elimination of even post elimination and re-introduction. During a recent meeting of the Measles Rubella Initiative on Research and Innovation POCT came out as one of the top research priorities. It will allow monitoring disease using effective surveillance and evaluate programmatic efforts to ensure progress. It will also aid in developing and maintaining outbreak preparedness, and respond rapidly to outbreaks and manage cases. Field studies are now in phase 2 in different epidemiological and health care settings, including countries in different phases of measles control and with different health care infrastructures (Africa and South East Asia). Particularly the operational feasibility of using POCT/OF in a field setting needs to be determined. Currently, besides the measles IgM assay for oral fluid, capillary blood and serum, a POCT for rubella IgM is being developed. POCT for measles and tetanus IgG are being evaluated for the use on oral fluid and dried blood spots on filter paper.
Vaccine delivery research	SAGE requested that IVIR-AC explore research studies and methods including behavioural science studies for ranking reasons behind lack of vaccine delivery and other 'barriers to access'.	Oct 2015	Ongoing	IVIR-AC reviewed methods, and encourages studies on vaccine delivery costing and financing (human papillomavirus (HPV), influenza and oral cholera vaccine (OCV)) and vaccine uptake/hesitancy.  Non-specific effects (NSE) of vaccination and missed opportunities for vaccination sessions were on the IVIR-AC agenda in 2016 and 2017. Economic tools for influenza vaccines were presented at the June 2016 meeting. A malaria costing tool to help countries cost and plan RTS,S vaccine in their country will be reviewed at the Sep 2017 meeting.
Vaccine Hesitancy	SAGE encourages validation of the developed compendium of survey questions on vaccine hesitancy, which have been assessed and validated only in some high-income countries or not at all.	Oct 2014	Ongoing	Discussions with various stakeholders are ongoing (Centre for Disease Control CDC, WHO EURO, Middle Income Countries MIC task force) on the ways forward to identify partners to take on the validation of the survey questions. The MIC task force framework was presented to SAGE during the April 2014 meeting, which highlighted the importance to advance this initiative. Currently, how to secure funding from donors in support of the listed activities and advance validation of the questions in LMIC settings is being explored. The survey questions have been translated in Arab and French and are available on the WHO hesitancy website: <a href="http://www.who.int/immunization/programmes_systems/vaccine_hesitancy/en/">http://www.who.int/immunization/programmes_systems/vaccine_hesitancy/en/</a> The promotion of their use and necessity to validate the research questions will be discussed further internally at WHO.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccine Hesitancy	SAGE 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. The in-depth tool, "A Guide to Tailoring Immunization Programmes (TIP)" is being used in at least 6 countries by WHO-EURO (European Regional Office), with at least 3 additional countries starting TIP projects in 2017, one of which in the Western Pacific Region. An evaluation of TIP implementation in the European Region from 2013-2016 was conducted in the second half of 2016. Findings will inform development of a new updated version of TIP in 2017.</p> <p>Additionally, the Univ. of Witwatersrand in South Africa has been contracted to adapt the TIP method for developing countries, with less intensive consultant-based inputs. This is being finalized and will be published in 2017.</p> <p>Lastly, in 2017 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, and other partners is also taking place to ensure alignment of efforts.</p>
Vaccine Hesitancy	SAGE underlined the importance of distributing the matrix of determinants, the definition of hesitancy and the other deliverables to countries and partners.	Oct 2014	Closed	<p>Discussions and presentations were held in the context of the immunization managers' meeting in the Eastern Mediterranean Region (EMR) and the African Region (AFR) Task force on immunization(TFI) meetings in 2014 and 2015.</p> <p>A Special Issue on Vaccine Hesitancy has been published in Aug 2015 in the journal Vaccine with a series of 10 full papers plus one editorial. In conjunction, a WHO press briefing was held on 18 Aug 2015 to emphasize WHO initiatives addressing vaccine hesitancy. This generated much positive media coverage. A compilation of centers to assist countries in addressing vaccine hesitancy has been finalized and sent to WHO regions to disseminate to countries. A paper which outlines the results of the 2015 Joint Reporting Form (JRF) indicators on vaccine hesitancy and contains the matrix of determinants and the definition of vaccine hesitancy was published open access on 1 Mar 2017: <a href="http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0172310">http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0172310</a>.</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 is planned for Q4/2017. Fractional dose non-inferiority studies for all 4 prequalified vaccines will be conducted (funded, Africa), and long term immunogenicity will be assessed in a Brazilian cohort (funded). Immunogenicity study in DRC is on track, and satisfactory interim immunogenicity data are available.</p>

## **Update on the Gavi Board meeting, Geneva, Switzerland, 14- 15 June 2017**

The Board Chair, Dr Ngozi Okonjo-Iweala, opened up the meeting with somber remarks on the changing geopolitical climate and potential impact in financing agreements for critical Sustainable Development Goals with fewer resources going to developing countries. She cited caution on the future expectations and impact on Gavi, noting that while Gavi has not been impacted by the broader climate to date, due to its focus and delivery of results, there is the need for Gavi to continue its focus with improved efficiencies, accountability and results, while not being extremely risk averse. Furthermore, she emphasized the need to support countries leverage their own domestic resource mobilization and for emerging markets to do more.

The deliberations of the Board were centered on heightened partner collaboration in supporting countries, managing donors expectations for zero risk tolerance, and the need for collective partner efforts in supporting countries build system capacities towards timely and sustained transition. The Board discussed the need for timely planning and positioning of Gavi post 2020 with the planned Mid-Term Review in 2018, while maintaining a clear focus and mandate and looking at the broader context and climate for opportunities and framing for its next strategy.

The main decisions of the Board, further detailed in the summary decisions, are the approval of the:

- Gavi Policy: “Fragility, Emergencies, Refugees” to replace the 2013 “Fragility and Immunisation Policy”.
- Approach to equitable allocation of available Cold Chain Equipment Optimisation (CCEOP) funding based on an on a Health System Strengthening (HSS) formula.
- Continuation of Gavi support to Yemen irrespective of its 2016 co-financing default status.
- Extending Gavi’s support for inactivated polio vaccine (IPV) from 2018 to 2020 under the arrangements agreed by the Board in November 2013 subject to polio specific funding being available.
- USD 19 million for UNICEF Supply Division fees for the procurement of vaccines and related devices and USD 2.4 million for procurement of cold chain equipment in 2018.

The next Board meeting will be held in Lao PDR, 29-30 November 2017.



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### Meeting of the Global Advisory Committee on Vaccine Safety, 7–8 June 2017

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides WHO with scientifically rigorous advice on vaccine safety issues of potential global importance.<sup>1</sup> GACVS held its 36th meeting in Geneva, Switzerland, on 7–8 June 2017.<sup>2</sup> The Committee examined 3 vaccine specific safety issues: pharmacovigilance planning for the pilot implementation programme for the anti-malaria vaccine, RTS,S/AS01 (RTS,S) in 3 countries; updates on the safety profiles of Bacillus Calmette-Guérin (BCG) vaccine and human papilloma virus (HPV) vaccine; and the generic issue of development of standards and a template for the review of the safety profile of vaccines during GACVS meetings.

### Safety monitoring of the RTS,S vaccine pilot implementation programme

GACVS has followed the development and safety evaluation of RTS,S for the past 8 years. A positive scientific opinion of RTS,S has been issued by the European Medicines Agency under Article 58,<sup>3</sup> and in January 2016, WHO recommended further evaluation of the vaccine. WHO's position is based on advice from the Strategic Advisory Group of Experts (SAGE)

### Réunion du Comité consultatif mondial pour la sécurité des vaccins, 7-8 juin 2017

Le Comité consultatif mondial pour la sécurité des vaccins (GACVS), un organe consultatif indépendant composé d'experts cliniques et scientifiques, fournit à l'OMS des conseils d'une grande rigueur scientifique sur des problèmes de sécurité des vaccins susceptibles d'avoir une portée mondiale.<sup>1</sup> Le GACVS a tenu sa 36<sup>e</sup> réunion à Genève (Suisse) les 7 et 8 juin 2017.<sup>2</sup> Il a examiné 3 questions spécifiques relatives à l'innocuité: la planification de la pharmacovigilance pour la mise en œuvre pilote du vaccin antipaludique RTS,S dans 3 pays et les mises à jour des profils d'innocuité du vaccin préparé à partir du bacille Calmette-Guérin (BCG) et du vaccin contre le papillomavirus humain (HPV). Il a aussi examiné une question générique: la mise au point de critères et d'un modèle pour l'examen du profil d'innocuité des vaccins lors des réunions du GACVS.

### Suivi de l'innocuité des mises en œuvre pilotes du vaccin RTS,S

Pendant les 8 dernières années, le GACVS a suivi le développement et l'évaluation sur le plan de l'innocuité du vaccin antipaludique RTS,S/AS01 (RTS,S). Ce vaccin a reçu un avis positif de la part de l'Agence européenne des médicaments au titre de l'article 58<sup>3</sup> et, en janvier 2016, l'OMS a préconisé la poursuite de son évaluation. La position de l'Organisation se fonde sur les conseils du Groupe stratégique

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<sup>1</sup> See No. 41, 1999, pp. 337–338.

<sup>2</sup> GACVS invited additional experts to present and discuss evidence related to particular topics. These experts included persons affiliated with: University of Malawi, Blantyre, Malawi; Food and Drugs Authority Ghana and University of Ghana Medical School, Accra, Ghana; Staten Serums Institut, Copenhagen, Denmark; University of Adelaide, Adelaide, Australia; Pharmacy and Poisons Board, Nairobi, Kenya; US Centers for Disease control and Prevention, Atlanta GA, USA; Public Health Metrika, Birmingham, United Kingdom; GlaxoSmithKline Biologicals, Wavre, Belgium.

<sup>3</sup> See [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000157.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp)

<sup>1</sup> Voir N° 41, 1999, pp. 337-338.

<sup>2</sup> Le GACVS a invité d'autres experts pour présenter et discuter d'éléments relatifs à des sujets particuliers. Ces experts étaient notamment affiliés aux entités suivantes: University of Malawi, Blantyre (Malawi); Food and Drugs Authority et University of Ghana Medical School, Accra (Ghana); Institut des Sérums, Copenhague (Danemark); University of Adelaide, Adelaide (Australie); Pharmacy and Poisons Board, Nairobi (Kenya); Centers for Disease control and Prevention des États-Unis d'Amérique, Atlanta GA (États-Unis d'Amérique); Public Health Metrika, Birmingham (Royaume-Uni); GlaxoSmithKline Biologicals, Wavre (Belgique).

<sup>3</sup> Voir [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000157.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp)

on Immunization and the Malaria Policy Advisory Committee (MPAC). A series of pilot implementation programmes has been proposed to address several gaps in knowledge before considering introduction of the vaccine at wider country level. These gaps include the extent to which the protection demonstrated in children in the Phase III<sup>4</sup> trial, carried out by the manufacturer GlaxoSmithKline (GSK), can be replicated in the context of routine health systems, particularly in view of the need for a 4-dose schedule that requires additional immunization visits; to assess if there is an impact on all-cause mortality, and whether the excess number of cases of meningitis and cerebral malaria identified during the Phase III trial are causally related to RTS,S/AS01 vaccination.<sup>5</sup>

Ghana, Kenya and Malawi are the 3 pilot implementation countries. Pilot programmes will be conducted in selected areas of moderate to high malaria transmission. Introduction of the vaccine will be through the national Expanded Programmes on Immunization (EPI) in each country, with some districts/counties randomized to receive the vaccine at the beginning of the programme, while others will not begin using the vaccine, allowing comparison of the impact and safety outcomes of interest. Within each country, regulatory approval for pilot introduction will be required prior to vaccine use. GACVS received updates on the draft design of the pilot programmes from WHO, the risk management plan from GSK, the state of routine vaccine pharmacovigilance from experts in the pilot countries, the proposed safety data flow, and the proposal to set up a Programme Safety Committee.

GACVS noted the substantial and continuing disease burden of malaria and the potential impact of the vaccine. The safety of RTS,S will be monitored both through a strengthened routine pharmacovigilance system operating across the entire pilot implementation programme area, and by a specific surveillance system established in sentinel hospitals covering part of the area. The meningitis and cerebral malaria signals previously identified<sup>6</sup> will be specifically evaluated through systematic, prospective, quality-assured paediatric inpatient surveillance at 8 sentinel hospitals in each country (4 in clusters receiving RTS,S and 4 in control clusters) which will also enable identification and evaluation of other potential safety signals. In addition, the manufacturer will be conducting a Phase IV study in 4 additional hospitals in each country. The Phase IV study, in contrast to the pilot implementation studies, will include follow-up of individuals using a cohort study design. Across the entire pilot area, safety monitoring will include spontaneous reporting of adverse events following immunization (AEFIs) as well as active surveillance (detection, investigation and ascertainment of immuni-

consultatif d'experts (SAGE) de la vaccination et du Comité de pilotage de la politique de lutte antipaludique (MPAC). Une série de mises en œuvre pilotes a été proposée pour répondre à plusieurs lacunes dans les connaissances avant d'envisager l'introduction plus large du vaccin à l'échelle d'un pays. On ignore notamment dans quelle mesure la protection mise en évidence chez les enfants dans l'essai de phase III<sup>4</sup> peut être reproduite dans le cadre des systèmes de santé classiques, compte tenu, en particulier, de la nécessité d'un calendrier vaccinal en 4 doses, imposant des visites de vaccination supplémentaires; si la vaccination a un impact sur la mortalité toutes causes confondues et si les excès de cas de méningite et de paludisme cérébral repérés pendant cet essai de phase III ont un lien de causalité avec la vaccination par le RTS,S/AS01.<sup>5</sup>

Les mises en œuvre pilotes seront organisées dans les 3 pays suivants: Ghana, Kenya et Malawi. Les programmes pilotes seront menés dans des zones choisies où la transmission du paludisme est modérée à forte. Le vaccin sera introduit dans chacun des pays par le Programme élargi de vaccination (PEV) national, certains districts ou comtés étant sélectionnés aléatoirement pour recevoir le vaccin au début du programme, tandis que d'autres ne débiteront pas son utilisation, pour permettre la comparaison de l'impact et de l'innocuité. Dans chaque pays, l'introduction pilote devra avoir été approuvée sur le plan réglementaire avant toute utilisation du vaccin. Le GACVS a reçu des mises à jour des projets de mise en œuvre de programmes pilotes de la part de l'OMS, le plan de gestion des risques fourni par GSK, les points sur la situation de la pharmacovigilance systématique pour le vaccin de la part des experts dans les pays pilotes, le flux de données d'innocuité proposées et la proposition de mettre en place un comité de sécurité programmatique.

Le GACVS a pris note de l'énormité de la charge de morbidité générée en continu par le paludisme. L'innocuité du vaccin RTS,S sera suivie par un système de pharmacovigilance systématique renforcé, opérant sur l'ensemble de la zone de mise en œuvre pilote, et par un système de surveillance spécifique, établi dans des hôpitaux sentinelles et couvrant une partie de la zone. Les signaux précédemment identifiés concernant la méningite et le paludisme cérébral<sup>6</sup> feront l'objet d'une évaluation spécifique par le biais d'une surveillance pédiatrique ambulatoire, prospective et systématique, de qualité garantie, exercée dans 8 hôpitaux sentinelles dans chaque pays (4 dans les grappes recevant le vaccin et 4 dans les grappes témoins), qui permettra également l'identification et l'évaluation d'autres signaux de sécurité potentiels. En outre, le fabricant mènera une étude de phase IV dans 4 autres hôpitaux dans chaque pays. A la différence des études de mise en œuvre pilote, cette étude comprendra un suivi des individus par le biais d'une étude de type cohorte. Dans l'ensemble de la zone pilote, le suivi de l'innocuité fera notamment appel à la notification spontanée des manifestations postvaccinales indésirables (MAPI), ainsi qu'à la surveillance active (détection, investigation et vérification du statut vaccinal de tous les cas détectés par le système de santé

<sup>4</sup> RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *The Lancet*. 2015;386(9988):31–45.

<sup>5</sup> See No. 4, 2016, pp. 33–52.

<sup>6</sup> See No. 3, 2016, pp. 24–26.

<sup>4</sup> RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *The Lancet*. 2015;386(9988):31–45.

<sup>5</sup> Voir N° 4, 2016, pp. 33-52.

<sup>6</sup> Voir N° 3, 2016, pp. 24-26.

zation status of all cases in the corresponding age group detected by the health-care system) for adverse events of special interest (AESIs). While both Ghana and Kenya are members of the WHO programme for international drug monitoring,<sup>7</sup> Malawi is currently an associate member. GACVS recommended that Malawi receives support to become a full member of the WHO programme.

To strengthen routine pharmacovigilance ahead of the pilot introduction, GACVS recommended that countries be supported with training and logistics. The Committee also discussed criteria for pharmacovigilance readiness. The criteria retained included: a minimum level of 10 annual AEFI reports per 100 000 surviving infants in pilot areas; functional AEFI committees that meet regularly; trained and resourced AEFI investigation teams; safety communication plans to be evaluated and tested; and each country to have an identified person in post within the EPI programme to oversee AEFI reporting and training, and ensure that they are, and remain, optimal. Each pilot country has also consulted, or will be consulting, experts to identify which AESI would be of interest and could practically be assessed by active surveillance. These are events that have been observed with the use of other vaccines, or that reflect theoretical concerns with RTS,S use. GACVS recommended that the list be of a practical size and be the same for all countries with agreed case definitions and procedures for investigation. These AESIs should be assessed as part of the pilot programme with monitoring starting prior to RTS,S introduction to establish a baseline and will be limited to the duration of the pilot programme. Regarding spontaneous AEFI reporting, active AESI surveillance should be in place 6 months prior to the first vaccine administration, also to establish baselines.

In addition, GACVS recommended between-country co-ordination to ensure comparability of AEFI data, and the standardization of causality assessment tools and training materials, including material used within the pilot programmes and by GSK's Phase IV programme. GACVS agreed that the establishment of a Programme Safety Committee, with membership from pilot and other countries, would enhance this coordination. This Committee would provide an overall evaluation of RTS,S safety and advise on pharmacovigilance capacity in pilot countries; it would also provide GACVS with updates from the pilot programme and prepare the report that would summarize safety data at completion. In the longer term the Programme Safety Committee could be transformed to become a vaccine safety committee for the WHO African Region.

GACVS also reviewed the proposed flow of safety data and recommended that the secretariat of the Malaria Vaccine Implementation Programme maintain a joint

dans la tranche d'âge correspondante) pour tous les événements indésirables présentant un intérêt particulier. Le Ghana et le Kenya sont membres du Programme OMS de pharmacovigilance internationale,<sup>7</sup> tandis que le Malawi en est actuellement membre associé. Le GACVS a recommandé d'accorder à ce dernier un soutien pour qu'il devienne membre à part entière du programme.

Pour renforcer la pharmacovigilance systématique en amont de l'introduction pilote, le GACVS a préconisé une assistance aux pays sur le plan de la formation et de la logistique. Le comité a discuté des critères permettant d'évaluer si la pharmacovigilance était suffisamment prête avant l'introduction pilote. Parmi les critères retenus figuraient un nombre annuel minimum de 10 notifications de MAPI pour 100 000 nourrissons survivants dans la zone pilote, des comités MAPI opérationnels se réunissant régulièrement, des équipes d'investigation des MAPI formées et disposant des moyens nécessaires, des plans de communication sur la sécurité évalués et testés et une personne identifiée dans chaque pays et en poste au sein du PEV pour superviser la notification des MAPI et la formation à leur identification et garantir que celles-ci restent optimales. Chaque pays de mise en œuvre pilote a aussi consulté ou consultera des experts pour déterminer quels événements indésirables présentant un intérêt particulier seront à retenir et pourront être évalués de manière pratique par la surveillance active. Ces événements seront ceux déjà observés avec d'autres vaccins ou ceux reflétant des inquiétudes théoriques à propos du vaccin RTS,S. Le GACVS a recommandé que la liste ne soit pas trop longue et la même pour tous les pays, avec des définitions de cas et des procédures d'investigation convenues. Ces événements pouvant présenter un intérêt particulier devront être évalués dans le cadre du programme pilote, avec un suivi débutant avant l'introduction du RTS,S pour établir une référence et limité à la durée du programme pilote. Comme la notification spontanée des MAPI, la surveillance active de ces événements devra être en place 6 mois avant la première administration du vaccin pour déterminer des niveaux de référence.

En outre, le GACVS a préconisé une coordination entre les pays pour garantir la comparabilité des données relatives aux MAPI et la standardisation des outils d'évaluation des liens de causalité et du matériel de formation, y compris celui utilisé dans les études pilotes et par le Programme de phase IV de GSK. Le GACVS a reconnu que la mise en place d'un comité de sécurité pour ce programme, comprenant des membres des pays de mise en œuvre pilote ou ayant d'autres affiliations, renforcerait cette coordination. Ce comité devrait fournir une évaluation globale de l'innocuité du vaccin RTS,S, ainsi que des conseils à propos des capacités de pharmacovigilance des pays de mise en œuvre pilote. Il devrait aussi fournir au GACVS des mises à jour du projet pilote et préparer le rapport qui résumera les données d'innocuité une fois l'étude pilote achevée. À plus long terme, ce comité pourrait devenir un comité de sécurité vaccinale pour la Région africaine.

Le GACVS a aussi examiné le flux de données d'innocuité proposé. Il est suggéré que le secrétariat du Programme de mise en œuvre du vaccin antipaludique conserve un jeu de données

<sup>7</sup> See [http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/National\\_PV\\_Centres\\_Map/en/](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/National_PV_Centres_Map/en/)

<sup>7</sup> Voir [http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/National\\_PV\\_Centres\\_Map/en/](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/National_PV_Centres_Map/en/)



dataset of AEFI for review by the Programme Safety Committee. GACVS acknowledged the need for each country to be regularly informed about progress with safety monitoring in other pilot sites including information exchange between each country and the manufacturer. This will be essential to ensure proper information about safety monitoring during Phase IV studies as well as to meet the regulatory requirements of the risk management plan. A pharmacovigilance plan will be prepared jointly with the 3 pilot countries.

As an expert committee, GACVS will continue to provide advice and support to the pilot countries and to the planned Programme Safety Committee. Specifically, it will assist with the interpretation and communication of safety questions and maintain a subcommittee with which the Programme Safety Committee can communicate. A current, or former, GACVS member will also be nominated to ensure proper liaison with the Programme Safety Committee. At its meeting in December 2017, GACVS will review progress with pharmacovigilance readiness ahead of the start of the pilot programmes and provide further advice on the way forward.

### Safety update of BCG vaccine

GACVS reviewed the safety profile of BCG vaccines in preparation for an updated WHO position paper on BCG vaccines, and safety information sheet.<sup>8</sup> Although the current global BCG vaccine supply is limited to only 3 prequalified manufacturers, the vaccine has been shown to be consistently protective against infant tuberculous meningitis and miliary tuberculosis, and remains an important tool for the prevention of tuberculosis. BCG vaccination has been part of immunization programmes since the 1960s and part of EPI programmes since 1974. While being shown to be effective in infants, evidence for BCG protection against pulmonary tuberculosis in older children and adults is more variable, ranging from 0% to 80%, and tends to be higher in individuals with no detectable prior exposure to mycobacterial infection or environmental mycobacteria. For this reason, the policy of BCG vaccination varies, particularly in low burden countries, with some countries electing not to administer it routinely. The currently available WHO BCG vaccine position paper was published in 2004.<sup>9</sup> Revised BCG vaccination guidelines for infants at risk for HIV infection were published separately in 2007.<sup>10</sup> The BCG position paper will be updated following a SAGE review of evidence currently scheduled for October 2017.

commun sur les MAPI pour examen par le comité de sécurité du programme. Il a reconnu la nécessité pour chaque pays d'être régulièrement informé des progrès du suivi de l'innocuité sur d'autres sites pilotes et également des échanges d'informations entre chacun des pays et le fabricant. Ces données seront essentielles pour assurer une information correcte à propos du suivi de l'innocuité pendant les études de phase IV et pour répondre aux exigences réglementaires du plan de gestion des risques. Un plan de pharmacovigilance sera élaboré conjointement avec les 3 pays de mise en œuvre pilote.

En tant que comité d'experts, le GACVS continue de prodiguer des conseils et un soutien à ces pays et sera bientôt établi en tant que comité de sécurité du programme. Il apportera notamment une assistance concernant l'interprétation et la communication des questions ayant trait à l'innocuité et maintiendra un sous-comité, avec lequel le Comité de sécurité du programme pourra communiquer. Un des membres actuels ou un ancien membre du GACVS sera aussi nommé pour assurer une liaison appropriée avec le Comité de sécurité du programme. Lors de sa réunion de décembre 2017, le GACVS examinera les progrès accomplis dans la préparation de la pharmacovigilance en amont des mises en œuvre pilote et délivrera d'autres conseils sur la marche à suivre.

### Le point sur l'innocuité des vaccins BCG

Le GACVS a examiné le profil d'innocuité des vaccins BCG dans le cadre de la préparation d'une note de synthèse actualisée sur les vaccins BCG et d'une fiche d'information sur les fréquences des réactions postvaccinales de l'OMS.<sup>8</sup> Actuellement, l'approvisionnement mondial en vaccins BCG repose sur 3 fabricants préqualifiés seulement. Néanmoins, malgré certaines limitations, ces vaccins restent un outil important pour prévenir la tuberculose car il a été démontré qu'ils offraient une protection systématique contre la méningite tuberculeuse du nourrisson et la tuberculose miliaire. Ils ont fait longtemps partie des programmes de vaccination menés depuis les années 1960 et des programmes PEV mis en œuvre à partir de 1974. Bien que ces vaccins soient efficaces chez les nourrissons, les taux de protection qu'ils procurent contre la tuberculose pulmonaire aux enfants plus âgés et aux adultes sont plus irréguliers, variant de 0 à 80%, et tendent à être plus élevés chez les individus sans exposition antérieure détectable à une infection mycobactérienne ou à une mycobactérie environnementale. De ce fait, les politiques relatives à la vaccination avec des vaccins BCG sont variables, en particulier dans les pays fortement touchés par la tuberculose, certains de ces pays choisissant de ne pas administrer du tout ces vaccins dans le cadre de la vaccination systématique. La note de synthèse de l'OMS actuellement disponible sur ces vaccins a été publiée en 2004.<sup>9</sup> Des lignes directrices révisées relatives à la vaccination par le BCG des nourrissons exposés au risque d'infection par le VIH ont été publiées séparément en 2007.<sup>10</sup> La note de synthèse de l'OMS sur les vaccins BCG sera actualisée après un examen par le SAGE des éléments disponibles, actuellement programmé en octobre 2017.

<sup>8</sup> See [http://www.who.int/vaccine\\_safety/initiative/tools/BCG\\_Vaccine\\_rates\\_information\\_sheet.pdf?ua=1](http://www.who.int/vaccine_safety/initiative/tools/BCG_Vaccine_rates_information_sheet.pdf?ua=1)

<sup>9</sup> See No. 4, 2004, pp. 27–38.

<sup>10</sup> See No. 21, 2007, pp. 193–196.

<sup>8</sup> Voir [http://www.who.int/vaccine\\_safety/initiative/tools/BCG\\_Vaccine\\_rates\\_information\\_sheet.pdf?ua=1](http://www.who.int/vaccine_safety/initiative/tools/BCG_Vaccine_rates_information_sheet.pdf?ua=1)

<sup>9</sup> Voir N° 4, 2004, pp. 27-38.

<sup>10</sup> Voir N° 21, 2007, pp. 193-196.

BCG has a well-established safety profile. Usually, a correct administration – intradermally on the upper arm (deltoid) – results in a local reaction consisting of a small pustule followed by a small scar. When administered subcutaneously, lymphadenitis can occur, with rare instances of suppuration and fistulae formation. Other severe reactions include injection site abscesses or severe ulcerations; regional adverse reactions such as ipsilateral regional lymph node enlargement; and rare episodes of distant disease, particularly in the skin, gut or bones. Osteitis or osteomyelitis may be detected, sometimes after 12 months following vaccination. Disseminated BCG disease having high case fatality is rare and is associated almost entirely with HIV and primary immune deficiency syndromes. BCG immune reconstitution inflammatory syndrome (IRIS) and eye problems including uveitis, optic neuritis and lupus vulgaris are also among the recognized adverse reactions to the vaccine.

The reactogenicity of BCG vaccine is influenced by the BCG strain, age at administration, immune status and revaccination. Most of the available data are obtained through passive surveillance methods, which could underestimate the actual number of AEFIs. The switching of BCG vaccine strains and manufacturing processes have occasionally been associated with increased reports of AEFIs.

The Committee noted that the live vaccine requires culture from controlled seed strains and comparison with reference standards regarding the number of culturable units per dose and laboratory tests of immunogenicity, lack of virulence and skin reactogenicity. However, the manufacturing process of this live vaccine, and not just vaccine strain differences, has been reported to affect reactogenicity and notifications of local and regional adenitis.<sup>11</sup>

A new systematic review of the published literature on safety is currently underway. Preliminary findings note mostly case reports of local reactions such as lupus vulgaris, adenitis, granuloma and other skin lesions. Case reports are also available on distal or disseminated adverse events such as osteomyelitis, meningitis, military tuberculosis and disseminated BCG. These case studies have a high risk of bias. Retrospective cohort studies are available that will be used to provide observed rates for some of the most frequent, known BCG reactions.

The review also identified limitations in the characterization of the safety profile of BCG vaccines. Data on strain-specific reactogenicity or on variations in reactogenicity within the same manufacturing process are fairly limited. New information will also be sought on reactogenicity rates and adverse events in newborns

Les vaccins BCG ont un profil d'innocuité bien établi. En général, une administration correcte – par voie intradermique dans la partie supérieure du bras (deltoïde) – entraîne une réaction locale qui consiste en une petite pustule donnant par la suite une cicatrice de faible ampleur. Lorsque ces vaccins sont administrés par voie sous-cutanée, une lymphadénite peut apparaître, avec dans de rares cas, une suppuration et la formation de fistules. Parmi les autres réactions graves possibles, on peut mentionner des abcès ou des ulcérations sévères au point d'injection, des réactions secondaires régionales comme le gonflement d'un ganglion lymphatique régional ipsilatéral, et de rares épisodes de maladie distante, affectant notamment la peau, les intestins ou les os. On détecte parfois une ostéite ou une ostéomyélite jusqu'à 12 mois après la vaccination. La tuberculose disséminée induite par le BCG accompagnée d'une forte létalité est rare et se rencontre presque uniquement en association avec le VIH et un syndrome d'immunodéficience sévère. Le syndrome inflammatoire de reconstitution immunitaire (IRIS) associé au BCG et certains problèmes oculaires comme des uvéites, des névrites optiques ou un lupus vulgaris font aussi partie des réactions indésirables reconnues au vaccin.

La réactogénicité des vaccins BCG dépend de la souche vaccinale, de l'âge du bénéficiaire lors de l'administration ainsi que de ses statuts immunitaire et vaccinal. La plupart des données dont on dispose à ce sujet ont été fournies par des méthodes de surveillance passive, qui sont susceptibles de sous-estimer le nombre réel de MAPI. Les changements de souche de BCG ou de processus de fabrication ont occasionnellement été associés à un accroissement des notifications de MAPI.

Le Comité a noté que le vaccin vivant devait être cultivé à partir de souches ensemencées contrôlées et faire l'objet de comparaisons avec des étalons de référence pour ce qui concerne le nombre d'unités cultivables par dose et les déterminations en laboratoire de l'immunogénicité, du manque de virulence et de la réactogénicité cutanée. Néanmoins, il a été signalé qu'outre les différences de souche vaccinale, le processus de préparation du vaccin vivant pouvait avoir une influence sur la réactogénicité et les notifications d'adénite locale ou régionale.<sup>11</sup>

Une nouvelle revue systématique de la littérature publiée sur l'innocuité de ces vaccins est actuellement en cours. Les résultats préliminaires relèvent principalement des rapports de cas de réactions locales telles que lupus vulgaris, adénite, granulome et autres lésions cutanées. On dispose aussi de rapports de cas concernant des événements indésirables distaux ou disséminés tels que: ostéomyélite, méningite, tuberculose miliaire ou maladie disséminée induite par le BCG. Ces études de cas ont une forte probabilité d'être biaisées. On dispose aussi d'études rétrospectives de cohortes qui seront utilisées pour déterminer les taux observés de certaines des réactions connues au BCG parmi les plus fréquentes.

La revue a aussi identifié des restrictions dans les possibilités de caractérisation du profil d'innocuité des vaccins BCG. Les données relatives à la réactogénicité en fonction de la souche ou aux variations de ce paramètre lorsque le procédé de fabrication est fixé sont assez limitées. On s'efforcera aussi d'obtenir de nouvelles informations sur les taux de réactogénicité et sur

<sup>11</sup> WHO Expert Committee on Biological Standards 2011. Recommendations to assure the quality, safety and efficacy of BCG vaccines, Annex. Available at: [http://www.who.int/biologicals/BCG\\_DB\\_HK\\_23\\_April\\_2012.pdf](http://www.who.int/biologicals/BCG_DB_HK_23_April_2012.pdf), accessed June 2017.

<sup>11</sup> WHO Expert Committee on Biological Standards 2011. Recommendations to assure the quality, safety and efficacy of BCG vaccines, Annex. Disponible à l'adresse: [http://www.who.int/biologicals/BCG\\_DB\\_HK\\_23\\_April\\_2012.pdf](http://www.who.int/biologicals/BCG_DB_HK_23_April_2012.pdf), consulté en juin 2017.



compared to the late neonatal period and post neonatal period in HIV and non-HIV affected infants to help inform any changes in the advice on use of BCG vaccine and schedules in Member States.

### Safety update of HPV vaccines

Since licensure in 2006, over 270 million doses of HPV vaccines have been distributed. GACVS first reviewed the safety data in 2007,<sup>12</sup> and subsequently in 2008,<sup>13</sup> 2009,<sup>14</sup> 2013,<sup>15</sup> 2014<sup>16</sup> and 2015.<sup>17</sup> Early on, the Committee was presented signals related to anaphylaxis and syncope. The risk of anaphylaxis has been characterized as approximately 1.7 cases per million doses, and syncope was established as a common anxiety or stress-related reaction to the injection. No other adverse reactions have been identified and GACVS considers HPV vaccines to be extremely safe.

Further safety data have been generated recently from Denmark, the United Kingdom and the United States of America and a comprehensive literature review has been conducted, prompting GACVS to review these new findings. Among the new data were studies looking at Guillain-Barré syndrome (GBS). The Committee has already assessed GBS as a signal and noted discrepant findings. Epidemiological studies assessing the risk of GBS following HPV vaccination have been published<sup>18</sup> including population cohort studies from Denmark and Sweden.<sup>19</sup> In 2017, in response to an online publication from France suggesting an increased risk,<sup>20</sup> a large self-controlled case-series study from the UK was conducted, based on a population where 10.4 million doses were administered. This most recent study found no significant increased risk for GBS after any dose of vaccine, in any of several risk periods assessed or for either vaccine brand.<sup>21</sup> In addition, GBS was specifically selected as an outcome in studies from the US using the Vaccine Adverse Events Reporting System (VAERS) and the Vaccine Safety Datalink (VSD). GACVS was presented with new data from VAERS following 60 million distributed doses, and the VSD data with over 2.7 million doses administered until the end of 2015. No

les événements indésirables affectant les nouveau-nés par comparaison avec la période néonatale tardive et avec la période postnatale chez les nourrissons infectés ou non par le VIH, en vue d'étayer toute modification éventuelle des conseils pour l'utilisation des vaccins BCG et des calendriers de vaccination des États Membres.

### Le point sur l'innocuité des vaccins contre le HPV

Depuis l'homologation du vaccin contre le HPV en 2006, plus de 270 millions de doses de ce vaccin ont été distribuées. Le GACVS a, une première fois, examiné les données d'innocuité en 2007,<sup>12</sup> puis en 2008,<sup>13</sup> 2009,<sup>14</sup> 2013,<sup>15</sup> 2014<sup>16</sup> et 2015.<sup>17</sup> A un stade précoce, on a présenté au Comité des signaux concernant l'anaphylaxie et la syncope. Le risque d'anaphylaxie a été caractérisé comme étant approximativement de 1,7 cas par million de dose et la syncope a été reconnue comme une réaction courante à l'injection, associée au stress ou à l'anxiété. Aucune autre réaction indésirable n'a été identifiée et le GACVS a considéré le vaccin anti-HPV comme extrêmement sûr.

En outre, des données d'innocuité ont été récemment générées par le Danemark, le Royaume-Uni et les États-Unis d'Amérique et une revue complète de la littérature a été menée, ce qui a incité le GACVS à examiner les nouveaux résultats. Parmi les nouvelles données, figurent des études étudiant le syndrome de Guillain-Barré (SGB). Le comité a déjà évalué le SGB en tant que signal et pris note de résultats contradictoires. Des études épidémiologiques évaluant le risque de SGB suite à une vaccination contre le HPV ont été publiées,<sup>18</sup> parmi lesquelles des études de cohorte en populations réalisées au Danemark et en Suède.<sup>19</sup> En 2017, en réponse à une publication française en ligne suggérant un risque accru,<sup>20</sup> une étude autocontrôlée de grande ampleur portant sur une série de cas a été menée au Royaume-Uni parmi une population à laquelle 10,4 millions de doses avaient été administrées. Cette étude la plus récente n'a relevé aucune augmentation significative du risque de SGB après une dose vaccinale quelconque, dans aucune des multiples périodes à risque évaluées ou pour aucune marque commerciale de vaccin.<sup>21</sup> De même, le SGB a été spécifiquement sélectionné en tant que critère de jugement dans des études effectuées aux États-Unis d'Amérique en utilisant le système Vaccine Adverse Events Reporting System (VAERS) et le Vaccine Safety Datalink (VSD). Il a été présenté au GACVS de nouvelles données émises par le VAERS suite à l'administration de 60 million de doses et

<sup>12</sup> See No. 28/29, 2007, pp. 245–260.

<sup>13</sup> See No. 5, 2009, pp. 37–40.

<sup>14</sup> See No. 32, 2009, pp. 325–332.

<sup>15</sup> See No. 29, 2013, pp. 301–312.

<sup>16</sup> See No. 7, 2014, pp. 53–60.

<sup>17</sup> See No. 3, 2016, pp. 21–32.

<sup>18</sup> Grimaldi-Bensouda L, Rossignol M, Koné-Paut I et al. Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance. *Journal of Autoimmunity*. 2017;79:84–90.

<sup>19</sup> Arnheim-Dahlström L, Pasternak B, Svanström H et al. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. *Bmj*. 2013;347:f5906.

<sup>20</sup> Agence nationale de sécurité du médicament et des produits de santé. Vaccins anti-HPV et risque de maladies auto-immunes: étude pharmaco-épidémiologique, 2015. Available only in French language at <http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Vaccination-contre-les-infections-a-HPV-et-risque-de-maladies-auto-immunes-une-etude-Cnamts-ANSM-rassurante-Point-d-information>, accessed June 2017.

<sup>21</sup> Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barré syndrome after human papilloma virus vaccine: A self-controlled case-series study in England. *Vaccine*. 2017;35(13):1729–1732.

<sup>12</sup> Voir N° 28/29, 2007, pp. 245-260.

<sup>13</sup> Voir N° 5, 2009, pp. 37-40.

<sup>14</sup> Voir N° 32, 2009, pp. 325-332.

<sup>15</sup> Voir N° 29, 2013, pp. 301-312.

<sup>16</sup> Voir N° 7, 2014, pp. 53-60.

<sup>17</sup> Voir N° 3, 2016, pp. 21-32.

<sup>18</sup> Grimaldi-Bensouda L, Rossignol M, Koné-Paut I et al. Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance. *Journal of Autoimmunity*. 2017;79:84–90.

<sup>19</sup> Arnheim-Dahlström L, Pasternak B, Svanström H et al. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. *Bm*. 2013;347:f5906.

<sup>20</sup> Agence nationale de sécurité du médicament et des produits de santé. Vaccins anti-HPV et risque de maladies auto-immunes: étude pharmaco-épidémiologique, 2015. Disponible sur <http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Vaccination-contre-les-infections-a-HPV-et-risque-de-maladies-auto-immunes-une-etude-Cnamts-ANSM-rassurante-Point-d-information>, consulté en juin 2017.

<sup>21</sup> Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barré syndrome after human papilloma virus vaccine: A self-controlled case-series study in England. *Vaccine*. 2017;35(13):1729–1732.

association between HPV vaccine and GBS was identified. Both the UK and US studies concluded, based on their respective data, that a risk of >1 case of GBS per million doses of vaccine could now be excluded.

In addition, GACVS was presented with new studies assessing other safety concerns, again from the US, as well as from Denmark. These studies included examination of specific outcomes that included complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), premature ovarian insufficiency, primary ovarian failure, and a further look at the risk of venous thromboembolism. With now large population level data from several countries, the Committee saw no new evidence for a causal association between HPV vaccine and those conditions. While safety data from Denmark and Sweden for >3 million women aged 18–44 years showed an apparent increased risk for celiac disease, the investigators considered that, most likely, this represented an unmasking of an existing condition during the vaccination visit rather than a causal association. Overall the study did not raise any other autoimmune safety issues of concern.

As HPV vaccine is often administered during potential childbearing years it is important to establish the safety profile in pregnant women when inadvertent administration occurs. To date no safety concerns have arisen during the pre-licensure clinical trials or in post-licensure surveillance.<sup>22</sup> These reassuring data now include a recent national cohort study from Denmark that assessed 540 805 pregnancies.<sup>23</sup> In addition, new data from the VSD for >92 000 eligible pregnancies were presented to the Committee. No adverse obstetric, birth or structural abnormality outcomes were observed. Inadvertent administration of HPV vaccine during pregnancy has no known adverse outcomes in either mother or infant.

CRPS and POTS continue to be presented as case reports in association with HPV vaccination, particularly from Denmark and Japan. These were initially assessed by GACVS in 2015.<sup>24</sup> These conditions include a spectrum of diverse symptoms, making assessment using administrative health collections challenging. In June 2017, new data from Japan that assessed cases with diverse symptoms, including pain and motor dysfunction, were presented to the Committee. The cases were identified from a nationwide epidemiological survey involving multiple hospital medical departments of various disciplines including pain, neurology, rheumatology, paedi-

par VSD après l'administration de plus de 2,7 millions de doses jusqu'à fin 2015. Aucune association entre le vaccin anti-HPV et le SGB n'a été identifiée. Les études britanniques et américaines ont conclu, sur la base de leurs données respectives, qu'un risque supérieur à 1 cas par million de doses pouvait maintenant être exclu.

En outre, on a présenté au GACVS de nouvelles études évaluant des aspects liés à l'innocuité et provenant également des États-Unis d'Amérique et du Danemark. Dans le cadre de ces études, on a examiné des critères de jugement spécifiques, dont le syndrome douloureux régional complexe (SDRC), le syndrome de tachycardie orthostatique posturale (POTS), l'insuffisance ovarienne prématurée et la défaillance ovarienne primaire, et on a étudié de manière plus poussée le risque de thromboembolisme veineux. Disposant maintenant de grandes quantités de données en population provenant de plusieurs pays, le comité a n'a relevé aucune preuve d'un lien causal entre le vaccin anti-HPV et ces affections. Bien que les données d'innocuité émanant du Danemark et de Suède et portant sur plus de 3 millions de femmes de 18 à 44 ans aient apparemment enregistré une augmentation du risque de maladie cœliaque, les enquêteurs ont considéré que cette observation reflétait très probablement la révélation d'une affection déjà existante lors de la visite de vaccination, plutôt que d'un lien de causalité. Globalement, l'étude n'a soulevé aucun autre problème d'innocuité préoccupant d'origine auto-immune.

Le vaccin anti-HPV étant souvent délivré pendant les années où les femmes sont en mesure de procréer, il importe de déterminer son profil d'innocuité chez les femmes enceintes pour les cas où ce vaccins leur aurait été administré par inadvertance. À ce jour, aucun problème d'innocuité n'est apparu pendant les essais cliniques précédant l'homologation ou pendant la surveillance postérieure à celle-ci.<sup>22</sup> Ces données rassurantes incluent maintenant une étude de cohorte nationale récente, menée au Danemark, dans laquelle on a évalué 540 805 grossesses.<sup>23</sup> De plus, de nouvelles données émanant du VSD et concernant plus de 92 000 grossesses répondant aux critères ont été présentées au comité. Aucune issue défavorable de la grossesse, qu'il s'agisse d'un problème obstétrical ou d'une anomalie congénitale ou structurale, n'a été observée. L'administration par inadvertance du vaccin anti-HPV pendant la grossesse ne provoque d'issue défavorable connue ni chez la mère, ni chez l'enfant.

Des rapports de cas de SDRC et de POTS continuent d'être présentés en association avec la vaccination anti-HPV, notamment au Danemark et au Japon. Ils ont été évalués au départ par le GACVS en 2015.<sup>24</sup> Ces affections couvrent un spectre de symptômes divers, ce qui rend leur évaluation par le biais de collectes de données sanitaires administratives passablement difficile. En juin 2017, de nouvelles données provenant du Japon et concernant l'évaluation de cas présentant divers symptômes, dont des troubles douloureux et moteurs, ont été soumises au comité. Ces cas avaient été identifiés à partir d'une enquête épidémiologique à l'échelle du pays, auprès de plusieurs services hospitaliers relevant de diverses spécialités, dont la prise en

<sup>22</sup> Bonde U, Joergensen JS, Lamont RF, et al. Is HPV vaccination in pregnancy safe? *Human vaccines & immunotherapeutics*. 2016;12(8):1960–1964.

<sup>23</sup> Scheller NM, Pasternak B, Mølgaard-Nielsen D et al. Quadrivalent HPV vaccination and the risk of adverse pregnancy outcomes. *New England Journal of Medicine*. 2017;376(13):1223–1233.

<sup>24</sup> See [http://www.who.int/vaccine\\_safety/committee/reports/Dec\\_2015/en/](http://www.who.int/vaccine_safety/committee/reports/Dec_2015/en/)

<sup>22</sup> Bonde U, Joergensen JS, Lamont RF, et al. Is HPV vaccination in pregnancy safe? *Human vaccines & immunotherapeutics*. 2016;12(8):1960–1964.

<sup>23</sup> Scheller NM, Pasternak B, Mølgaard-Nielsen D et al. Quadrivalent HPV vaccination and the risk of adverse pregnancy outcomes. *New England Journal of Medicine*. 2017;376(13):1223–1233.

<sup>24</sup> Voir [http://www.who.int/vaccine\\_safety/committee/reports/Dec\\_2015/fr/](http://www.who.int/vaccine_safety/committee/reports/Dec_2015/fr/)

atrics and psychiatry/psychosomatic medicine. These complex syndromes manifested in both sexes, although were more common in girls, and occurred in both vaccinated and unvaccinated individuals. The Committee concluded that since their last review, there is still no evidence to suggest a causal association between HPV vaccine and CRPS, POTS or the diverse symptoms that include pain and motor dysfunction.

Also in 2017, the WHO commissioned a systematic review of serious adverse events (SAEs) following HPV vaccines. A draft was presented to GACVS at the meeting. Using the GRADE system to systematically assess the quality of evidence, the quality of evidence in the studies was considered high across randomized controlled trials. The outcomes considered were all SAEs, medically significant conditions, new onset of chronic diseases, and deaths. Data for 73 697 individuals were reviewed. Lower level studies were excluded in favour of the large body of higher level evidence available. For all outcomes, the evidence from randomized controlled trials was supported by good quality cohort studies, with no difference in rates of selected SAEs between exposed and unexposed to HPV vaccine observed.

There are now accumulated safety studies that include several million persons<sup>25</sup> and which compare the risks for a wide range of health outcomes in vaccinated and unvaccinated subjects. However, despite the extensive safety data available for this vaccine, attention has continued to focus on spurious case reports and unsubstantiated allegations. The Committee continues to express concern that the ongoing unsubstantiated allegations have a demonstrable negative impact on vaccine coverage in a growing number of countries, and that this will result in real harm.<sup>26</sup> While ongoing monitoring and collection of robust data are important to maintain confidence, one of the challenges associated with the continued generation of data is that artefacts will be observed, which could pose further challenges for communication when taken in haste, out of context, and in the absence of the overall body of evidence.

GACVS discussed the importance of ensuring that immunization policy-makers and other stakeholders have ready access to articulate summaries of the vaccine safety information, to assist in evidence-based decision-making. One concrete step will be to update the HPV adverse reaction rate sheet, to reflect the most recent evidence available.<sup>27</sup>

charge de la douleur, la neurologie, la rhumatologie, la pédiatrie et la médecine psychiatrique/psychosomatique. Les syndromes complexes observés se manifestaient chez les deux sexes, même s'ils étaient plus fréquents chez les filles, et touchaient à la fois des personnes vaccinées et non vaccinées. Le comité a conclu que depuis le dernier examen, il n'y avait toujours pas d'élément suggérant un lien de causalité entre le vaccin anti-HPV et le SDRC, le POTS ou les divers symptômes incluant des troubles douloureux ou moteurs.

En 2017 également, l'OMS a commandité une revue systématique des événements indésirables graves suite à l'administration des vaccins anti-HPV. Une version préliminaire de cette revue a été présentée au comité lors de sa réunion. La qualité des preuves produites dans les études a été considérée comme grande pour les essais contrôlés randomisés d'après l'évaluation systématique de ces preuves avec le système GRADE. On a considéré comme critères de jugement tous les événements indésirables graves, les affections ayant des conséquences médicales, les résurgences de maladies chroniques et les décès. Des données relatives à 73 697 individus ont été examinées. Des études de bas niveau ont été exclues en faveur de l'important corpus de preuves de plus haut niveau disponible. Pour l'ensemble des critères de jugement, les preuves fournies par les essais contrôlés randomisés étaient confirmées par des études de cohorte de bonne qualité, sans différence observée entre les taux d'événements indésirables graves sélectionnés chez les personnes exposées et non exposées au vaccin anti-HPV.

On a maintenant accumulé des études d'innocuité couvrant plusieurs millions de personnes<sup>25</sup> et comparant les risques pour une large palette de critères de jugement chez des sujets vaccinés et non vaccinés. Néanmoins, malgré les quantités considérables de données disponibles concernant l'innocuité des vaccins anti-HPV, l'attention continue de se focaliser sur des rapports de cas fallacieux et des allégations non substantiées. Le comité continue également d'exprimer la crainte que les allégations non substantiées actuellement propagées aient un impact négatif démontrable sur la couverture vaccinale dans un nombre grandissant de pays et qu'il en résulte des effets préjudiciables bien réels.<sup>26</sup> Si le suivi et la collecte en cours de données robustes sont importants pour préserver la confiance, l'une des défis associés à la génération continue de données réside dans l'observation d'artefacts, qui pourraient entraîner des difficultés supplémentaires de communication s'ils étaient relevés à la hâte, hors de leur contexte et en l'absence du corpus global de preuves.

Le GACVS a discuté de l'importance d'assurer aux personnes chargées d'élaborer les politiques de vaccination et aux autres parties prenantes un accès facile à des résumés clairs et précis des informations sur l'innocuité des vaccins, pour les aider à prendre des décisions reposant sur une base factuelle. Une étape concrète sur cette voie consistera à mettre à jour la fiche d'informations sur les fréquences des réactions indésirables au vaccin anti-HPV, pour qu'elle reflète les éléments disponibles les plus récents.<sup>27</sup>

<sup>25</sup> Gee J, Weinbaum C, Sukumaran L et al. Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States. *Human vaccines & immunotherapeutics*. 2016;12(6):1406–1417.

<sup>26</sup> See [http://www.who.int/vaccine\\_safety/committee/topics/hpv/GACVS\\_Statement\\_HPV\\_12\\_Mar\\_2014.pdf](http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HPV_12_Mar_2014.pdf)

<sup>27</sup> See [http://www.who.int/vaccine\\_safety/initiative/tools/vaccinfosheets/en/](http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/)

<sup>25</sup> Gee J, Weinbaum C, Sukumaran L et al. Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States. *Human vaccines & immunotherapeutics*. 2016;12(6):1406–1417.

<sup>26</sup> Voir [http://www.who.int/vaccine\\_safety/committee/topics/hpv/GACVS\\_Statement\\_HPV\\_12\\_Mar\\_2014.pdf](http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HPV_12_Mar_2014.pdf)

<sup>27</sup> Voir [http://www.who.int/vaccine\\_safety/initiative/tools/vaccinfosheets/fr/](http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/fr/)



Where HPV vaccination programmes have been implemented effectively, the benefits are already very apparent. Several countries that have introduced HPV vaccines to their immunization programme have reported a 50% decrease in the incidence rate of uterine cervix precancerous lesions among younger women. In contrast, the mortality rate from cervical cancer in Japan, where HPV vaccination is not proactively recommended, increased by 3.4% from 1995 to 2005 and is expected to increase by 5.9% from 2005 to 2015. This acceleration in disease burden is particularly evident among women aged 15–44 years.<sup>28</sup> Ten years after introduction, global HPV vaccine uptake remains slow, and the countries that are most at risk for cervical cancer are those least likely to have introduced the vaccine. Since licensure of HPV vaccines, GACVS has found no new adverse events of concern based on many very large, high quality studies. The new data presented at this meeting have strengthened this position.

### Template for reviewing the safety profile of new vaccines

GACVS evaluates information from multiple sources to assess vaccine safety. Standardizing, where possible in order to facilitate the assessment process and increase efficiency, was one of the recommendations of the recent 15-year review of GACVS.<sup>29</sup> The Committee has developed guidelines and a presentation template for reviewing the safety profile of new vaccines. The objective of this guidance document is to provide, for presenters, a framework that includes the essential safety information that GACVS requires in order to make an assessment of vaccine safety. It is acknowledged that safety data and issues may be diverse, and that presentations may need to be adapted accordingly. It is also recognized that while such a template may guide the presentation of safety data, such a document is not intended to replace existing documentation (such as the International Conference on Harmonisation *Guideline for Good Clinical Practice*) which details how clinical trials should be performed and what safety data should be collected.

For guidance in developing the template document, a subcommittee of GACVS has considered previous presentations. These include documents from the Advisory Committee for Immunization Practice (*Guidance for Health Economics Studies*) and the Council for International Organizations of Medical Sciences (*CIOMS Guide to Active Vaccine Safety Surveillance*).

The draft template is divided into 7 sections. Section 1 addresses the presenters and any conflicts of interest, an overview of product development, and the product

Dans les cas où les programmes de vaccination contre le HPV sont mis en œuvre efficacement, leurs bénéfices sont déjà très visibles. Plusieurs pays ayant introduit un vaccin contre ce virus dans leur programme de vaccination ont signalé une baisse de 50 % du taux d'incidence des lésions précancéreuses du col utérin chez les jeunes femmes. À l'inverse, le taux de mortalité dû à ce cancer au Japon, où la vaccination contre le HPV n'est pas recommandée proactivement, s'est accru de 3,5% entre 1995 et 2005 et devrait avoir augmenté de 5,9 % entre 2005 et 2015. L'accélération de la charge de morbidité est particulièrement visible chez les femmes de 15 à 44 ans.<sup>28</sup> Dix ans après l'introduction du vaccin anti-HPV, son rythme de mise en place dans le monde reste lent et les pays où le risque de cancer du col utérin est le plus important sont aussi ceux où la probabilité que la vaccination anti-HPV ait été instaurée est la plus faible. Depuis l'homologation des vaccins anti-HPV, le GACVS n'a relevé aucun nouvel événement indésirable préoccupant en exploitant de nombreuses études de grande ampleur et de haute qualité. Les nouvelles données présentées à la réunion ont renforcé cette position.

### Modèle pour l'examen du profil d'innocuité des nouveaux vaccins

Le GACVS évalue des informations provenant de multiples sources pour juger de l'innocuité de vaccins. La standardisation, lorsqu'elle est possible, en vue de faciliter le processus d'évaluation et d'accroître son efficacité, faisait partie des recommandations formulées à l'issue du récent bilan sur 15 ans du GACVS.<sup>29</sup> Le Comité a mis au point des lignes directrices et un modèle de présentation pour l'examen du profil d'innocuité des nouveaux vaccins. L'objectif de ce document d'orientation est de fournir, à l'attention des présentateurs, un cadre recensant les informations essentielles concernant l'innocuité des vaccins dont le GACVS a besoin pour réaliser son évaluation. Il est reconnu que les données et les questions relatives à l'innocuité peuvent être très diverses et que les présentations doivent être adaptées en conséquence. Il est également reconnu que si un tel modèle peut guider la présentation des données d'innocuité, il n'est pas destiné à remplacer la documentation existante (comme celle émanant de la Conférence internationale sur l'harmonisation des lignes directrices relatives aux bonnes pratiques cliniques), qui décrit en détail comment les essais cliniques devront être réalisés et quelles données d'innocuité devront être collectées.

Pour élaborer le document modèle, un sous-comité du GACVS a pris en compte les présentations faites antérieurement à ce Comité pour dégager ceux de leurs éléments qui s'étaient révélés utiles. Des documents tels que ceux émanant de l'Advisory Committee for immunization practice (*Guidance for Health Economics Studies*) ou du Council for International Organizations of Medical Sciences (*CIOMS Guide to Active Vaccine Safety Surveillance*) ont aussi été consultés.

La version préliminaire du modèle est divisée en 7 sections. La section 1 présente la liste des présentateurs et de tous les conflits d'intérêt qu'ils peuvent avoir, puis donne un exposé

<sup>28</sup> Iwata S et al. Consensus statement from 17 relevant Japanese academic societies on the promotion of the human papillomavirus vaccine. *Vaccine*. 2017;35:2291–2292.

<sup>29</sup> Asturias EJ, Wharton M, Pless R et al. Contributions and challenges for worldwide vaccine safety: The Global Advisory Committee on Vaccine Safety at 15 years. *Vaccine*. 2016;34(29):3342–3349.

<sup>28</sup> Iwata S et al. Consensus statement from 17 relevant Japanese academic societies on the promotion of the human papillomavirus vaccine. *Vaccine*. 2017;35:2291–2292.

<sup>29</sup> Asturias EJ, Wharton M, Pless R et al. Contributions and challenges for worldwide vaccine safety: The Global Advisory Committee on Vaccine Safety at 15 years. *Vaccine*. 2016;34(29):3342–3349.

characteristics. Section 2 is an Integrated Summary of Safety. Section 3 addresses the pre-licensure clinical trials; if possible these should be presented as a meta-analysis or collated studies. If there are a limited number of key trials, detailed description can be presented. Details, for example, would then focus specifically on the methodology and results that have led to the safety conclusions reached. Limitations should be specified. Section 4 covers the methodology and results from post-licensure trials and/or surveillance studies. Section 5 should detail the limitations of the pre- and post-licensure trials/studies, and should then detail any identified or potential risks. Section 6 details plans for future post-marketing studies or pharmacovigilance activities that will be conducted and include a summary of the product Risk Management Plans if one was developed. The final section includes supporting material such as lists of references, product labels, etc.

An accompanying draft document proposes guidance for preparing the session. Presenters will be identified, and invited by the WHO GACVS Secretariat 12 weeks prior to the planned session. Presentations and supporting documentation will be required 8 weeks prior to the session to allow time for review and comment of drafts. This presentation material will be reviewed by the WHO Secretariat and a GACVS committee member who will subsequently chair the relevant session at the time of the GACVS meeting. The presentation will be reviewed and 6 weeks prior to presentation will be returned to the presenter for points of clarification and to address any outstanding issues. The final presentation is required by the WHO Secretariat 4 weeks prior to presentation so that it can be provided to the committee members well in advance for their review.

Comments from the Committee included a suggestion to separate information gained from pre-licensure studies from those obtained through post-licensure studies. Clarifications on the information needed for novel adjuvants and information to be displayed in integrated safety summaries versus information from individual trials were also requested. GACVS also noted that the template requirements will not be met if clinical trials are not designed to generate this information. In some past presentations reviewed by GACVS, a lack of critical information prevented the Committee from reaching a definite conclusion on safety issues. The template will therefore help GACVS highlight areas of missing evidence more systematically. A revised version of the template and accompanying document will be produced based on the discussion at this meeting, and will be posted on the GACVS website after final endorsement. ■

général de la mise au point du produit et enfin indique les caractéristiques de celui-ci. La section 2 est un résumé intégré des questions d'innocuité. La section 3 présente les essais cliniques pré-homologation et, dans la mesure du possible, devrait exposer une méta-analyse ou des études collationnées. Si le nombre d'essais clés est limité, leur description détaillée peut être fournie. On pourra ensuite décrire en détail la méthodologie et les résultats ayant conduit aux conclusions en termes d'innocuité. Les limitations rencontrées devront être spécifiées. La section 4 couvrira la méthodologie et les résultats des essais post-homologation et/ou des études de surveillance. La section 5 devra décrire précisément les limites des essais/études pré-homologation et post-homologation et tous les risques repérés ou potentiels. On trouvera dans la section 6 les plans détaillés des études postcommercialisation futures ou des activités de pharmacovigilance qui seront menées, ainsi qu'un résumé des plans de gestion des risques liés au produit, si de tels plans ont été élaborés. La dernière section contient des éléments de référence comme des listes de références, des étiquettes du produit, etc.

Une version préliminaire du document d'orientation pour préparer la session accompagne le modèle. Les présentateurs seront désignés et invités par le Secrétariat du GACVS de l'OMS 12 semaines avant la session prévue. Les présentations et les éléments de référence devront être disponibles 8 semaines avant la session afin de ménager du temps pour l'examen et le commentaire des versions préliminaires. Les éléments présentés seront examinés par le Secrétariat de l'OMS et un membre du comité GACVS, qui présidera ultérieurement la session concernée lors de la réunion de ce comité. La présentation fera l'objet d'un examen et 6 semaines avant la présentation en session, sera renvoyée au présentateur pour qu'il clarifie certains points et réponde à toute question en suspens. Le Secrétariat de l'OMS demande à disposer de la présentation finale 4 semaines avant la présentation de manière à la faire parvenir aux membres du comité suffisamment à l'avance pour qu'ils puissent l'examiner.

Parmi les observations du comité, il a été suggéré de séparer les informations fournies par les études pré-homologation de celles obtenues avec les études post-homologation. Il a également été demandé des clarifications concernant les informations nécessaires pour les nouveaux adjuvants et celles devant être présentées dans les résumés intégrés des questions d'innocuité, en regard des données des différents essais. Le GACVS a également noté que les exigences du modèle ne seraient pas satisfaites si les essais cliniques n'étaient pas conçus pour générer ces informations. Dans certaines présentations antérieures examinées par le GACVS, un manque d'informations critiques avait empêché ce comité de parvenir à une conclusion définitive sur les questions d'innocuité. Le modèle aidera donc le GACVS à faire ressortir plus systématiquement les domaines où il manque des données. Une version révisée de ce modèle et du document d'accompagnement sera élaborée à partir des discussions menées pendant la réunion et chargée sur le site Web du comité après approbation finale. ■

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**WHO's 4<sup>th</sup> Product Development for Vaccines Advisory committee (PDVAC) meeting**  
**21-23 June 2017**  
**Executive Summary**

On 21-23<sup>rd</sup> June 2017, WHO's Product Development for Vaccines Advisory Committee (PDVAC) convened for its 4<sup>th</sup> annual meeting. Product development progress in 10 pathogen areas that had been previously prioritized was discussed, and 4 new pathogens with candidates in, or approaching clinical development were reviewed. In addition, 6 key cross-cutting topics that have implications across several priority pathogens were considered.

There have been significant advances in the product development of vaccines and other technologies since the June 2016 PDVAC meeting, including:

- **Global Vaccine Action Plan (Objective 6) / Decade of Vaccines (Goal 5):**
  - **Human Immunodeficiency Virus (HIV):** Two HIV vaccine candidates are currently in late stage clinical trials in HIV-uninfected populations, as heterologous prime-boost approaches. Data from these studies are anticipated in 2020-21, and may be proposed as the basis for licensure application in some countries, if safety and efficacy is demonstrated. A number of broadly neutralising antibody approaches for HIV are also in development, with a prototype monoclonal antibody in Phase IIb studies, and pivotal proof-of-concept data are anticipated in the same timeframe as the vaccine candidates.
  - **Tuberculosis (TB):** There are seven tuberculosis vaccine candidates in phase II clinical studies, and one in phase III. Two candidates target reduction of disease in adolescents and adults, previously identified and endorsed by PDVAC as the priority public health goal for TB vaccine development, and will deliver clinical proof-of-concept data over the next 12 months. BCG replacement candidates are also advancing, with the leading candidate in Phase IIb studies.
  - **Malaria:** Development status of second generation malaria vaccines will be covered by a separate consultation (MALVAC) in 2017-18.
  - **Influenza:** WHO Preferred Product Characteristics for Next-Generation Influenza Vaccines have been published. Several candidate vaccines designed to elicit antibodies to conserved epitopes on the hemagglutinin head or stem are advancing to early stage clinical development with the goal of achieving broad and durable immunity.
- **Major currently non-vaccine preventable diseases:**
  - **Respiratory Syncytial Virus (RSV):** The RSV vaccine and monoclonal antibody (mAb) pipeline remains well-populated and diverse, with 15 vaccine candidates in clinical studies, and two mAbs in late stage clinical development. Two recombinant protein, post-fusion F-based vaccine candidates did not demonstrate efficacy in clinical proof-of-concept studies in the elderly. The majority of candidates in clinical evaluation incorporate alternative antigens or constructs and are targeting maternal or pediatric immunization strategies. Anti-F antigen mAbs are in phase IIb and III clinical development. WHO Preferred Product Characteristics (PPCs) and the Technical Roadmap for development of RSV vaccines have been finalized and are publically available.
  - **Enteric and diarrheal diseases:** Recently published global burden of disease estimates for enterotoxigenic E. coli (ETEC) and Shigella differ markedly from previous estimates with respect to mortality and are incomplete with respect to morbidity. Further work will be needed to evaluate the global public health need for, and potential impact of, vaccines

against each of these pathogens. The leading ETEC vaccine candidate has advanced to a Phase IIb proof-of concept field study in adult travellers; the leading Shigella candidates have been evaluated in Phase I and are undergoing evaluation in a controlled human infection model (CHIM). The proof-of-concept Phase IIb study with the leading Norovirus candidate in adults continues.

- **Group A streptococcus (GAS):** Updated global disease burden estimates for GAS are eminent. There are currently 4 candidates in preclinical, or early clinical development. Following a global consultation convened by WHO and the International Vaccine Institute (IVI) in 2016, WHO technical vaccine roadmap and preferred product characteristics documents will be published in the coming weeks.
- **Sexually Transmitted Infections:**
  - **Herpes Simplex Virus:** Several therapeutic vaccine candidates against Herpes Simplex Virus (HSV) are in late stage clinical development, and have demonstrated clinical proof-of-concept in Phase II studies. In line with the previously published Roadmap for Sexually Transmitted Infections, development of PPCs for therapeutic and prophylactic HSV vaccines is underway, in tandem with a value proposition to articulate the public health need for these vaccines in low- and middle-income country contexts.
  - **Gonorrhoea :** Gonorrhoea is associated with a significant infertility burden, is a strong co-factor for HIV infection, and is the leading cause of preventable neonatal blindness. While previously relatively easy to treat, first line therapy is now failing as a result of increasing antimicrobial resistance. No vaccine candidates are currently in clinical development, but recently published data demonstrates that outer membrane vesicle (OMV)-based Group B meningococcal vaccine provides some cross-protection. This supports the feasibility of reverse vaccinology approaches to Gonorrhoea vaccine development in the near term.
- **Maternal immunization:** The development of vaccines specifically for use during pregnancy are advancing, for example against both Respiratory Syncytial Virus (RSV) and Group B Streptococcus (GBS). In addition, there has been substantial progress in the development of several vaccines that could offer protection against diseases that are important to maternal and child health, through maternal immunization strategies, for example those against Zika, influenza and Cytomegalovirus (CMV). Whilst these vaccines may be evaluated in men and non-pregnant women, priority should be given to identifying mechanisms for evaluation of these vaccines for use in pregnant women.
  - **Group B Streptococcus (GBS):** WHO PPCs and the Technical Roadmap for development of GBS vaccines have been finalised and are publically available. There are currently two GBS vaccine candidates undergoing clinical evaluation, with several in preclinical development. Global assay standardization efforts, particularly in support of establishing a correlate of protection, are continuing in parallel with consultations regarding an acceptable regulatory route to licensure.
  - **Cytomegalovirus (CMV):** Congenital cytomegalovirus infections are common throughout the world, and severely affect the central nervous system resulting in a range of sequelae; however, the burden of CMV in low and middle income countries (LMICs), and its contribution to developmental disorders in these contexts is not well defined. Several live and recombinant vaccine approaches are in clinical development, and may have utility in LMICs, in which CMV seropositivity in women of child-bearing age is considered to be significantly higher than in high income countries.

- **Platform delivery technology:**
  - **Passive immunization:** Monoclonal antibody products to prevent infection and disease are in development against an increasing number of pathogens, for example HIV, RSV, Staphylococcus aureus and rabies. Candidates for HIV and RSV are currently in Phase IIb and Phase III development, respectively.
  - **Nucleic acid-based delivery technologies:** A new generation of DNA and RNA-based vaccine candidates are in pre-clinical and early clinical development, the former delivered by a variety of devices (e.g., electroporation or needle-free injection devices) and the latter through enhancements in stability and/or expression levels in conjunction with lipid nanoparticle emulsions and/or incorporation of self-amplifying replicon sequences. To date, clinical studies in humans have not manifested the theoretical safety concerns that were raised when these vaccines first entered the clinic.
- **WHO R&D Blueprint:** The R&D Blueprint is a global strategy and preparedness plan that allows the rapid activation of R&D activities, such as vaccine development, during epidemics. In support of this, target product profiles (TPPs) have been developed for prioritized pathogens.
  - **Zika Virus:** The TPP for a vaccine to protect against congenital Zika syndrome for use during an emergency has been updated twice through public consultation. There are now 47 Zika virus vaccine candidates in development, 7 of which are in clinical studies. The most advanced candidates (3 of 7 in clinical studies) are based on nucleic acid platforms.
  - **Other of priority diseases:** Vaccine TPPs have been developed for three other diseases: Nipah, Lassa fever, and Middle East Respiratory Syndrome (MERS).
- **Antimicrobial resistance (AMR):** WHO published its first ever list of antibiotic-resistant "priority pathogens" that pose the greatest threat to human health. The role of vaccines in the overall strategy to combat AMR has been underestimated and should always be considered in the estimation of the medical need and value proposition of vaccines available or in development.
- **Cholera (2<sup>nd</sup> Generation):** In the context of the challenges experienced with uptake of previously licensed oral cholera vaccines, several second generation cholera vaccine candidates are in the pipeline, with three in late stage clinical studies. A TPP for second generation cholera vaccines is in development, to articulate the incremental improvements that will be needed to offer significant benefit over existing and available vaccines.
- **Rabies:** Although Rabies immunoglobulin is licensed for both pre-exposure (PreP) and post-exposure (PEP) prophylaxis, it is costly and its administration schedule is challenging with respect to compliance. The development of a human prophylactic vaccine is considered key to an effective rabies control strategy. Three candidates are in clinical studies, and a WHO PPC may be developed, resources permitting.

\*\*\*\*\*

**Specific recommendations** that emerged from the meeting include to:

*Pathogen-specific:*

- **HIV:** Facilitate scenario planning and development of communication strategies in preparation for HIV vaccine and monoclonal antibody study outcomes. Evaluate the development pathway beyond ongoing proof-of-concept studies. Identify gaps in guidelines to support licensure, availability and use in LMICs for both adult and infant populations.



- **TB:** Continue to facilitate and seek to accelerate development of vaccines for prevention of tuberculosis in adults and adolescents, including development of a PPC for this indication.
- **RSV:** Review the data from the late stage, clinical trials in the elderly of recombinant protein based post-fusion F-RSV vaccine candidates, and consider implications for product development of other F-antigen based approaches, specifically with respect to the recently finalized RSV vaccine PPC and technical roadmap. Develop WHO Preferred Product Characteristics for RSV monoclonal antibodies.
- **GBS:** Pursue implementation of the priorities identified in the R&D technological roadmap for Group B Streptococcus vaccines, including efforts to identify a correlate of protection. Evaluate the vaccine value proposition considering health, economic and societal dimensions.
- **CMV:** Undertake a vaccine landscape analysis of CMV vaccines, including the global public need and potential product development pathways and target populations for use in LMICs. Consider as part of maternal immunization/platform strengthening agenda.
- **ETEC/Shigella:** Evaluate the mortality and morbidity estimates for ETEC and Shigella, and the methodology used to derive them. Both ETEC and Shigella remain priority pathogens; PPCs and clarity on development pathways for use in LMICs are needed for both.

*Cross-cutting and platform delivery technology*

- **Maternal immunization:** Consider the clinical and regulatory pathway for the safe and ethical evaluation of vaccine candidates in pregnant women, in order to expedite the licensure and availability of vaccines that would have public health impact through maternal immunization strategies.
- **Passive immunization:** Evaluate the technical, regulatory and commercial barriers to development, licensure and availability of mAb, specifically for use in LMICs.
- **Nucleic acid-based delivery technologies:** Evaluate the product development considerations for nucleic acid vaccine platforms, including in the context of maternal immunization strategies.
- **AMR:** Develop a quantitative framework through which the public health impact of vaccines to combat AMR can be evaluated, to inform the incremental value that these vaccines could offer over and above reduction of disease. Such an analysis will inform vaccine R&D investment and prioritization.
- **Value propositions:** For pathogens areas where there are candidates that are targeted for launch in high income countries, for example GAS, develop value propositions early on in product development to evaluate and articulate the need in LMIC contexts, and thereby strengthen their *global* investment case.

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**BACKGROUND PAPER TO SAGE**

**ON**

**TYPHOID VACCINE POLICY**

**RECOMMENDATIONS**

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Prepared by the SAGE Working Group on Typhoid  
Vaccines & the WHO Secretariat

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## ABBREVIATIONS

AMR	Antimicrobial resistance
DOMI	Diseases of the Most Impoverished Programme
DTP	Diphtheria-Tetanus-Pertussis vaccine
EPI	Expanded Programme on Immunization
GMT	Geometric mean titre
LMIC(s)	Low and middle income countries
MDR	Multi-drug resistant (in the context of typhoid fever, defined as resistance to the traditional first line antibiotics of ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole)
OLT	Open label trial
OPV	Oral polio vaccine
RCT	Randomized controlled trial
SEAP	Surveillance of Enteric Fever in Asia Project
SETA	Severe Typhoid in Africa Program
STRATAA	Strategic Typhoid Alliance across Africa and Asia
TCV	Typhoid conjugate vaccine
TSAP	Typhoid Fever Surveillance in Africa Program
TyVAC	Typhoid Vaccine Acceleration Consortium
ViPS	Vi polysaccharide vaccine
Vi-rEPA	Vi polysaccharide antigen linked to the recombinant exoprotein A of <i>Pseudomonas aeruginosa</i>
Vi-TT	Vi polysaccharide antigen linked to tetanus toxoid protein
WASH	Water Sanitation and Hygiene

## EXECUTIVE SUMMARY

Typhoid fever remains an important cause of enteric disease in children in Low and middle income countries with global estimates of disease burden ranging between 11 and 21 million typhoid fever cases and approximately 145 000 to 161 000 deaths annually.

Transmission of *Salmonella* Typhi is by the feco-oral route through a short-cycle (contamination of food and water in the immediate environment through inadequate hygiene and sanitation measures, either by shedding from temporary or chronic carriers) or long-cycle transmission (defined as contamination of the broader environment, such as pollution of water supplies by sewage, inadequate treatment of piped water or use of raw human feces as a crop fertiliser).

The often non-specific symptoms of typhoid fever makes clinical diagnosis difficult as it may be confused with a wide range of other febrile illnesses common in typhoid fever endemic regions. Laboratory confirmation of cases by blood culture (the most commonly used diagnostic test) has a limited sensitivity of approximately 50% and is further complicated by the common practice of pre-treatment with antibiotics or is often not performed for the majority of cases in LMICs.

A consistent finding of typhoid fever disease burden studies in the last two decades has been the high incidence of typhoid fever in South and South-East Asia with marked intra-country heterogeneity in both age-specific and geographic incidence. New data from sub-Saharan Africa have improved the understanding of the burden and risk factors in that region. Furthermore, new data confirm that typhoid fever with severity sufficient for an outpatient visit or hospital admission is common in the 0-4 year age group with a large proportion of disease occurring between 6 months and 2 years of age. Among all age groups, 27% of typhoid fever episodes are estimated to occur in the age group 0-4 years; including 29.7% of typhoid fever episodes in the  $\leq 2$  year age group, 9.9% in the  $\leq 1$  year age group, and 2.9% in infants  $\leq 6$  months.

Access to safe water and adequate sanitation, health education, appropriate hygiene among food handlers, and typhoid vaccination and appropriate antibiotic treatment are all effective strategies for prevention and control of typhoid fever. Multi-drug resistant (MDR) strains of *S. Typhi* emerged in the late 1980s leading to widespread use of fluoroquinolones, followed in the 1990s and 2000s by the appearance of fluoroquinolone resistant strains. More recently, MDR *S. Typhi* has caused large outbreaks in East Asia and Africa that are of significant concern. The *S. Typhi* H58 clade is responsible for much of the recent and current spread of resistant strains. AMR in typhoid fever leads to increased clinical treatment failure and complications, an

increased frequency of hospital admission and prolonged hospital stay, and more expensive treatment options not affordable in many endemic settings.

Despite SAGE recommendations in 2008 for the use of Vi polysaccharide (ViPS) and Ty21a vaccines for the control of typhoid in endemic and epidemic settings, routine public health use has been very limited. The evidence review did not change the current recommendations for ViPS and Ty21a vaccines. Two Vi-tetanus toxoid (Vi-TT) conjugate vaccines are licensed in India. Based on the data available for review, the SAGE Working Group concluded that there is moderate-certainty evidence that at least one licensed Vi-TT vaccine (Typbar-TCV<sup>TM</sup> manufactured by Bharat Biotech International Limited) results in improved GMTs and seroconversion rates compared to ViPS vaccine (there are no comparative data with Ty21a). Further the data on co-administration of Typbar-TCV with measles-containing vaccines (measles and MMR) do not show evidence of interference with the immune responses to either vaccine. Data from a human challenge study using Typbar-TCV in a population of immunologically naïve adult volunteers produced an estimate of efficacy of 87.1% (95% CI 47.2-96.9%) based on an endpoint of persistent fever followed by positive blood culture. This was considered as good supporting evidence for the vaccine.

The available data from modelling indicate that routine immunization with TCV would lead to a gradual but sustained decrease in typhoid fever cases while routine vaccination with catch-up would lead to both an immediate and sustained decline in incidence. Further, cost-effectiveness analysis has shown that at a price of up to USD 2 per dose, routine vaccination with TCV is likely to be cost-effective in high incidence settings and in most medium incidence settings depending on the willingness to pay.

Currently, no reliable risk prediction tools are available to support implementation of typhoid vaccination programmes using a risk-based approach. Where reliable data are available to assess the level of typhoid fever incidence with confidence, the vaccine delivery strategy should take into account the local epidemiological and programmatic considerations. In particular, in countries with reliable epidemiological evidence of high incidence in well-defined sub-populations, a vaccination strategy based on risk assessment (high incidence population groups) should be considered. This may be particularly important for large countries where resources are limited. In countries with substantial typhoid fever burden but where surveillance does not allow characterisation of typhoid fever incidence among sub-populations, a universal (country-wide) strategy should be considered, and may prove more feasible and cost-effective.

**Draft recommendations:** The Working Group was tasked to address the following overall policy questions:

1. Should TCV be recommended in addition to the available ViPS and Ty21a vaccines for routine use in persons 2 years of age and older?<sup>a</sup> (Critical question<sup>b</sup>)
2. Should TCV be recommended for routine use in children less than 2 years of age? What should be the lower age limit for use in this group? (Critical question)
3. Should different recommendations be developed for use of the above vaccines in endemic settings versus outbreaks or humanitarian emergencies? (Non-critical question)

Based on its evidence review, the Working Group proposed the following draft recommendations for consideration by SAGE.

***Recommendation for individuals 2 years and above***

Given the continued high burden of typhoid fever and the increasing antimicrobial resistance of *S. Typhi*, and in view of the currently available evidence on safety, efficacy, feasibility, and affordability of at least one licensed typhoid conjugate vaccines and of the previously recommended ViPS and Ty21a vaccines, SAGE re-emphasizes the importance of the programmatic use of typhoid vaccines for controlling endemic disease.

Specifically, countries should consider the routine use of typhoid conjugate vaccine or ViPS vaccine or Ty21a vaccine in individuals aged 2 years and above. The evidence reviewed for at least one licensed TCV (Typbar-TCV) demonstrate that it is likely offering longer and higher protection than ViPS and Ty21a, and supports a recommendation for its public health use. These vaccines should be given irrespective of the intensity of other control strategies.

***Recommendation for children below 2 years***

Given the high proportion of typhoid fever that is sufficiently severe to require outpatient or inpatient care in children <2 years in many areas, SAGE recommends the use of TCV in children <2 years of age, administered as a single dose at any time between 6 months to 23 months of age in endemic countries. The evidence reviewed for at least one licensed TCV (Typbar-TCV) demonstrate that it is likely offering longer and higher protection than ViPS and Ty21a, and supports a recommendation for its public health use. The decision on the age of TCV administration should be based on the local epidemiology of typhoid fever, geographic heterogeneity, and taking into account programmatic considerations of the routine childhood immunization programme.

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<sup>a</sup> It should be noted that this question was worded to avoid any sense of prioritizing TCV over ViPS or Ty21a.

<sup>b</sup> Critical questions required an assessment of the quality of evidence.

There are opportunities to administer one dose of TCV at 9 months of age with MCV1, or at 15-18 months of age with MCV2, recognizing that in many places the appreciable burden of typhoid fever starts to appear at 12 months of age.

### ***Recommendation for vaccine use in outbreaks and humanitarian emergencies***

Given the epidemic potential of typhoid fever, and observations on the effectiveness of vaccination in interrupting outbreaks, typhoid fever vaccination is recommended for outbreak control. Typhoid vaccines may be considered in humanitarian emergencies depending on the risk assessment in the local setting. However, it should be emphasized that the mainstay of typhoid fever prevention in such settings is often the provision of clean water and chlorination of water supplies, along with promotion of hygiene measures. The WHO has published guidance for the risk assessment of typhoid and other vaccine-preventable diseases in humanitarian settings as a framework for decision making on the use of vaccines in those settings.

### ***Recommendations for special groups***

SAGE recommends vaccination of the following specific groups of epidemiological relevance, by virtue of being at high risk or important for transmission, in line with the above age-appropriate recommendations. When ViPS or Ty21a is used, SAGE emphasizes the current recommendations for revaccination.

- **Clinical microbiology laboratory staff** with a recognized risk of occupational exposure to *S. Typhi*.
- **Professional food handlers:** where possible, preference for use of a Vi negative vaccine, such as Ty21a should be considered in order to protect the possibility for serological identification of a chronic carrier status among vaccinated persons. However, professional food handlers should not go unvaccinated due to lack of Ty21a vaccine. The value of not vaccinating this group (where Ty21a is not available) needs to be carefully weighed within the existing national policies.
- **Travellers from non-endemic to endemic areas:** Typhoid vaccination may be offered to travellers to destinations where the risk of typhoid fever is high. Where available, licensed combination Typhoid-Hepatitis A vaccines may be used for travellers.

### ***General recommendations***

- All typhoid vaccination programmes should be implemented in the context of other efforts to control the disease, including health education, water quality and sanitation improvements, and training of health professionals in diagnosis and treatment.
- Ideally, cost-effectiveness analyses should be part of the decision-making and planning process to initiate programmatic use of typhoid vaccines.



- SAGE recommends post-licensure monitoring of effectiveness of TCV (including serological and clinical endpoints) and robust monitoring of safety in line with the GACVS recommendations.
- SAGE recommends that countries monitor the occurrence of AMR strains of *S. Typhi* in endemic and epidemic disease and contribute to the global database on antimicrobial resistance.

## 1. MAGNITUDE OF THE PROBLEM

### 1.1 Background on the pathogen, the disease and risk factors

Typhoid fever is an acute generalized infection, caused by the bacterium *Salmonella enterica* serovar Typhi (commonly referred to as *S. Typhi*), which remains an important public health problem in many low and middle income countries (LMICs). *Salmonella enterica* serovar Paratyphi A and Paratyphi B (and uncommonly Paratyphi C) cause a clinically indistinguishable disease, particularly in parts of Asia. Typhoid fever and paratyphoid fever are collectively referred to as enteric fever. Typhoid fever exhibits a wide range of clinical severity, including a broad spectrum of illness, with more severe forms being characterized by persisting high fever, abdominal discomfort, malaise, and headache.

#### Key new data since 2008 SAGE recommendations

- Global estimates of disease burden ranging between 11 and 21 million typhoid fever cases and approximately 145 000 to 161 000 deaths annually.
- Improved overall understanding of the burden and risk factors in sub-Saharan Africa.
- New data on age-specific occurrence confirm that typhoid fever with severity sufficient to seek medical care is common in the 0-4 year age group, with a large proportion of disease occurring between 6 months and 2 years of age.
- An increasing record of major outbreaks, in some cases with antimicrobial resistant *S. Typhi* strains.
- Large population-based studies of the burden of typhoid fever are ongoing in Africa and Asia.

Humans are the only known reservoir of infection of *S. Typhi* and transmission is by the feco-oral route through consumption of contaminated water or food. Transmission may occur via short-cycle (defined as contamination of food and water in the immediate environment through inadequate hygiene and sanitation measures, either by shedding from temporary or chronic carriers) or by long-cycle transmission (defined as contamination of the broader environment, such as pollution of water supplies by sewage, inadequate treatment of piped water or use of raw human feces as a crop fertiliser) [1].

The incubation period of typhoid fever lasts 7 to 14 days on average, but can range from 3 to 60 days and the untreated illness often lasts several weeks and occasionally months. Complications are estimated to occur in 10 to 15% of hospitalized patients and are more common amongst untreated patients whose illness has persisted for  $\geq 2$  weeks, the most common life-threatening complications being intestinal haemorrhage, intestinal perforation and encephalopathy with haemodynamic shock [1]. Recent reports of typhoid fever epidemics in the Democratic Republic of Congo [2] and Uganda [3] described unexpectedly frequent rates of intestinal perforation ( $>40\%$ ) associated with high mortality (18 to 43%). Other less common complications include shock, typhoid hepatitis, empyema, osteomyelitis, and psychosis. In the

pre-antibiotic era, a case-fatality ratio of approximately 10 to 20% was reported however current estimates range from 1 to 4% in those who receive adequate therapy [4]. In approximately 2 to 5% of typhoid fever cases, depending on the individual's age and whether there is pre-morbid disease of gallbladder mucosa, gallbladder infection during the acute illness persists to establish a chronic carrier state [4]. Chronic biliary carriers have an elevated risk of hepatobiliary cancers [5,6].

Variable hospitalization rates of 2 to 40% have been reported for typhoid fever indicating that the disease can be severe in a notable proportion of patients, while the majority of remaining cases either self-medicate or are treated on an outpatient basis [7,8]. In population-based studies in five Asian countries conducted by the Diseases of the Most Impoverished (DOMI) Programme, the average length of hospital stay was nearly 15 days in China and 9 days in India [8]. A more recent systematic review and meta-analysis of typhoid intestinal perforation in LMICs, covering the period 1991-2011 (23 studies), reported an overall mean length of hospital stay of 18.4 days (N = 2,542; 95% CI 15.6, 21.1) [9].

The often non-specific symptoms of typhoid fever makes clinical diagnosis difficult as it may be confused with a wide range of other febrile illnesses including malaria, dengue fever, influenza and other infections that are common in typhoid fever endemic regions. Reliance on clinical diagnosis not only leads to inaccurate surveillance and a considerable mis-representation of the incidence of typhoid fever, but also can result in inappropriate treatment. In areas where malaria is perceived to be common, patients with typhoid fever may remain undiagnosed and receive inappropriate or delayed treatment, making them more likely to experience more complications and higher mortality. In most settings, confirmation of the diagnosis depends on isolation of *S. Typhi* in the laboratory through blood cultures. Unfortunately, blood culture is limited by modest sensitivity of approximately 50%. Sensitivity may be further diminished by the common practice of pre-treatment with antibiotics. Blood culture is not often performed for the majority of cases in LMICs, especially among those treated in non-hospital settings and in some countries may be underutilized in both infants and young children. The currently available serological tests are compromised by a variable antibody response to the pathogen that may persist for shorter or longer periods, and cross reactivity of *S. Typhi* and *S. Paratyphi A* with other enteric bacteria [10].

### ***Risk factors for typhoid fever***

The risk of transmission of typhoid fever is increased in populations that lack access to safe water and adequate sanitation, and in the context of poor hygiene among food handlers. Population density, elevation and overcrowding have been associated with an increased risk of enteric fever in surveillance studies in urban areas in India, [11]. However clustering of typhoid fever cases was not associated with population

density in other sites [12]. The risk of typhoid fever has also been associated with lower socioeconomic status, lower literacy rates, increased household size, and handling of *S. Typhi* by clinical microbiology laboratory staff [1,4].

The precise role of chronic carriers in transmission is not fully understood and is thought to vary between settings of high, medium and low disease incidence generally defined as >100 per 100 000, 10-100 per 100 000 and <10 per 100 000 cases per year respectively in typhoid fever endemic areas [13]. Published studies suggest that chronic carriers account for a limited proportion of within-household transmission of typhoid fever, primarily to children [12,14]. By contrast, chronic carriers represent a reservoir of infection, and contribute to the long-term persistence of typhoid fever through ongoing shedding of *S. Typhi* into the environment and possibly contaminating water supplies.

## **1.2 Epidemiological patterns**

### ***The global burden of typhoid fever***

The evidence base [15] and sophistication of methods [16] for estimating the global burden of typhoid fever has grown markedly over the past decade. Estimates of the global burden of typhoid fever have been made by a number of groups with some updating their estimates periodically. The most recent estimate of the global burden of typhoid fever from the World Health Organization, in 2010, was 21.0 million illnesses and 144 890 deaths accounting for 10.3 million disability adjusted life years (DALYs) [17]. The Institute for Health Metrics and Evaluation (IHME) has estimated for 2013 and 2015, 11.0 and 12.5 million illnesses [18,19], 160 700 and 148 800 deaths [20,21], accounting for 11.1 and 10.6 million DALYS [22,23] respectively. A group from Yale University recently estimated that 17.8 million typhoid fever illnesses occurred in 2015 in LMICs [16].

A systematic review of global published and grey literature with mixed methods case studies in eight selected countries was recently performed for the time period 1990 to 2015, to examine trends in typhoid fever incidence and to evaluate contextual factors which could potentially be associated with reduction in incidence of typhoid fever over time at the national level or in large, representative sub-national populations [24]. Contextual factors examined included access to improved drinking water, hand washing, reduction of open defecation, consumption of raw vegetables and fruits or street foods, household size, literacy rates, and antimicrobial resistance (AMR) patterns. No clear pattern was observed in general population incidence trends nor in the reduction of typhoid fever incidence. In contrast to most areas studied, Nepal experienced a possible increase in national incidence between 2008 and 2013. There also

appeared to be no clear pattern in typhoid fever incidence by income level, however the authors reported a lack of adequate information on socio-economic strata. At the subnational level no substantial changes were seen over time, except during outbreaks. In the same project, the country case studies showed a mixed picture with evidence of consistent reduction in typhoid fever rates in some countries including Chile, Thailand and Viet Nam. There appeared to be no clear association with socio-economic development.

Together the data since 2000 show some evidence of a reduced burden of typhoid fever compared to the 1990s, but with little consistency in trends observed [24], and that typhoid fever incidence rates appear to have plateaued in recent years (Figure 1).

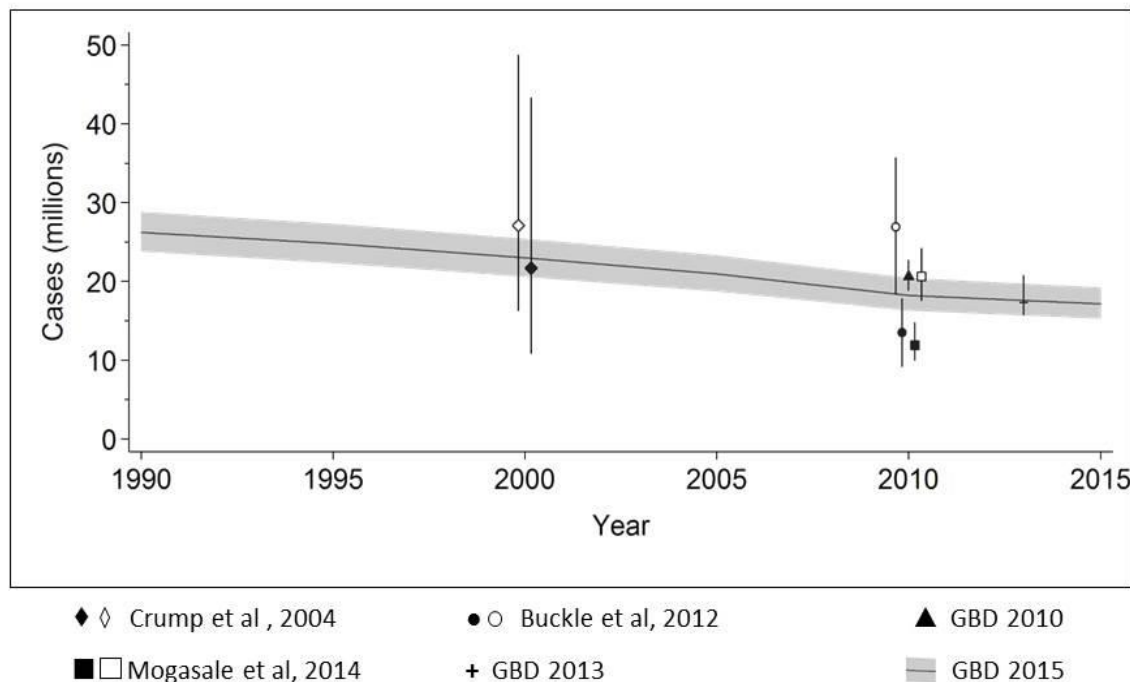


Figure 1. Trends in estimates of the global burden of typhoid  
 Crump et al: estimates are for typhoid + paratyphoid (hollow diamond) and typhoid only (solid diamond)  
 Buckle et al: estimates are adjusted for low diagnostic sensitivity (hollow circle) and unadjusted (solid circle)  
 Mogasale et al: estimates are adjusted for water-related risk (solid square) and unadjusted (hollow square)  
 Courtesy of JD Stanaway [25]

**Country-specific incidence rates and intra-country variations**

A consistent finding of typhoid fever disease burden studies in the last two decades is the high incidence of typhoid fever in South and South-East Asia. Within these regions, there is marked inter- and intra-country heterogeneity in typhoid fever incidence [8,26]. For example, data from the DOMI programme highlighted

incidence rates varying between 24.2 per 100 000 person years in Viet Nam to 493.5 per 100 000 person years in parts of India [8]. A systematic review and meta-analysis of published studies of typhoid and paratyphoid fever in India between 1950 and 2015 reported a statistically significant decline in laboratory-confirmed typhoid fever apparent since the early 1990s but still with a pooled estimate of typhoid fever incidence, based on three population-based studies, of 377 per 100 000 person years [27]. The heterogeneity of typhoid fever disease incidence may be even more pronounced in Africa. Recent data from the Typhoid Fever Surveillance in Africa Program (TSAP) highlighted marked differences between sites with adjusted incidence rates ranging from 0 per 100 000 person years at a site in Sudan to 383 per 100 000 person years at a site in Burkina Faso [15].

In both Asia and Africa, previous studies demonstrated marked intra-country variation suggesting that typhoid fever occurs predominantly in urban areas with high population density. Surveillance in two sites in Kenya between 2006 and 2009 found the incidence of blood-culture confirmed typhoid fever varied from 29 to 247 cases per 100 000 person years in rural and urban sites respectively [28]. However, recent studies have demonstrated high rates of typhoid fever in rural areas in both regions - for example Cambodia [29], Ghana [15] and Tanzania [30] - showing that the disease is not restricted to urban settings with poor sanitation systems. Although populations are small, many island nations of Oceania experience high typhoid fever incidence [16] and large outbreaks.

Seasonal trends in typhoid fever incidence in a given population have been described in some sites (Figure 2) [31] but not found in other sites [15].

### ***Typhoid fever in infants and children***

The incidence of enteric fever within the paediatric population has historically been an area of debate. Peak incidence has long been described in school-age children 5-19 years of age [4], however conflicting data on the burden of disease among infants and preschool children were published from the 1970s to 1990s. More recently, data from surveillance studies have emerged underlining the large burden of disease in preschool children. The prospect of typhoid vaccines that can be used in infants and young children has focused attention on the occurrence of typhoid fever early in life. A recent systematic review and meta-analysis of studies in Asia and Africa sought to compare the relative proportion of children with enteric fever in the age groups <5 years, 5-9 years, and 10-14 years [32]. This meta-analysis showed that in Africa a relatively smaller proportion of disease occurred in the youngest age group, whereas in Asia there was marked variation between studies in the proportion of disease <5 years of age with some studies showing considerable disease in this age group. Estimates of the proportion of typhoid fever cases in those aged <5

years ranged from 14 to 29%, compared with 30 to 44% in those 5–9 years of age and 28 to 52% in those 10–14 years of age. The review demonstrated that infants and preschool children experience a substantial proportion of disease that would be missed by school-based vaccination campaigns. A limitation of this review however was the lack of age stratification in published reports within the <5 years age group.

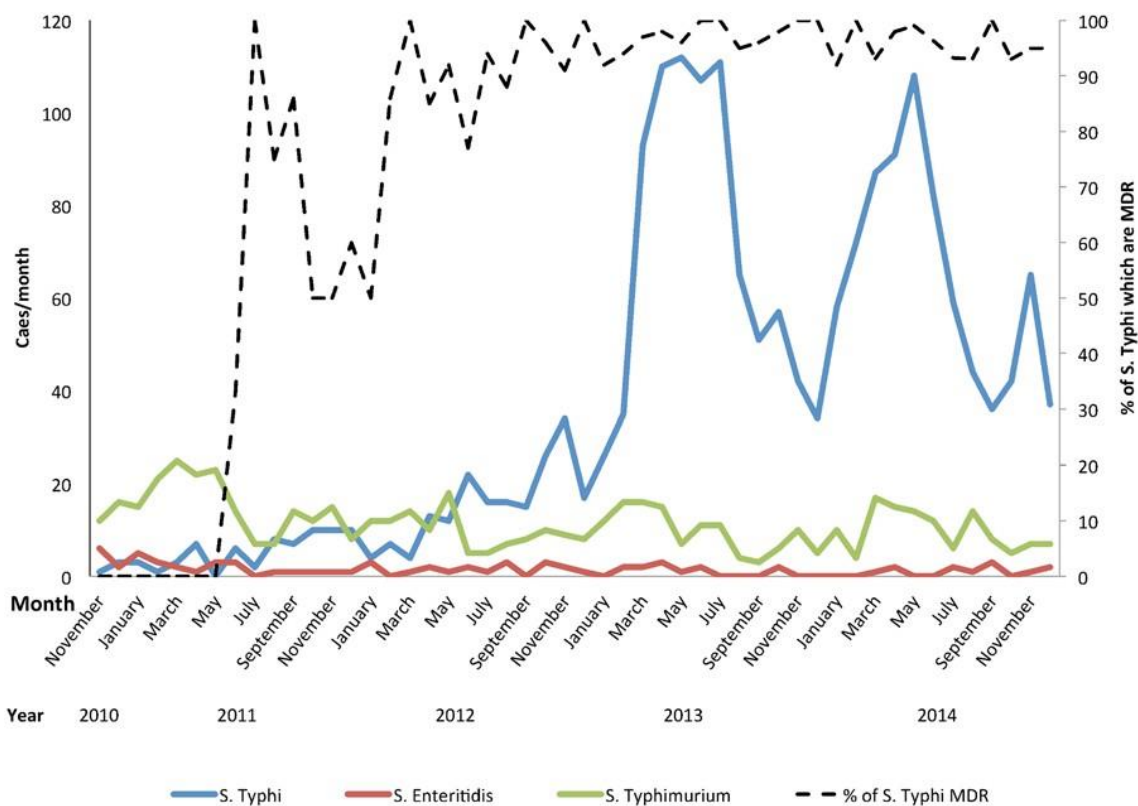


Figure 2. Monthly trends in bloodstream infections of invasive *Salmonella* diagnosed at the Queen Elizabeth Central Hospital, Blantyre, Malawi from November 2010–October 2014 [31].

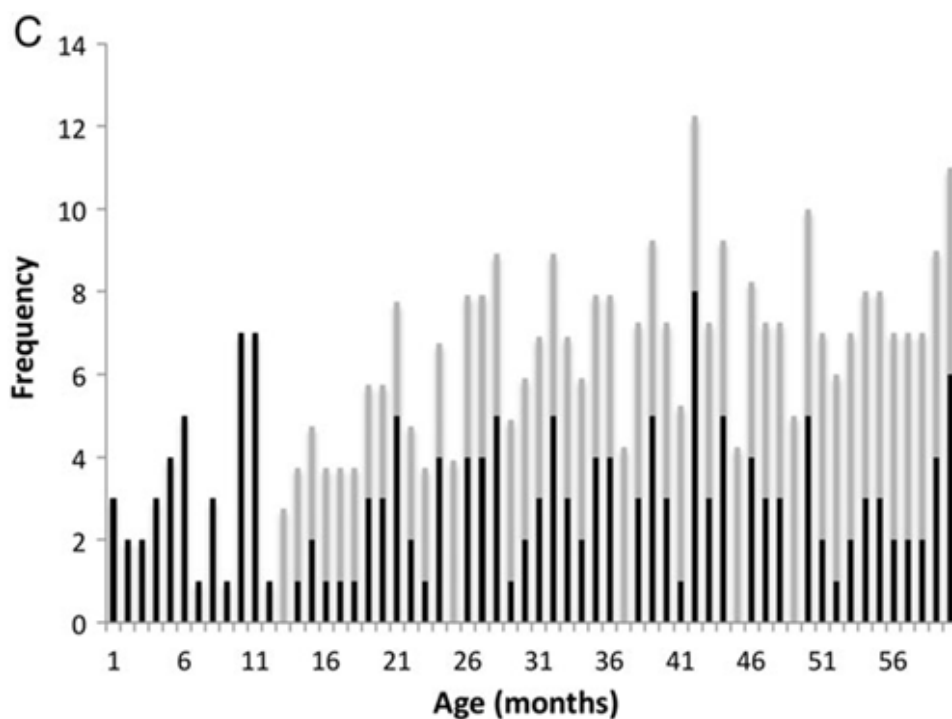
To address the limitation of lack of age stratification in the published literature in the <5 years age group, the WHO SAGE Working Group on Typhoid Vaccines sought unpublished data from sites conducting typhoid fever surveillance and from ongoing studies of typhoid fever epidemiology<sup>a</sup>. Data were received from 15 sources from Africa, Asia, and the Americas that allowed typhoid fever occurrence to be calculated by month of age from 0 to 60 months, and in age intervals of 5 years. Available data were of inpatients, outpatients, or both, collected between 1998 and 2017 representing >10 000 blood culture confirmed

<sup>a</sup> Current disease burden studies are conducted by the following projects: SEAP (Surveillance of Enteric Fever in Asia Project) in Bangladesh, Nepal and Pakistan; SETA (Severe Typhoid in Africa Program) in Burkina Faso, Democratic Republic of Congo, Ethiopia, Ghana, Madagascar and Nigeria; STRATAA (Strategic Typhoid Alliance across Africa and Asia) in Malawi, Bangladesh and Nepal; and the Navi Mumbai TCV Introduction Program in India.

episodes of typhoid fever. These data showed that among studies of all age groups, 27% of typhoid fever occurred in the age group 0-4 years. Of typhoid fever cases in the age group 0-4 years, giving equal weighting to data collected in these studies, 29.7% of typhoid fever episodes occurred at age  $\leq 2$  years; 9.9% at age  $\leq 1$  year; and 2.9% at age  $\leq 6$  months. While the data sources likely reflect locations with high typhoid fever incidence, these data confirm that typhoid fever with severity sufficient for an outpatient visit or hospital admission is common in the 0-4 year age group with a large proportion of disease occurring between 6 months and 2 years of age. Figure 3 illustrates the age distribution by month of typhoid fever in children  $< 5$  years of age; similar patterns were observed in some but not all of the unpublished datasets reviewed.

Figure 3. Age distribution in children  $< 2$  years  
Frequency plots of aggregate age distribution data by month for *S. Typhi* in children  $< 5$  years of age.

Black bars represent cases where age in months is known and gray bars represent the cases where age is known in years evenly distributed across the year [33].



### ***Typhoid fever outbreaks***

Typhoid fever cases reported in outbreaks are mostly excluded from estimates of typhoid fever burden and there are currently no published estimates of the true burden of typhoid outbreaks in endemic or non-endemic settings. Nonetheless, typhoid fever outbreaks have been reported with increasing frequency in published literature and these substantially improve insights into the public health problem.

In the last decade, well characterized outbreaks of confirmed typhoid fever in sub-Saharan Africa have been



reported in Malawi [33], Mozambique [34], Uganda [3,35], Zambia [36], and Zimbabwe [37] among others.

The increased occurrence of outbreaks due to multi drug resistant *S. Typhi* is of particular concern (see Section 1.3 for discussion in the context of antimicrobial resistance).

Typhoid fever outbreaks can also reveal important epidemiological data that may not be observed with sporadic cases such as the increased frequency of perforations observed in Uganda and DRC [2,3]. A high frequency of neurological manifestations, including altered mental status, dysarthria, upper motor neurone syndromes, ataxia, tremors and Parkinsonism was described in an outbreak of typhoid fever in 2009 along the Malawi-Mozambique border [34].

Overcrowding, inadequate hygiene and disruption to water supplies following humanitarian disasters can lead to typhoid fever outbreaks. However, there are very few documented reports of typhoid fever outbreaks in humanitarian emergencies such as in Fiji in 2011 during the post-Cyclone Thomas response [38].

Recent work by WHO, US Centers for Disease Control and Prevention (CDC) and the International Vaccine Institute (IVI) to review typhoid fever outbreaks, published from 1990 to 2017 in endemic and non-endemic settings, has yielded preliminary descriptive data on the magnitude of the public health problem. Forty one published reports on typhoid fever outbreaks were considered to have enough epidemiological data to contribute to the initial descriptive analysis; approximately 95% (39/41) of these papers reported confirmation of the outbreak by blood culture isolation of *S. Typhi* cases, however data on the proportion of blood culture confirmed cases (among all cases reported in the outbreak) was only available for 41% of those (37/39). Not unexpectedly the majority of outbreaks have been reported in Asia and Africa. Among a total of 35 distinct outbreaks described, 10 (25.6%) and 8 (20.5%) were reported in the WHO South-East Asia Region and African Region respectively while the remaining were equally distributed across the other four WHO Regions. Two (of 9) outbreaks in the period 2010 to June 2017 and 2 (of 15) outbreaks in the period 2000 to 2009 were of substantial magnitude, based on the duration (from first to last case) and number of cases (suspected and confirmed) reported: in Lusaka, Zambia (989 days, 2 040 cases) [36], Kasese District, Uganda (875 days, 1 341 cases) [35], Kasese District, Uganda (551 days, 577 cases) [3] and on the Malawi-Mozambique border (252 days, 303 cases) [34]. Such large scale outbreaks point to the potential public health burden, particularly in low resource settings, for the appropriate management of outbreaks. The remaining outbreaks in this period (across all WHO Regions) ranged in duration from 6 to 219 days (mean of 70 days). Notably, some of these relatively shorter-lasting outbreaks had substantial numbers of cases (suspected and confirmed) reported; a range of 6 to 5 963 cases (with a mean of 896

cases) indicating that several epidemiological features - including the attack rate (when reported or possible to calculate), disease severity, fatality, frequency of antimicrobial resistance - are important to fully characterise the magnitude of the public health burden of typhoid outbreaks. Further work is ongoing to finalize this review.

### 1.3 Trends in antimicrobial resistance of *S. Typhi* and implications for control

#### Key new data since 2008 SAGE recommendations

- A relentless increase in antimicrobial resistance (AMR) in some regions, including emergence of strains resistant to fluoroquinolones and extended spectrum cephalosporins.
- Spread of the drug-resistant *S. Typhi* H58 clade. New drug-resistant clades are emerging.
- Increasing frequency of outbreaks of multi drug resistant *S. Typhi*.
- AMR leading to increases in morbidity and possibly mortality, with an economic impact due to prolonged hospitalization and cost of antimicrobials.
- WHO published (February 2017) the *Global Priority Pathogen List*, including fluoroquinolone-resistant *Salmonella* spp. as a high priority pathogen, to guide the research, discovery and development (R&D) of new and effective antibiotics.

As previously noted, typhoid fever mortality ranged between 10 and 20% in the pre-antibiotic era, and the introduction of effective antibiotics reduced this to 1 to 4%. Significant antibiotic resistance began to appear in *S. Typhi* in the 1970s in the form of resistance to chloramphenicol, then the antibiotic of choice for treatment. At this time resistance was sporadic in the sense that resistant *S. Typhi* would emerge in a particular region but not become fixed in the population for substantial lengths of time. Multi-drug resistant (MDR) strains of *S. Typhi*, defined in the typhoid fever literature as resistance to the traditional first line antibiotics of ampicillin, chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole, first appeared in the late 1980s in South Asia and the Middle East [39,40]. More recently, MDR *S. Typhi* has caused large outbreaks in East Asia and Africa [3,30,34-36,41]. The MDR phenotype is encoded by resistance genes that are carried on transferrable plasmids. The appearance of MDR strains led to widespread use of fluoroquinolones, but in turn was followed in the 1990s and 2000s by the appearance of strains with decreased susceptibility to fluoroquinolones, mediated by point mutations in the fluoroquinolone target genes, and associated with an impaired response to fluoroquinolone treatment [7, 39-42]. A Cochrane review of fluoroquinolone use conducted in 2011 found some evidence that gatifloxacin, the “newest fluoroquinolone” at the time, remained effective in some regions where resistance to older fluoroquinolones has developed [43]. Strains with full resistance to fluoroquinolones, such as ciprofloxacin and gatifloxacin, are now increasingly common in South Asia [44,45] and have been spreading into sub-Saharan Africa [46,47]. As resistance to fluoroquinolones has emerged in particular regions, other

antibiotics such as cephalosporins and azithromycin have become the drugs of choice. Sporadic reports of resistance to azithromycin has appeared but as yet has not become common [39,40,48,49]. Extended-spectrum cephalosporins such as cefixime, ceftriaxone have been reliably active until recently. Since 2010 there have been increasing reports of extended-spectrum cephalosporin resistant strains in Asia and Africa (often due to the CTX-M ESBL gene) [39,40]. A large outbreak in Pakistan of MDR typhoid resistant to fluoroquinolones and extended spectrum cephalosporins has recently been reported and is still ongoing [50]. These patients are needing treatment with oral azithromycin and intravenous meropenem, a drug class of last resort.

AMR in typhoid fever leads to an increased proportion of patients experiencing clinical treatment failure and complications, an increased proportion requiring hospital admission and prolonged hospital stay, and the need to use more expensive treatment options [39,40,51-53]. Mortality may increase depending on specific local AMR patterns and drug availability [39,40,51]. Acute faecal shedding of *S. Typhi* for the initial weeks after completion of treatment can be five-fold higher after treatment of more resistant strains, so that although patients are clinically cured, there is an increased transmission of such resistant strains [54]. AMR in typhoid fever could also lead to an increase in chronic carriers, through poorly effective therapy, and the prevalence of chronic carriers is associated with long-term risk of increased prevalence of hepatobiliary carcinoma [56]. AMR is associated with typhoid fever outbreaks. Recent outbreaks have occurred in Malawi [33], Mozambique [34], Uganda [3,35] and Zambia [36] due to the H58 multidrug resistant clade with a high proportion of patients developing complications. The ongoing outbreak in Hyderabad, Pakistan of MDR *S. Typhi* infections with additional resistance to fluoroquinolones and ceftriaxone is a cause for serious concern [50]. Although, at present ciprofloxacin and ceftriaxone resistance is found in less than 1% of all strains in Pakistan, historical parallels suggest that resistance rates can change quickly. In Ho Chi Minh City, Viet Nam in 1998, strains with decreased susceptibility to fluoroquinolones increased from less than 5% to 80% in a few months [55].

The global pattern of AMR is dynamic (Figure 4) and changing in each location and over time [56]. In a recent systematic review of published reports of antimicrobial resistance of *S. Typhi* over the last 20-30 years, a general decline in MDR strains as well as an increase in strains with decreased susceptibility to fluoroquinolones have been seen [56]. There are limitations in the data on AMR, in that typhoid rates based on hospitalized cases are generally biased towards more resistant strains and data from young children are often lacking because of the reluctance of clinicians to take blood from this group. Nevertheless, it is clear that antimicrobial resistant *S. Typhi* infections are common in many areas and that the introduction of a resistant strain in a new area can lead to large outbreaks. The *S. Typhi* H58 clade, with IncHI1 plasmids

carrying MDR genes and target site mutations causing fluoroquinolone resistance, is responsible for much of the recent and current spread of resistant strains. The clade is considered to have emerged on the Indian subcontinent 30 years ago, and then spread to South-East Asia and most recently to sub-Saharan Africa [57,58]. The H58 clade appears to remain fit and competitive and is able to rapidly reacquire the MDR phenotype, suggesting that it may be adapted to the MDR state in a manner we do not understand. Other recent studies indicate that H58 is also acquiring other new phenotypes such as increased bile resistance [56]. New clades are also appearing in Nigeria and Democratic Republic of Congo [59].

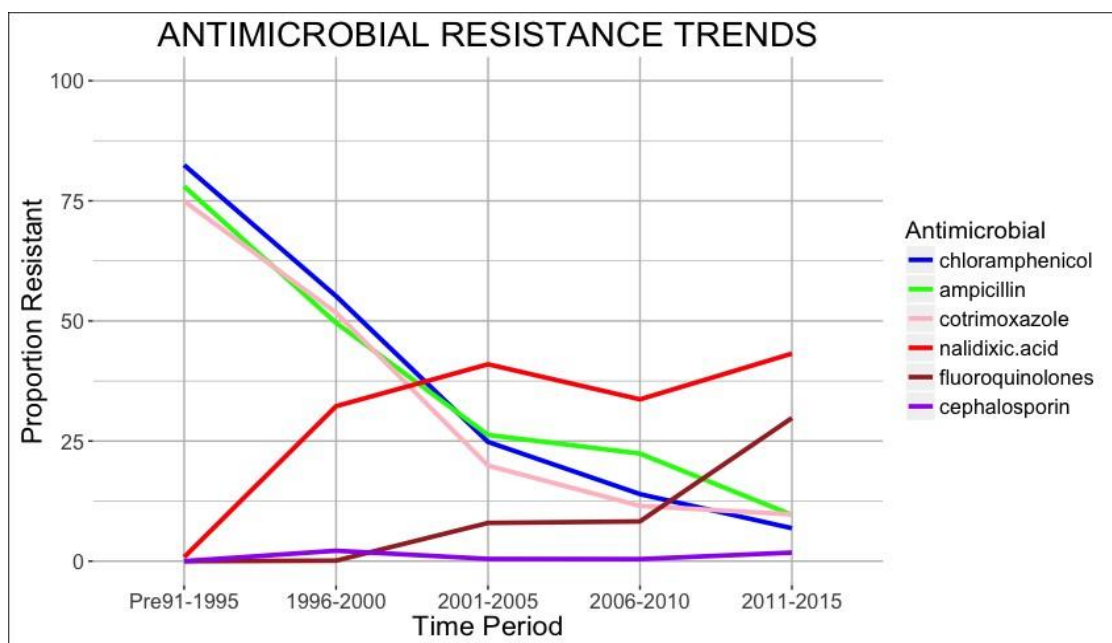


Figure 4. Trends in antimicrobial susceptibility of *S. Typhi* over time [56]

Graphical representation of the proportion of *S. Typhi* isolates globally that are resistant to antimicrobials (indicated by coloured lines). Isolates represented in this graph were consolidated from published reports assembled systematically between 1973 and 2015 from endemic and epidemic sources. Note that Nalidixic acid susceptibility is sometimes used as an indirect indicator of fluoroquinolone resistance, although this is not a tight correlation. In addition the CLSI guidelines for ciprofloxacin have changed periodically and the more recent revisions are likely to be more accurate.

A febrile illness is one of the commonest reasons for individuals to seek healthcare and antibiotic treatment in LMICs [60]. This antibiotic usage is likely both directly (through targeted treatment) and indirectly (through general usage) to be driving the emergence of resistance in *S. Typhi*. In regions where typhoid fever is common, anyone presenting with a persistent fever is a suspect typhoid fever case once malaria has been excluded, and is likely to be treated with antibiotics [61,62]. As vaccination is not in routine use in almost all endemic countries, antibiotics are the treatment of choice even when a confident diagnosis of

typhoid fever is lacking. Population and hospital based studies of febrile illness in children and healthcare utilization in LMICs have shown a high prevalence of antibiotic prescription for febrile illness [63-65] as well as a common practice of seeking healthcare in pharmacies [28,56,66]. Efficacious antibiotics can speed recovery (within days), reduce the risk of complications and can limit the shedding of *S. Typhi*. Where there is resistance to the antibiotic of choice recovery can be significantly delayed and relapse of the disease (even months later) may become more common [42]. Complicating things further is the risk in LMICs that antibiotics will be bought without prescription and without clinical supervision and the quality of the antibiotic is not guaranteed. The deployment of typhoid vaccines could therefore have a dual effect of reducing the levels of circulating *S. Typhi* that are resistant to the local treatment of choice, and also reducing the levels of patients presenting with a febrile syndrome who are currently being prescribed antibiotics. Over time this may change physician practices towards prescribing less antibiotics. The consequent reduction in antibiotic usage could reduce the antibiotic pressure that is driving the current emergence and spread of new resistant *S. Typhi* phenotypes.

## 2. TYPHOID FEVER PREVENTION AND CONTROL MEASURES

### Key new data since 2008 recommendations

- Despite SAGE recommendations almost a decade ago for use of Vi polysaccharide and Ty21a vaccines, their uptake has been limited and mostly implemented through short-term programmes or demonstration projects.
- The UN Sustainable Development Goals (SDGs) provide a relevant framework within which control of typhoid and paratyphoid fever, through integration of vaccination with other intervention, should be leveraged and implemented by policy makers (most notably SDG #6: Ensure availability and sustainable management of water and sanitation for all).

Access to safe water and adequate sanitation, health education, appropriate hygiene among food handlers, and typhoid vaccination are all effective strategies for prevention and control of typhoid. Further, acute typhoid fever and *S. Typhi* chronic carriage can be effectively treated with antibiotics and thereby curtail faecal shedding. The growing prevalence of antibiotic resistance has made this treatment option increasingly difficult and costly.

Improvements to water supplies, including filtration and chlorination can reduce the burden of typhoid fever and have led to its virtual elimination in many high-income settings. Conversely, contamination of municipal water supplies and drinking un-boiled water have been implicated in several outbreaks of typhoid fever in diverse settings [1]. In one outbreak in Tajikistan in 1997, associated with inadequate treatment of

municipal water supplies, the re-introduction of chlorination of water supplies was effective in leading to a marked decline in typhoid fever cases [67].

There is evidence that typhoid immunization can substantially reduce typhoid fever burden, especially when targeted towards high-risk age groups and geographic areas, and when combined with improved sanitation. Unlike the significant investment required for major infrastructure development, vaccination is relatively more affordable to governments, does not require substantial behavioural change and has been shown to be cost-effective [68]. In general, most policymakers agree that routine public health use of typhoid vaccines should be integrated with other control strategies: access to safe water supply, sanitation improvements, hygiene education messages, community or national food hygiene measures, and appropriate case and chronic carrier detection and management.

### **3. POLICY QUESTIONS REVIEWED BY THE SAGE WORKING GROUP ON TYPHOID VACCINES**

The Working Group reviewed and assessed the currently available evidence on typhoid fever and typhoid vaccines (including Ty21a and Vi polysaccharide (ViPS) vaccine, in addition to typhoid conjugate vaccine (TCV)), to inform policy recommendations to be submitted to SAGE for consideration in October 2017 and for the subsequent update of the current WHO *Position Paper on Typhoid Vaccines* [69]. The Working Group defined an overall set of policy questions on which recommendations would be based as well as a set of questions to guide the assessment of the quality of evidence and inform the assessment of the overall policy questions.

#### ***Overall vaccine policy questions:***

4. Should TCV be recommended in addition to the available ViPS and Ty21a vaccines for routine use in persons 2 years of age and older?<sup>a</sup> (Critical question<sup>b</sup>)
5. Should TCV be recommended for routine use in children less than 2 years of age? What should be the lower age limit for use in this group? (Critical question)
6. Should different recommendations be developed for use of the above vaccines in endemic settings versus outbreaks or humanitarian emergencies? (Non-critical question)

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<sup>a</sup> It should be noted that this question was worded to avoid any sense of prioritizing TCV over ViPS or Ty21a.

<sup>b</sup> Critical questions required an assessment of the quality of evidence.

**Specific (critical) questions on vaccine performance:**

1. What is the effectiveness of ViPS and live attenuated oral Ty21a vaccines in preventing typhoid fever in the target age groups?
2. What is the effectiveness of TCV in preventing typhoid fever in persons aged 2 years and above, in children aged 12-23 months, and in infants less than 12 months of age?
3. What is the duration of protection following vaccination with TCV? Is there a need for a booster dose following primary immunization with typhoid conjugate vaccine?
4. What is the risk of serious adverse events (SAEs) following vaccination with ViPS, Ty21a and TCV?

In order to address these policy-related questions, the most recent available data and evidence on the following topics were reviewed: the epidemiology of typhoid fever; global and country trends of typhoid fever and its risk factors; antimicrobial resistance of *S. Typhi* and implications for typhoid fever control; and data on the composition and performance of licensed typhoid vaccines; mathematical modelling of typhoid fever transmission and vaccine impact; and a cost-effectiveness evaluation of TCV. For the assessment of the quality of evidence in relation to the critical questions, a systematic review and meta-analysis of immunogenicity, efficacy and safety data for typhoid vaccines was commissioned by WHO and performed by the Cochrane Response and the Cochrane Infectious Disease Group (see Annex C).

## 4. CHARACTERISTICS AND PERFORMANCE OF TYPHOID VACCINES

### Key new data since 2008 recommendations

- Field effectiveness trials of ViPS in Kolkata, India and Karachi, Pakistan showed moderate protection (56-59%) of older children 5-16 years old while there was variable protection of preschool children 2-4 years of age in the 2 settings. Indirect protection was shown in the Kolkata trial but not in the Karachi trial.
- New data on typhoid conjugate vaccines; two products licensed in India (and other countries for one of the 2 products) and available in the private market.
- Large field effectiveness trials are planned under the Typhoid Vaccine Acceleration Consortium (TyVAC).

### 4.1 Vaccines currently recommended by WHO

Two currently licensed typhoid fever vaccines – a live oral Ty21a vaccine and a parenteral Vi polysaccharide (ViPS) vaccine - have been recommended by WHO for use since 2000. In 2007, SAGE endorsed updated recommendations for public health use of both vaccines for the control of endemic and epidemic disease [69]. The recommendations emphasized the immunization of school-age and/or preschool-age children in areas where typhoid fever in these age groups is shown to be a significant public health problem, particularly where antibiotic-resistant *S. Typhi* is prevalent. However, since the 2008 WHO Position Paper, a

low typhoid vaccine uptake in endemic countries has been observed. Multiple contributing factors have been reported, including challenges with (a) national level decision-making (e.g., lack of disease burden estimation and ascertainment of high-risk groups for a risk-based vaccination strategy); (b) financing (lack of national funds and donor support) and (c) implementation strategies, including integration with existing vaccination schedules.

### ***Vi polysaccharide vaccine***

This subunit vaccine was first licensed in the United States in 1994 and is recommended for use in individuals  $\geq 2$  years of age. It is composed of a purified Vi capsular polysaccharide from the Ty2 *S. Typhi* strain and elicits a T-cell independent IgG response. ViPS vaccine is given parenterally as a single dose (with a target value of about 25 $\mu$ g of Vi antigen) and is followed by high levels of seroconversion of serum IgG anti-Vi antibodies [70-73]. Administering a booster dose one or two months later is not helpful, since unconjugated ViPS is a T-independent antigen that does not confer immunological memory. In persons immunized with Vi who live in non-endemic areas the titres of serum anti-Vi drop rapidly after the second year [73]. Hypo-responsiveness upon subsequent re-vaccination with ViPS, as is seen with meningococcal C and pneumococcal polysaccharide vaccines, was suggested in some studies but was not observed in others [74-77]. In the pre-licensure trials in Nepal, South Africa and China, vaccine effectiveness was 72% (95% CI 42, 86 ) [70], 64% (95% CI 36, 79) [71], and 69% (95% CI 28, 87) [78] over 17 months, 21 months and 19 months of follow-up, respectively. In a post-licensure cluster randomized trial in Kolkata, vaccine effectiveness was 56% (95% CI, 18,77) in the older children 5-14 years of age, and 80% (95% CI 53, 91 ) in children under 5 years of age [79]. This finding of a higher level of protection in younger children was unusual among field trials of typhoid vaccines. Immunization of older age groups within the same community could have resulted in a possible herd immunity that may have influenced the estimate of protection in the young children. When the same Vi vaccine was evaluated in another cluster randomized trial in children in Karachi, Pakistan, no protection was seen in younger children <5 years of age, while the vaccine effectiveness in children 5-16 years of age was 57% (95% CI 6, 81) [80], and very similar to the protection observed in this age group in the Kolkata trial [79]. An outbreak of typhoid fever in a contingent of vaccinated French soldiers in Cote d'Ivoire showed that an interval since vaccination of greater than three years was a significant risk factor for development of typhoid fever [81]. In volunteers immunized with ViPS or placebo and challenged experimentally with virulent *S. Typhi*, the level of efficacy of Vi vaccine was 56%. Results of pre-licensure clinical trials of ViPS vaccine and the results of the post-licensure effectiveness trials in Kolkata and Karachi are summarized in Annex A.



Several Vi products have been licensed and marketed globally or locally; there is currently one WHO prequalified product, Typhim Vi™ produced by Sanofi Pasteur.

### ***Vi combination vaccines***

Two Vi polysaccharide–hepatitis A combination vaccines are licensed mainly for use by travellers: Hepatyrax™ produced by GSK Biologics and Viatim™ produced by Sanofi Pasteur MSD. Each of these combination vaccines is described as stimulating seroconversion to the component vaccine antigens in a manner equivalent to monovalent Vi and hepatitis A vaccines [4].

### ***Ty21a vaccine***

This vaccine was first licensed in Europe in 1983 and in the USA in 1989, and is recommended for use in individuals aged  $\geq 5$  years of age. It is an orally administered, live attenuated Ty2 strain of *S. Typhi* which harbours a number of attenuating mutations among which the inactivation of *galE* (encoding an enzyme involved in lipopolysaccharide biosynthesis) and the inability to synthesize Vi polysaccharide capsule are of particular importance [82-84]. The Ty21a vaccine stimulates serum and mucosal antibodies to O, H and other surface antigens and elicits powerful, long-lived cell-mediated immune responses (including cytokine production and cytotoxic lymphocytes that recognize cellular targets expressing *S. Typhi* antigens) [85-86]. However, because the antigen is lacking, Ty21a cannot stimulate Vi antibodies.

One non-mechanistic correlate of protection is serum IgG anti-O seroconversion [87] and another is the magnitude of the IgA antibody secreting cell (ASC) response 7 days following oral immunization [88]. These responses correlated with immunization schedules and formulations that conferred the highest levels of efficacy during field trials of efficacy in Chile. The magnitude of cell-mediated immune responses is now considered to be the best predictor of protection.

Vaccine efficacy of Ty21a was 87% in early volunteer challenge studies in the early 1970s [89], and 96% (95% CI 77, 99) in the first cluster randomized efficacy trial in Alexandria, Egypt in school children 6-7 years of age who were followed for three years [90]. The formulation used in the Alexandria trial was not amenable to large-scale manufacture. Four additional trials of different formulations and immunization schedules of Ty21a were carried out in Santiago, Chile in the 1980s. Three doses of Ty21a in enteric-coated capsules, taken orally every other day conferred 67% (95% CI 47, 79) protection over three years [91] and 62% protection over seven years [92] of follow-up in a cluster randomized (by school classes), placebo-controlled field trial of efficacy. Vaccine efficacy increased with age and was 59% in 5-9 year old children, 67% in 10-14 year olds and 85% in teenagers >15 years of age [91]. A double sachet formulation that allowed

administration in a liquid cocktail amenable to reliably immunizing younger and older children conferred 77% protection over three years [93] and 78% protection over five years [92] of follow-up in another field trial in Santiago, Chile. In a large-scale effectiveness trial in which 216 692 Santiago school children were randomly allocated to receive two, three or four doses of vaccine in an every other day schedule, the incidence of typhoid fever diminished significantly with increasing number of doses administered [94]. Ty21a vaccine was also found to confer a moderate level of protection (49%) against *S. Paratyphi B* disease [95]. In a trial of children and adults in a very high incidence setting in Plaju, Indonesia, where vaccine or placebo was randomly allocated at the level of the individual, three doses (one week apart) of a double sachet “liquid” formulation conferred 53% efficacy, while three doses of enteric-coated capsules taken one week apart provided 42% efficacy over three years of follow-up [96]. In this trial, Ty21a did not confer protection against *S. Paratyphi A*, which was also circulating in the trial region. The previously marketed liquid formulation of Ty21a is no longer produced.

Results of pre-licensure clinical trials of the Ty21a vaccine are summarized in Annex A.

### ***Safety of ViPS and Ty21a vaccines***

No serious adverse events and a minimum of local adverse events were associated with ViPS vaccination of >11 000 children in South Africa, almost 7 000 individuals aged 5–44 years in Nepal, approximately 130 000 subjects aged 3–50 years in China and nearly 195 000 individuals in 5 Asian sites. The ViPS vaccine has also proved to be well tolerated and safe when co-administered with routine childhood vaccines. Furthermore, re-vaccination of children aged 9–14 years two years after the first dose of ViPS has been shown to be safe. Currently, WHO recommends no contraindications to the use of ViPS vaccine other than previous severe hypersensitivity reaction to vaccine components. Although the ViPS vaccine is safe for HIV-infected individuals, the induction of protective antibodies is directly correlated to the levels of CD4 positive T-cells [69].

Ty21a is remarkably well tolerated and has low rates of adverse events. In 3 double-blinded, randomized placebo-controlled efficacy trials in Chile and Indonesia involving approximately 325 000 schoolchildren and both formulations of the vaccine, reactogenicity was assessed through active surveillance. The rates of diarrhoea, vomiting, fever and rash were not significantly different between the vaccinated and the control groups [4]. Proguanil and antibacterial drugs should be stopped from 3 days before until 3 days after giving Ty21a, as such drugs may harm live bacterial vaccines. The vaccine is unlikely to be efficacious if administered at the time of ongoing diarrhoea. It is not known whether this live attenuated vaccine may

cause fetal harm when administered to pregnant women. Ty21a can be administered to HIV positive, asymptomatic individuals as long as the T-cell count (CD4) is  $>200/\text{mm}^3$ .

The Global Advisory Committee on Vaccine Safety (GACVS) reviewed data on the ViPS and Ty21a vaccines in December 2016 and concluded that both vaccines have a good safety profile, with the most common adverse events being fever, erythema and localized pain, and gastrointestinal events (latter primarily with Ty21a), and that other adverse events are generally rare [97].

The results of the Cochrane systematic review and meta-analysis of serious adverse events for ViPS and Ty21a vaccines are included in Annex C.

## 4.2 Typhoid conjugate vaccines

Covalently linking polysaccharides to carrier proteins to produce conjugate vaccines that are administered parenterally modifies fundamentally the manner in which the polysaccharides are seen by the immune system and the magnitude and quality of the immune responses that ensue. The practical consequence being that the T-independent antigen behaviour of unconjugated polysaccharides (characterized by limited affinity maturation and relatively short-lived production of antibody of low avidity, poor (or absent) immunogenicity in infants, and lack of immunologic memory) is replaced by more robust responses involving high avidity antibody and evidence of immunologic memory, including in young infants. A succession of safe, well tolerated, immunogenic and highly protective conjugate vaccines ensued to prevent invasive disease caused by *Haemophilus influenzae* type b, 13 serotypes of *Streptococcus pneumoniae*, and four serogroups of *Neisseria meningitidis*. Collectively, these conjugate vaccines constitute among the best tolerated, most immunogenic and most protective vaccines ever developed and have been amongst the most impactful public health tools for disease control.

Despite the extraordinary achievements of various conjugate vaccines, there are subtleties and complexities that influence their performance. Even within a broad category such as Hib conjugate vaccines, the immunogenicity and level and duration of protection can vary widely from one conjugate to another depending on the specific carrier protein, the length and structure of the polysaccharide and the method of conjugation [98]. This should be taken into account as one reviews the various new typhoid Vi conjugates that are already licensed or in clinical development.

### **Development of Vi conjugate vaccines**

Recognizing that *S. Typhi* expresses a highly regulated Vi (for “virulence”) capsular polysaccharide on its surface and that purified Vi polysaccharide was immunogenic and moderately protective in adults and children >3 years of age, stimulated research to develop typhoid Vi conjugate vaccines that might enhance and extend protection and allow immunization of infants and toddlers, something that unconjugated Vi as a T-independent antigen cannot do successfully. This work, which began in the early 1980s, included the evaluation of multiple potential carrier proteins [99,100]. Substantial data on human immunogenicity and evidence of efficacy are available for two specific TCVs, one consisting of Vi linked to the recombinant exoprotein A of *Pseudomonas aeruginosa* (Vi-rEPA) and the other linked to tetanus toxoid protein (Vi-TT). Two Vi-TT products are licensed in India (Typbar-TCV™ manufactured by Bharat Biotech International Limited [or Bharat Biotech] and PedaTyph™ manufactured by Bio-Med Private Limited). Two additional products are undergoing licensure review by national regulatory authorities including a Vi-TT and a Vi-rEPA product in India and China, respectively.

### **Vi-rEPA vaccine (US National Institutes of Health)**

Extensive clinical data exist for a prototype Vi-rEPA vaccine developed by the US National Institutes of Health (NIH) which demonstrated safety, immunogenicity and clinical efficacy in the course of trials in infants, children and young adults in Viet Nam. A Phase III efficacy study in 11 091 Vietnamese children 2-5 years old showed a two-dose efficacy (per protocol analysis) of 91.5% (95% CI 77.1, 96.6) during 27 months of active surveillance. During these 27 months there was 87.7% efficacy among 771 recipients of a single dose of vaccine (intent-to-treat analysis). Passive surveillance was continued for 19 additional months during which vaccine efficacy was 82.4% (95% CI 22.3, 91.1) (intent-to-treat analysis). The efficacy over the full 46 months of surveillance was 89.0% (95% CI 76.0, 96.9) (intent-to-treat analysis) [101]. When disease occurred among children vaccinated with Vi-rEPA, illness severity (determined by rate of hospitalization) was reduced. Vaccination with a full dose (25µg of Vi polysaccharide) and half dose (12.5 µg) elicited similar responses.

Vi-rEPA was demonstrated to be safe and immunogenic in infants when given on a primary schedule of 2, 4 and 6 months plus a booster dose at 12 months of age with concomitant administration of routine EPI vaccines (DTP, OPV and Hepatitis B) [102]. The Vi-rEPA trials in Viet Nam showed persistence of antibodies above putative protective levels for 8 years in 75 children who were given a single-dose of Vi-rEPA at 5-8 years of age upon completion of the efficacy trial and whose titres were followed for 8 years thereafter

[103]. This experimental vaccine was not commercialized and remains the only conjugate candidate for which clinical efficacy data have been generated in the target population.

***Typbar-TCV® (Bharat Biotech): Clinical trials by the manufacturer***

Typbar-TCV consists of 25µg of Vi polysaccharide from *S. Typhi* conjugated to tetanus toxoid carrier protein in isotonic saline, licensed as a single intramuscular dose for use in children aged 6 months and above and in adults ≤ 45 years.

Four key clinical trials have been conducted by Bharat Biotech with their Vi-TT conjugate vaccine as outlined below (see Annexes B1 to B4 for flow charts):

1. A randomized controlled trial (RCT) comparing the clinical tolerability and relative immunogenicity of Typbar-TCV versus Typbar vaccine (unconjugated ViPS produced by Bharat Biotech, 25 µg Vi polysaccharide per 0.5ml dose) in subjects 2-45 years of age.
2. An open label trial (OLT) that assessed the safety and immunogenicity of Typbar-TCV in infants 6-11 months and toddlers 12-23 months of age. This trial represented the first use of Typbar-TCV in young children <2 years of age. A proportion of the infants and toddlers were given a booster dose of Typbar-TCV two years after primary immunization (day 720) which allowed the response to a booster to be assessed, as well as the magnitude and kinetics of the antibody titres up to 5 years after primary immunization in some boosted and unboosted children who were followed long-term.
3. A randomized controlled trial comparing the reactogenicity and immunogenicity of Typbar-TCV versus Sanofi Pasteur ViPS (Typhim Vi) in subjects 2-15 years of age. Typhim Vi is currently the only WHO pre-qualified typhoid vaccine.
4. A comparison of the reactogenicity and immunogenicity following co-administration of measles vaccine with Typbar-TCV at ~9 months of age versus either vaccine administered alone and of Typbar-TCV co-administered with measles-mumps-rubella (MMR) vaccine in subjects 2-15 years of age at 15 months of age to determine whether there is clinical or immunologic interference. One sub-group that received Typbar-TCV with measles got a booster with Typbar-TCV one month later. Another subgroup got a booster with Typbar-TCV 180 days later.

1. RCT comparing the immunogenicity of Typbar-TCV versus Typbar (Annex B1, Table 1)

This trial was undertaken to compare directly, in randomly allocated groups of subjects 2-45 years of age, the relative immunogenicity and clinical tolerability of unconjugated ViPS (Typbar) versus conjugated Vi-TT

(Typbar-TCV). Serum specimens collected at day 0 and day 42 showed the rise in geometric mean titre (GMT) and the percent seroconversion (4-fold or greater) following administration of a single dose of either vaccine. While the rates of seroconversion of serum IgG anti-Vi antibody were similar in recipients of each vaccine (97.3% for Typbar-TCV and 93.1% for Typbar), the day 42 GMT of the Typbar-TCV group (1292.5 [95% CI 1153, 1449]) was significantly higher than for the recipients of the unconjugated ViPS (411.1 [95% CI 359, 471]) [104].

The clinical protocol was amended so that a homologous booster dose of Vi-TT or ViPS could be administered to a proportion of subjects 720 days after they had received their first dose of vaccine; serum was obtained on day 720 and 42 days later (day 762) to measure Vi antibody titres. Six weeks following receipt of the second immunization with Typbar-TCV or Typbar, the GMTs of subjects given either vaccine rose 19-fold (Typbar-TCV) and 9-fold (Typbar), with the Typbar-TCV GMT reaching a day 762 anti-Vi titre ~3.6-fold higher than the subjects boosted with Typbar [104]. The anti-Vi antibody responses to the ViPS and Vi-TT vaccines following the primary and the booster dose of ViPS or Vi-TT vaccines were previously reported [104]. Some of these results are also summarized in Figure 5A.

The clinical protocol for this trial was further amended to allow follow-up blood specimens to be obtained from any participants, boosted or unboosted, who were available on days 1095 and 1825, i.e., 3 years and 5 years after initial vaccination, and 2 years and 3 years after the day 720 booster for those who were boosted. This amendment allowed the longevity of the Vi antibody responses to be assessed. The serological data summarized as the GMT observed at different time points in the various groups are shown in Figure 5A. Light blue bars (solid and hatched) show the kinetics of anti-Vi antibody in a group of 84 compliant subjects, the “all specimens cohort”, who received primary immunization with Typbar-TCV on day 0 and a second immunization on day 720, and had serum specimens collected at all time points including days 0, 42, 720, 762, 1095 and 1825. The baseline day 0 GMT of this compliant “all specimens cohort” of individuals closely resembles the baseline GMT of the other groups. The GMT rose markedly on day 42 following primary immunization but fell ~10-fold by day 720. Following the booster dose of Typbar-TCV the GMT rose notably to reach a level slightly higher than day 42. Sera collected on days 1095 and 1825 from this highly compliant group of subjects showed that the GMT fell significantly from the day 762 GMT but nevertheless remained significantly higher than the day 720 GMT. Although the day 1825 GMT was somewhat lower than day 1095 GMT, the difference was not significant and the slope of the antibody decline between these last two time points two years apart was gradual.

For comparison, Figure 5A also shows the kinetics of the Vi antibody GMTs in a compliant “all specimens cohort” of 26 subjects who received primary immunization with Typbar ViPS vaccine (dark blue bars, solid and hatched) and provided serum specimens at all key time points including days 0, 42, 720, 762, 1095 and 1825. The GMT on day 42 was significantly lower in the Typbar ViPs subjects than for the recipients of Typbar-TCV, as was the day 762 GMT of Typbar ViPs recipients following a re-immunization with the same vaccine on day 720, when compared to the “all specimens” subjects who were boosted with Typbar-TCV (light blue hatched bars). However, by day 1095 and 1825 the GMTs of the compliant “all specimens cohort” who received a primary and a second immunization (day 720) with Typbar were not significantly lower than the “all specimens cohort” who received primary and booster doses of Typbar-TCV. Similar observations were made for less compliant “any available specimens” subjects who received primary immunization, were boosted on day 720 and had serum specimens collected on days 0 & 42 and at least one other time point (day 762, 1095 or 1825). Thus, the numbers of subjects on any given day were much larger. These subjects are represented by light orange (Typbar-TCV) and dark orange (Typbar) bars in Figure 5A. The kinetics of these larger groups which include subjects who did not provide specimens at all time points show parallel results as the smaller “all specimens cohorts” (light and dark blue). The GMT of Typbar-TCV recipients (light orange) was significantly higher than Typbar recipients (dark orange) on days 42 and 762 but was not so on days 1095 and 1825 (Figure 5A).

Importantly, significant differences were noted between Typbar-TCV and Typbar vaccinees who were not boosted at day 720 and had specimens collected at day 1095 and 1825. The small numbers of unboosted subjects among the compliant “all specimens cohorts” who provided specimens on days 0 and 42 as well as on both days 1095 and 1825 are seen in Figure 5A for unboosted Typbar-TCV recipients (light brown, N=38) and Typbar recipients (dark brown, N=83). The GMTs between these two groups (higher in Typbar-TCV) was not significantly different on day 1095 but it was significantly different on day 1825. In larger cohorts of unboosted individuals who provided sera on days 0 and 42 and either day 1095 or 1825 (but not both), the GMT of the Typbar-TCV group (white bars) was significantly higher on both days 1095 and 1825, versus the Typbar ViPS recipients (grey bars). These data indicate that an initial vaccination with Vi conjugate (Typbar-TCV) elicits a significantly longer-lived antibody responses in the absence of a booster than unconjugated ViPS (Typbar).

Figure 5B charts the longevity of antibody elevation among the different groups by tracking in boosted and non-boosted cohorts the percent of individuals on any given day post-vaccination whose titres remained at least four-fold above their day 0 baseline. Since there is not an agreed-upon threshold cut-off of serum IgG Vi antibody that designates protection, the cut-off of four-fold or greater over baseline as the common

measure of comparison was used. Analysing the data portrayed in Figure 5B, one notes that among the “all specimens cohorts” who received an initial dose of Typbar-TCV or Typbar vaccine, and a second vaccination on day 720, (light blue versus dark blue) and the “any available specimen” subjects (light versus dark orange) who received both an initial and a second dose of vaccine, there was a significantly higher prevalence of elevated titres observed among the Typbar-TCV recipients on day 720; there was borderline significance on day 762. In contrast, among the unboosted “all specimens cohorts” (light versus dark brown) and the “any available specimen” subjects (white versus grey), the Typbar-TCV recipients had significantly higher prevalence of elevated titres on both days 1095 and 1825. This analysis corroborates the GMT data demonstrating that a single dose of Typbar-TCV elicits higher titres of Vi antibody which remain elevated for longer than Vi antibody stimulated by Typbar.

Beyond demonstrating that Vi conjugate elicits a significantly higher magnitude and longevity of IgG anti-Vi antibodies than ViPS, comparisons were made of the quality of the antibodies elicited by each vaccine at various time points. The assays included measurement of antibody avidity and an analysis of IgG sub-classes. Data for sera collected from a subset of subjects on days 0, 42, 720 and 762 were previously reported [104]. An Avidity Index (AI) of 60 provided a useful cut-off for comparison [105], with significantly more Typbar-TCV recipients having an AI >60 than Typbar recipients. Figure 6 adds data for subjects whose sera from day 1825 were tested for persons who were boosted on day 720 as well as unboosted subjects. At day 42, six weeks following primary immunization, there was no difference in the avidity of anti-Vi in recipients of the two vaccines [104]. In contrast, by day 720 there was a notable increase in the proportion of Typbar-TCV recipients who had high avidity antibodies compared to Typbar recipients [104]. This difference in high avidity antibodies was even more striking at day 1825 in both boosted and non-boosted subjects.

Although the numbers of sera tested were small, the distribution of IgG subclasses of anti-Vi in recipients of Typbar-TCV was qualitatively different from that for Typbar recipients [104].

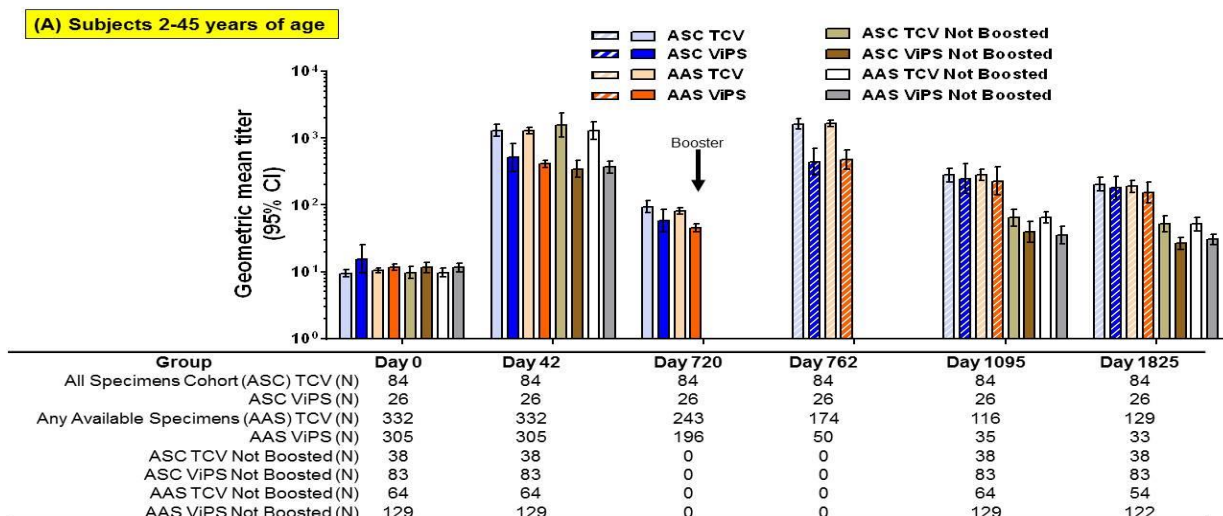
The anti-Vi antibody responses in children 2-4 years of age who received an initial immunization with Typbar-TCV closely resembles the responses observed among older children and adults.

In multi-dose vials (5 doses per vial), 2-phenoxyethanol serves as the preservative to maintain sterility. Mohan et al also compared anti-Vi responses in recipients of mono-dose versus multi-dose vials of Typbar-TCV and showed that the responses did not differ [104].

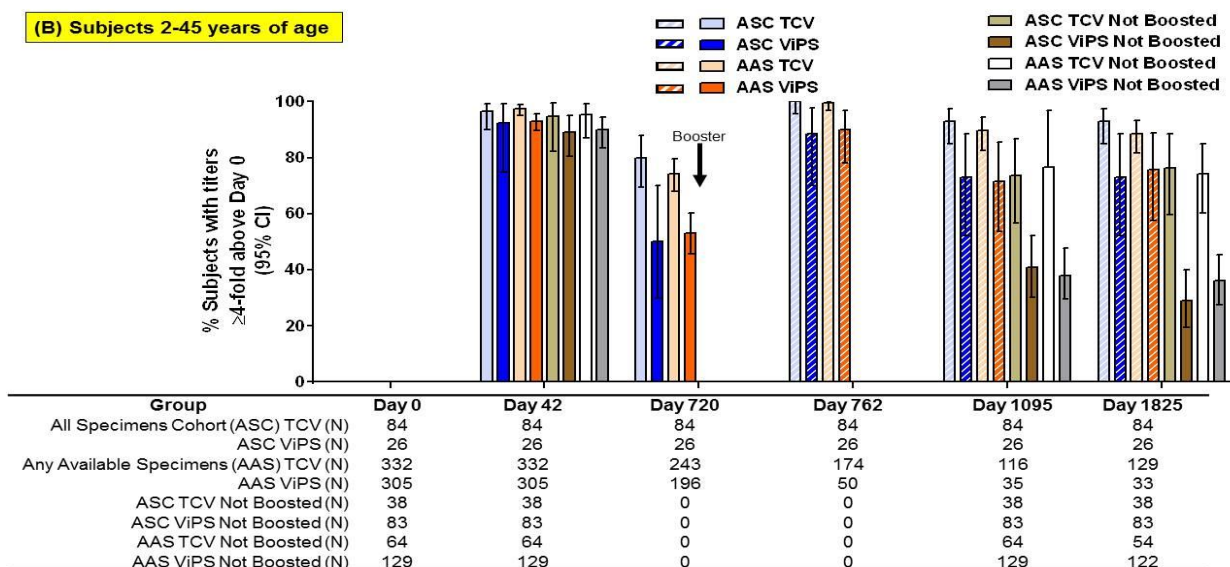


Table 1. GMTs of anti-Vi IgG antibodies at baseline and at various time points after administration of an initial dose of vaccine (Day 0) and after a second dose of the same vaccine (Day 720 after the initial immunization) – Randomized Controlled Trial (RCT) and Open Label Trial (OLT)

	Day 0	Day 42	Day 720	Day 762	Day 1095	Day 1825
<b>RCT (subjects 2-45 years of age): Typbar-TCV</b>						
Subjects with serum specimens on days 0 & 42 and at least one other time point on days 762, 1095 or 1825	332	332	243	174	116	129
GMT EU/mL (95% CI)	10.4 (9.6,11.3)	1292.5 (1152.9,1448.9) 97.3 (95.0,98.8)	81.7 (72.6,91.9) 74.1 (68.1,79.5)	1680.6 (1498.3,1885.1) 99.4 (96.8,99.9)	282.3 (229.4,347.4) 89.7 (82.6,94.5)	190.1 (155.2,232.9) 88.4 (81.6,93.3)
Percent of subjects whose titres are ≥4-fold above their day 0 baseline titre		84	84	84	84	84
Subjects with the full series of specimens on days 0, 42, 720, 762, 1095 and 1825	84	84	84	84	84	84
GMT EU/mL (95% CI)	9.5 (8.3,10.9)	1305.4 (1069.6,1593.2) 96.4 (89.9,99.3)	94.1 (75.9,116.6) 79.8 (69.6,87.8)	1632.2 (1370.1,1944.3) 100.0 (95.7,100.0)	280.8 (222.2,355.0) 92.9 (85.1,97.3)	203.6 (160.9,257.7) 92.9 (85.1,97.3)
Percent of subjects whose titres are ≥4-fold above their day 0 baseline titre		84	84	84	84	84
<b>RCT (subjects 2-45 years of age): Typbar (VIPS)</b>						
Subjects with serum specimens on days 0 & 42 and at least one other time point on days 762, 1095 or 1825	305	305	196	50	35	33
GMT EU/mL (95% CI)	11.6 (10.5-12.9)	411.1 (358.9-470.9) 93.1 (89.7,95.7)	45.7 (39.6,52.6) 53.1 (45.8,60.2)	475.0 (339.9,663.6) 90.0 (78.2,96.7)	228.8 (139.5,375.4) 71.4 (53.7,85.4)	153.7 (108.5,217.7) 75.8 (57.7,88.9)
Percent of subjects whose titres are ≥4-fold above their day 0 baseline titre		26	26	26	26	26
Subjects with the full series of specimens on days 0, 42, 720, 762, 1095 and 1825	26	26	26	26	26	26
GMT EU/mL (95% CI)	15.6 (9.6,25.4)	513.9 (316.8,833.6) 92.3 (74.9,99.1)	58.8 (39.9,86.6) 50 (29.9,70.1)	442.9 (279.5,701.9) 88.5 (69.9,97.6)	249.5 (148.4,419.5) 73.1 (52.2,88.4)	179.3 (118.8,270.7) 73.1 (52.2,88.4)
Percent of subjects whose titres are ≥4-fold above their day 0 baseline titre		26	26	26	26	26
<b>OLT (subjects 6-23 months of age) Typbar-TCV</b>						
Subjects with serum specimens on days 0 & 42 and at least one other time point on days 762, 1095 or 1825	307	307	220	179	148	148
GMT EU/mL (95% CI)	9.4 (8.7,10.3)	1937.4 (1785.0,2102.9) 98.1 (95.8,99.3)	48.7 (42.4,55.9) 59.5 (52.7,56.1)	1706.8 (1529.8,1904.2) 98.3 (95.2,99.7)	307.7 (257.6,367.6) 90.5 (84.6,94.7)	132.3 (111.3,157.3) 83.8 (76.8,89.3)
Percent of subjects whose titres are ≥4-fold above their day 0 baseline titre		126	126	126	126	126
Subjects with the full series of specimens on days 0, 42, 720, 762, 1095 and 1825	126	126	126	126	126	126
GMT EU/mL (95% CI)	9.4 (8.2,10.8)	1902.7 (1670.0,2167.8) 96.8 (92.1,99.1)	53.8 (44.7,64.7) 65.1 (56.1,73.4)	1700.2 (1500.2,1927.0) 97.6 (93.2,99.5)	319.2 (266.7,381.9) 91.3 (84.9,95.6)	132.3 (109.1,160.4) 84.1 (76.6,90.0)
Percent of subjects whose titres are ≥4-fold above their day 0 baseline titre		126	126	126	126	126
Anti-Vi IgG antibody titres estimated by VaccZyme ELISA kit						
CI = confidence interval; ELISA= enzyme-linked immunosorbent assay; EU = enzyme-linked immunosorbent assay units; GMT = geometric mean titre; VIPS = Vi polysaccharide vaccine						



For AS TCV Not Boosted, graphed values are from the group with N=64. Values from the N=54 group are Day 0= 10.1 (8.4, 12.1); Day 42=1347.8 (933.2,1946.5); For AS ViPS Not Boosted, graphed values are from the group with N=129. Values from the N=122 group are Day 0=11.7 (10.1,13.7); Day 42=387.7 (308.4, 487.5)



For AS TCV Not Boosted, graphed values are data from the group with N=64. Values from the N=54 group are Day 42=96.3 (99.5,87.3); For AS ViPS Not Boosted, graphed values are data from the group with N=129. Values from the N=122 group are Day 42=90.2 (94.8,83.4)

**Figure 5. Serum anti-Vi IgG responses in RCT of older children, adolescents and adults, 2-45 years of age, given a primary and booster immunizations with Typbar-TCV and Typbar vaccines\***

TCV: Typhoid conjugate vaccine (Typbar-TCV); ViPS: Vi Polysaccharide vaccine (Typbar); \*N = number of subjects for whom serum specimens were available for measurement of anti-Vi antibodies at each time point  
 Data for unboosted subjects at Days 0 and 42 show the titres at baseline and post-Dose 1 for the subset of children who were subsequently not boosted (hatched bars), in comparison to those for the whole cohort at Days 0 and 42. This shows that relatively high titres observed for the non-booster group at Days 1095 and 1825 do not appear to correlate with significantly higher titres at baseline and Day 42.

Source: Bharat Biotech

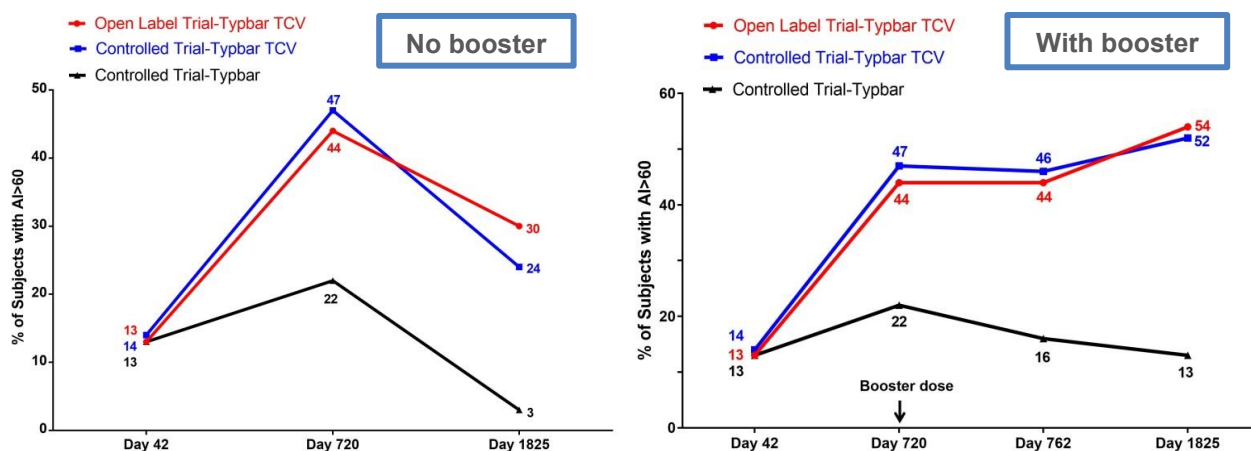


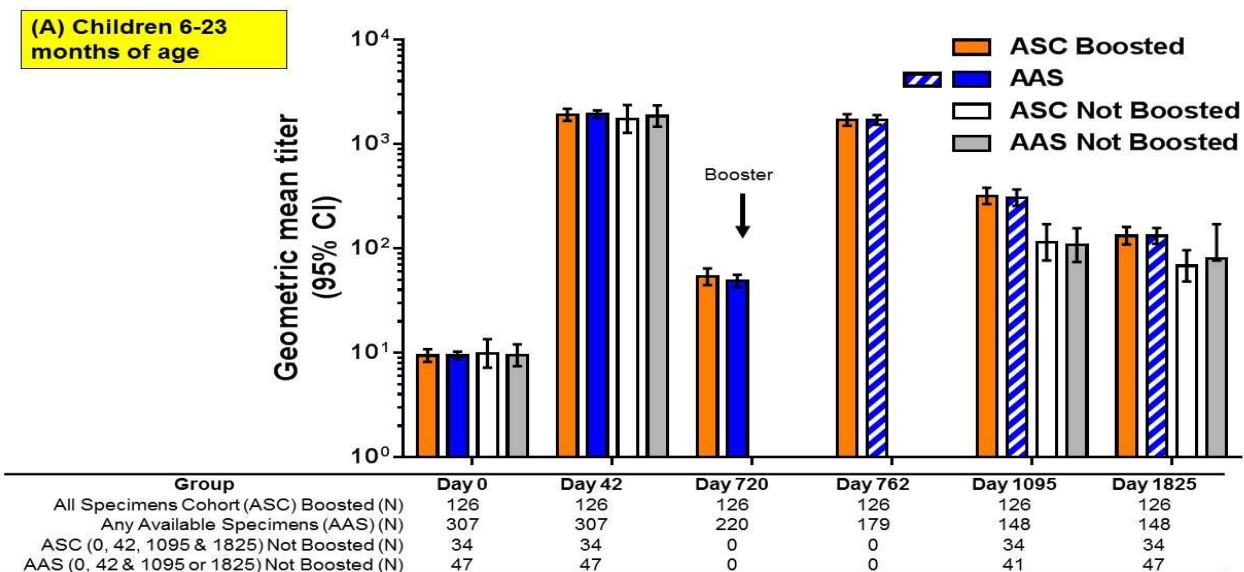
Figure 6. Proportions (%) of each study cohort with Avidity Index (AI) values > 60 at Days 42, 720 and 1825, with and without a booster vaccination at Day 720  
 Source: Bharat Biotech International Limited

**Salient observations and conclusions from the randomized trial comparing Typbar-TCV and Typbar.**

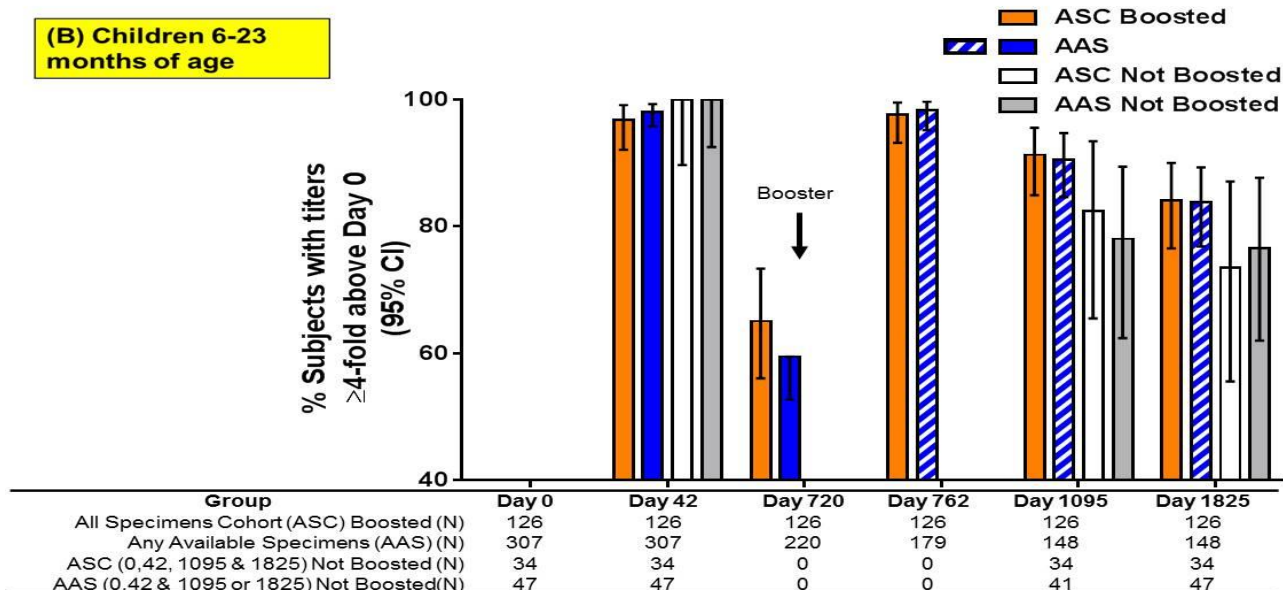
- The Typbar-TCV conjugate vaccine elicits significantly higher titres of IgG Vi antibody at 6 weeks after a primary immunization and 6 weeks after a second immunization than unconjugated Typbar.
- With respect to duration of elevated antibody titres at 3 and 5 years after a single immunization, the GMT of anti-Vi and the proportion of individuals with titres  $\geq 4$ -fold over their baseline was significantly higher among recipients of the conjugate vaccine.
- The proportion of subjects with IgG antibody exhibiting an AI >60 was significantly higher in Typbar-TCV recipients compared to Typbar recipients.
- Among these subjects aged 2-45 years who were mainly adults and children >4 years of age, the GMT of anti-Vi IgG attained 42 days after administration of a second dose of Typbar-TCV closely resembled the GMT recorded at 42 days after the initial dose of conjugate vaccine.

2. Open Label Trial (OLT) (Annex B2, Table 1)

An open label trial was undertaken in which 327 infants and toddlers 6-23 months of age were administered Typbar-TCV, representing the first time that this conjugate vaccine was evaluated in children too young to receive unconjugated ViPS. Of these 327 children, 307 (93.9%) had serum specimens collected on day 0 and 42. On day 720, 193 of these young children were boosted with a second dose of Typbar-TCV



Values for ACS Not Boosted used data from group with N=47. Values for group with N=41 (Day 0=97.7(7.5, 12.7); Day 42 =1610.4 (1170.1,2212.7))



Values for ASC Not Boosted used data from group with N=47. Values for group with N=41 (Day 42 =97.6% (99.9%, 87.1%))

**Figure 7A & B. Serum anti-Vi IgG responses in Open-Label Trial of infants and toddlers, 6-23 months of age, given a primary and booster immunizations with Typbar-TCV\***

\*N = number of subjects for whom serum specimens were available for measurement of anti-Vi antibodies at each time point

Data for AAS subjects at Days 0 and 42 (dark blue solid bar) show the titres at baseline and post-Dose 1 for the subset of children who were subsequently boosted while the (hatched bars) shows their titres at day 720 (pre-boost) and 3 and 5 years post-boost.

Source: Bharat Biotech

and 187 of these boosted children provided serum specimens on both day 720 and day 762 to assess the response to the booster. The strong serological responses of these young children to an initial and a booster dose of Typbar-TCV through day 762 have been published [104] and they are also summarized in Figures 7A and 7B. Serum specimens were obtained from available boosted and unboosted infants and toddlers at 3 years (day 1095) and 5 years (day 1825) following initial immunization.

Serological results involving specimens collected beyond day 762 are summarized in Figures 7A and 7B. Figure 7A shows that a cohort of fully compliant “all specimens” children (specimens on days 0, 42, 1095 and 1825) and a cohort of somewhat less compliant “any available specimen” children who provided specimens on days 0 and 42 and either 1095 or 1825 (but not both) and who were boosted (orange and blue hatched bars) exhibited very similar GMTs on days 1095 and 1825, with the latter GMTs being significantly lower than the former. Similarly, the “all specimens cohort” and “any available specimens subjects” who were not boosted at day 720 (white and gray bars) showed nearly identical GMTs that were significantly lower at day 1095 and 1825 than the GMTs of the boosted cohorts (Figure 7A); the day 1825 GMTs were somewhat lower than the day 1095 values.

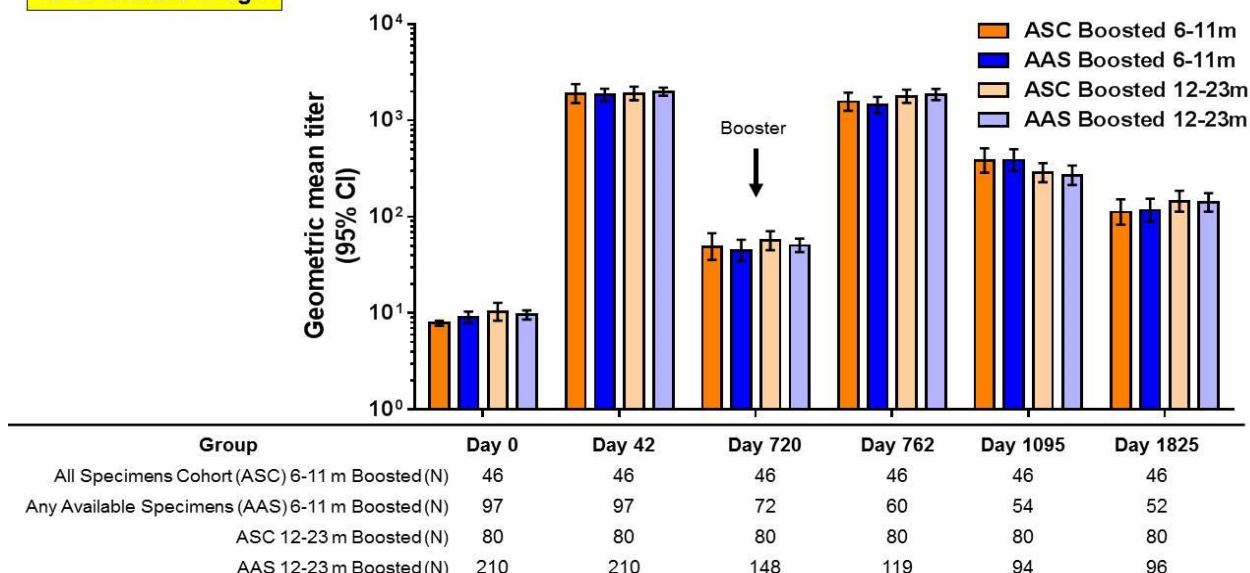
Figure 7B displays the longevity of the elevated anti-Vi titres by displaying the proportion of subjects at each time point following initial immunization at day 0, whose titres were still  $\geq 4$ -fold above their day 0 titre. The proportion of elevated titres was higher in boosted cohorts (orange and blue hatched bars) than the unboosted subjects (white and gray bars).

Figures 7C and D portray the data in the same way, albeit with the cohorts ages 6-11 months (dark orange and dark blue) displayed alongside the cohorts immunized at age 12-23 months. These figures show that, with respect to both GMTs and longevity of elevated titres (percent of subjects at each study day whose titres remain 4-fold or greater above their day 0 titre), the infants ages 6-11 months responded as robustly as the toddlers ages 12-23 months.

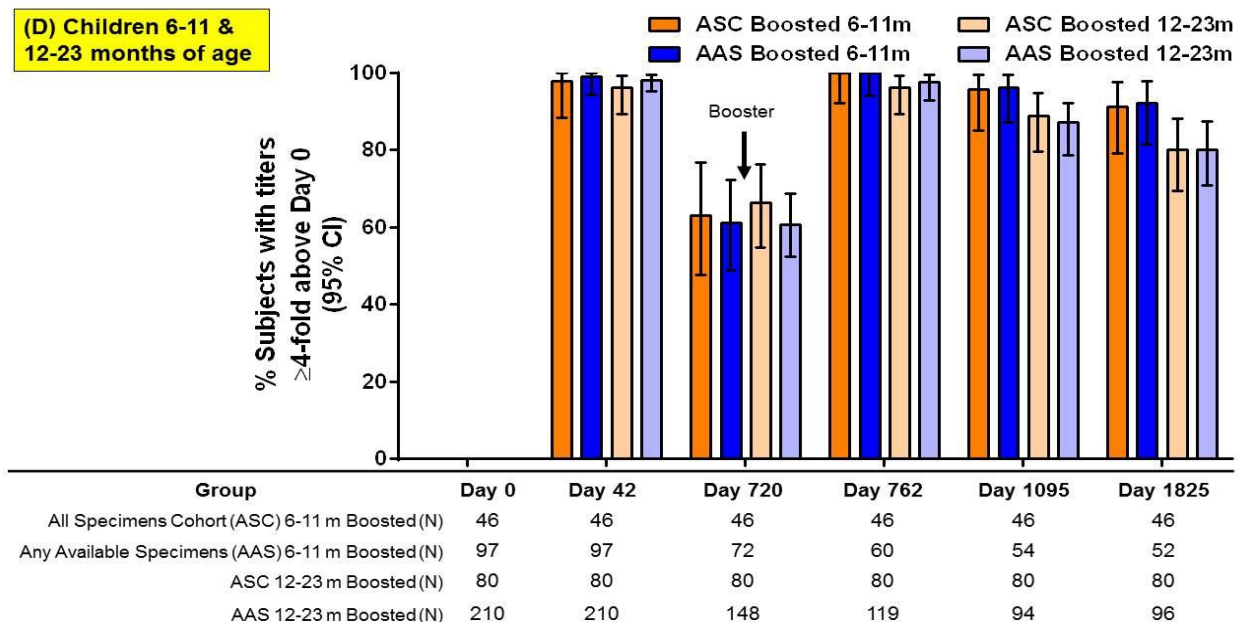
**Salient observations and conclusions from the Open Label Trial of Typbar-TCV in infants and toddlers.**

- Tested for the first time in infants 6-11 months and toddlers 12-23 months of age, Typbar-TCV was not only well tolerated but a single dose was impressively immunogenic eliciting high titres of IgG anti-Vi antibody that endured up to 5 years in a proportion of young children.
- Responses in infants 6-11 months were as robust as responses in toddlers age 12-23 months.

**(C) Children 6-11 & 12-23 months of age**



**(D) Children 6-11 & 12-23 months of age**



**Figure 7C & D: Serum anti-Vi IgG responses in Open-Label Trial of infants and toddlers, 6-23 months of age, given a primary and booster immunizations with Typhar-TCV\***

\*N = number of subjects for whom serum specimens were available for measurement of anti-Vi antibodies at each time point

Data for AAS subjects at Days 0 and 42 (dark blue solid bar) show the titres at baseline and post-Dose 1 for the subset of children who were subsequently boosted while the (hatched bars) shows their titres at day 720 (pre-boost) and 3 and 5 years post-boost.

Source: Bharat Biotech



3. RCT comparing Typbar-TCV versus Sanofi Pasteur ViPS vaccine (Typhim Vi) (Annex B3)

Although the reactogenicity and immunogenicity of Bharat Biotech Typbar-TCV was compared directly to unconjugated ViPS Typbar vaccine, it was important to undertake an analogous comparison using the WHO-prequalified ViPS (Typhim Vi, Sanofi Pasteur).

Figures 8A and 8B summarize the results of this study. On day 0, 340 subjects 2-15 years of age were randomly allocated to receive a single intramuscular dose of Typbar-TCV (N=170) or Typhim Vi (N=170). Serum specimens collected on day 28 were tested along with day 0 specimens to determine the rate of seroconversion stimulated by each vaccine and the GMT. Sera collected on day 90 and 180 allowed the longevity of the antibody responses to each vaccine (GMT and percent of subjects whose anti-Vi titre remained  $\geq 4$ -fold above their day 0 baseline). On day 180, one-half of the Typbar-TCV cohort was allocated to receive a booster dose of Typbar-TCV and serum was obtained thirty days later (day 210) to assess the rate of seroconversion versus unboosted Typbar-TCV recipients and unboosted Typhim Vi recipients.

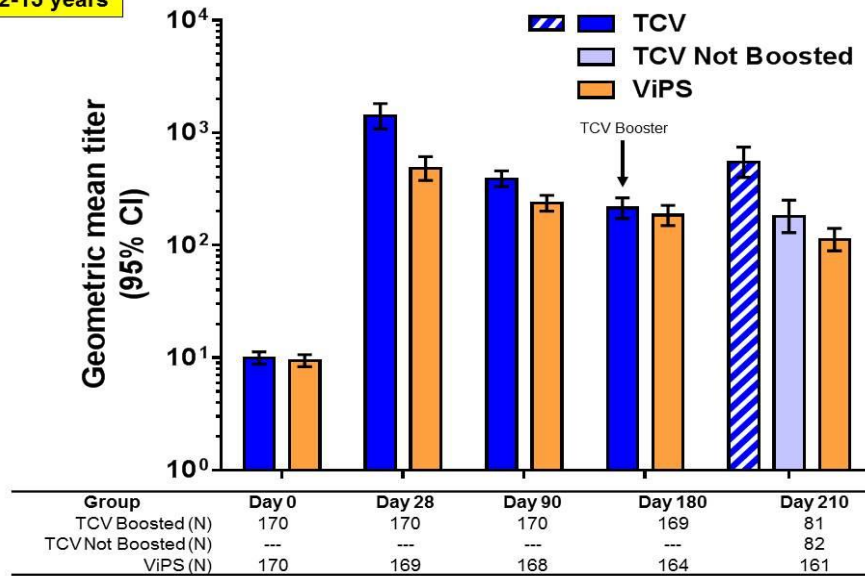
Figure 9A shows that the GMT on day 28 of the Typbar-TCV recipients was significantly (approximately one-half log) higher than the Typhim Vi recipients. On day 90 the GMT of the Typbar-TCV cohort remained significantly higher than the Typhim Vi recipients, although the GMTs of recipients of both vaccines had fallen from the day 28 titre. Administration of a booster dose of Typbar-TCV on day 180 raised the GMT recorded on day 210 over the unboosted Typbar-TCV and Typhim Vi groups. Interestingly, the GMT of the boosted Typbar-TCV subjects did not reach the level recorded on day 28. Whereas the GMT on day 210 of the unboosted Typbar-TCV vaccinees was higher than the Typhim Vi recipients, the difference was not significant (Figure 9A).

Figure 9B displays the percent of individuals in each group on the different study days whose titres remained  $\geq 4$ -fold above their day 0 baseline. The Typbar-TCV recipients had a prevalence slightly higher than Typhim Vi recipients but the differences were not statistically significant except for the boosted Typbar-TCV group on day 210.

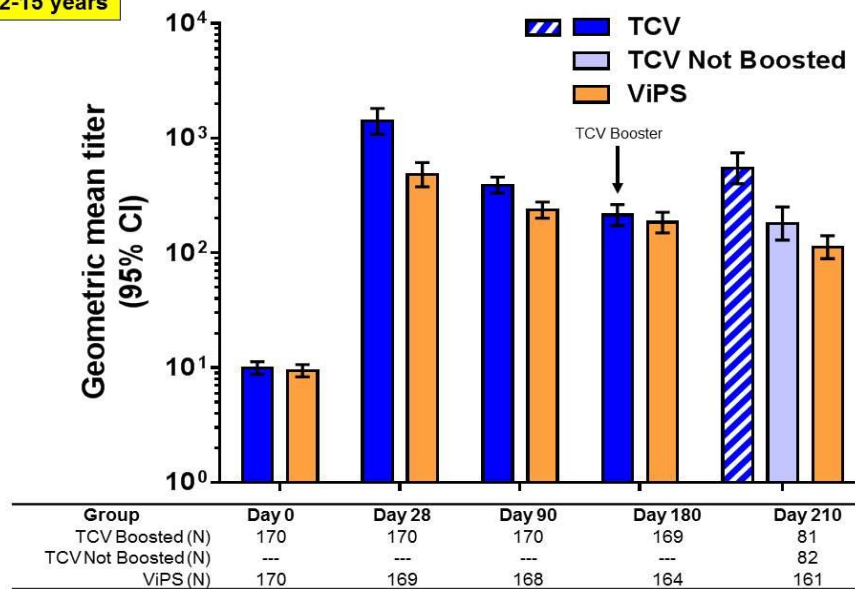
Analysis of the results with the subjects broken down by age into 2-4 year olds and 5-15 year old age groups showed similar patterns in the younger age group compared to the older age group, documenting that Typbar-TCV was as immunogenic in preschool children as in school age children (data not shown).

The results of the Typbar-TCV versus Typhim Vi randomized controlled trial corroborate the results of the earlier randomized trial comparing Typbar-TCV versus Typbar.

(A) Subjects 2-15 years



(B) Subjects 2-15 years



**Figure 8. Serum anti-Vi IgG responses in subjects 2-15 yrs of age, given a primary and booster immunizations with Typhbar-TCV and ViPS (Typhim Vi) vaccines\* in a randomized open label study**

TCV: Typhoid conjugate vaccine (Typhbar-TCV); ViPS: Vi Polysaccharide vaccine (Typhim Vi); N = number of subjects for whom serum specimens were available for measurement of anti-Vi antibodies at each time point. Data for TCV subjects at Days 0, 28 and 90 show baseline and post Dose-1 titres (dark blue solid bar) and for the 2 subgroups of subjects boosted and not boosted at day 210 (hatched bar for post-boost titres and light blue solid bar for unboosted subjects)



**Salient observations and conclusions from the randomized trial of Typbar-TCV versus Typhim Vi in children 2-15 years of age.**

- A single intramuscular dose of Typbar-TCV was significantly more immunogenic than Typhim Vi, the only WHO pre-qualified typhoid vaccine.
- A booster dose of Typbar-TCV administered to children 6 months after their primary immunization with Typbar-TCV raised Vi antibody titres but not as high as the peak that followed the primary immunization.

4. Co-administration of measles vaccine with Typbar-TCV at ~9 months of age versus either vaccine alone and of Typbar-TCV co-administered with measles-mumps-rubella vaccine at 15 months of age (Annex B4)

The ability of a single intramuscular dose of Typbar-TCV to elicit high rates of seroconversion and high GMTs of IgG anti-Vi antibody in infants 6-11 months and in toddlers 12-23 months of age stimulated interest in administering this conjugate vaccine at either 9 months of age, concomitant with measles containing vaccine 1 (MCV1) or with MCV2, which is administered at 15-18 months of age, or at both ages. Thus, a randomized controlled trial was designed to compare the immunogenicity of Typbar-TCV when co-administered with measles vaccine at 9 months of age compared to infants who received Typbar-TCV alone one month before (age 8 months) or one month after measles vaccine (age 10 months). Similarly, the effect of co-administration of Typbar-TCV and MCV1 on the measles antibody response was assessed by comparing IgG measles antibody in sera from infants who received both vaccines concomitantly versus measles vaccine alone. Six months after primary immunization (15 months of age), all children received measles-mumps-rubella (MMR) vaccine with one group receiving concomitantly administered Typbar-TCV along with MMR.

Co-administering two different vaccines such as TCV and measles at the same EPI visit should not produce an immune response that is inferior with respect to either anti-Vi or anti-measles antibodies. The concern is one-directional because there is no safety concern about whether the co-administration of the two vaccines is superior to each vaccine administered alone in the absence of the other. A non-interference (non-inferiority) trial aims to show that co-administration of two vaccines stimulates immune responses that are not inferior to the responses elicited by the individual vaccines by as much as a sufficiently small pre-specified **non-inferiority margin**. The two immune response end points that are commonly used for assessing non-inferiority are geometric mean titre (GMT) and the proportion of vaccine recipients who

reach a critical antibody threshold that is considered protective. Bharat Biotech did not pre-specify a non-inferiority margin or present a point estimate and 95% confidence interval for the ratio of GMTs or the difference in proportions reaching a threshold of protection. Rather, Bharat Biotech calculated 95% confidence intervals around the point estimates of GMT (Figure 9A) and around the percent of infants on a given study day whose titres of anti-Vi remained  $\geq 4$ -fold above the day 0 value and looked for CIs that did not overlap. That analysis does not allow conclusions about non-interference.

Effect of co-administration of measles vaccine on anti-Vi responses to Typbar-TCV.

Figure 9A summarizes the anti-Vi antibody GMTs in the five different groups that were allocated to receive vaccine on day 0 as in the box below:

Group 1A	Typbar-TCV + Measles	(N=98)	dark orange bars
Group 1B	Typbar-TCV + Measles	(N=99)	light orange bars
Group 2	Measles	(N=98)	dark blue bars
Group 3	Typbar-TCV	(N=98)	light blue bars
Group 4	Measles	(N=100)	white bars

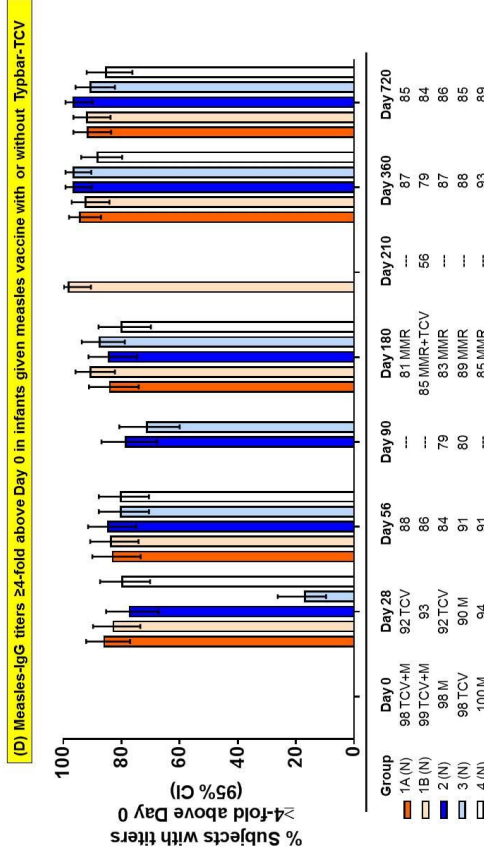
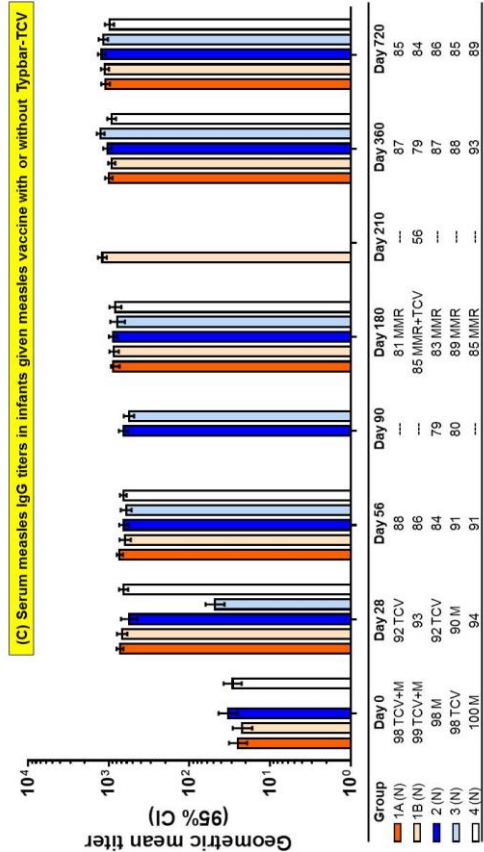
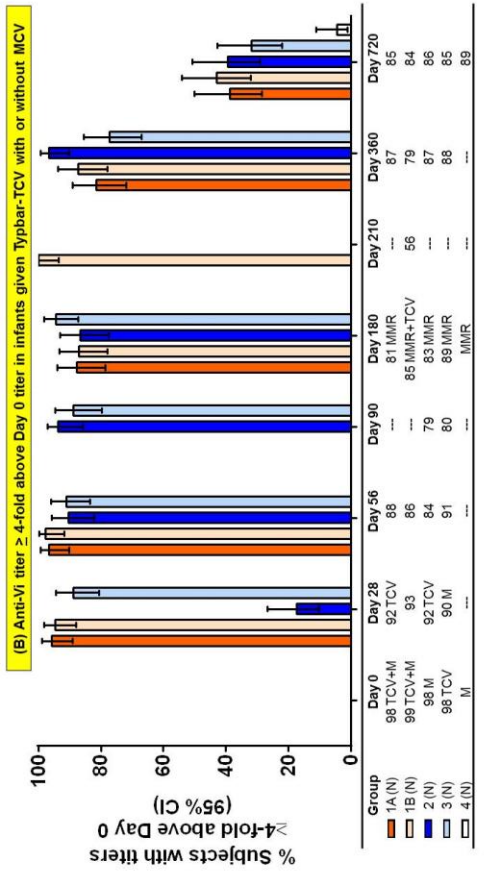
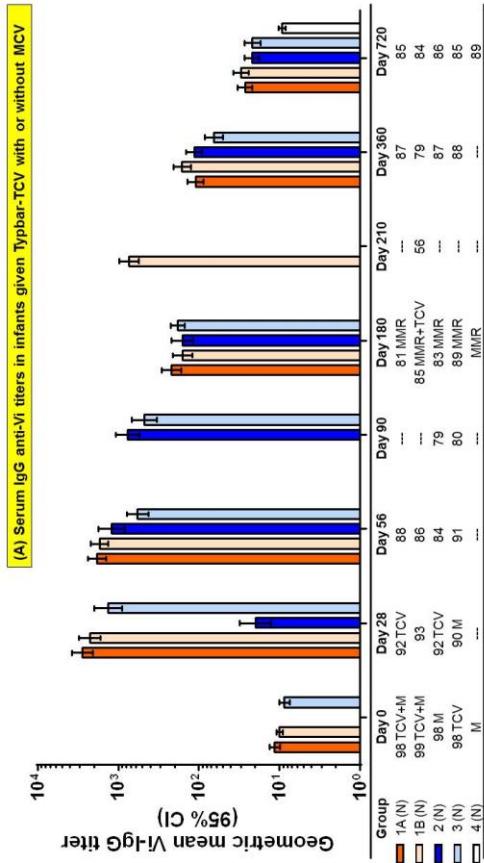
The baseline (day 0) GMT of anti-Vi antibody did not differ among the five groups. The anti-Vi GMT on day 28 in infants of these five groups provides the evidence for or against interference between the two vaccines. Bharat Biotech calculated 95% confidence intervals around the point estimates of GMT (Figure 9A) and around the percent of infants on a given study day whose titres of anti-Vi remained  $\geq 4$ -fold above the day 0 value (Figure 9B). The day 28 GMT of anti-Vi antibody in Group 3 constitutes the positive control, i.e., the GMT observed when Typbar-TCV is administered without measles vaccine. The day 28 anti-Vi GMT of Group 3 must then be compared with the day 28 GMTs of Groups 1A and 1B, both of whom were given Typbar-TCV concomitantly with measles vaccine. Interestingly, the 95% CIs overlap but the Group 1A and 1B GMTs were actually each higher than the Group 3 GMT (Figure 9A). The Group 3 infants received their Typbar-TCV alone at 8 months of age, whereas all the other groups received their day 0 vaccinations at 9 months of age. The somewhat lower (albeit non-significant) anti-Vi GMT of Group 3 may be consequent to their younger age. Nevertheless, the anti-Vi response of Group 3 infants was long-lived. They received no booster dose of Typbar-TCV through day 720, the termination of surveillance. Yet their GMT at day 720 was significantly higher than Group 4 who had received no Typbar-TCV and lower than Groups 1A (who received two doses of Typbar-TCV on days 0 & 28) and Group 1B (who received two doses of Typbar-TCV on days 0 and 180).

Figure 9B displays the longevity of the anti-Vi responses assessed as the percent of infants in each group on each study day who exhibit anti-Vi titres  $\geq 4$ -fold above their pre-vaccination baseline. The only significant difference observed was on day 360 between Group 2 (dark blue bar) who received a dose of Typbar-TCV 338 days earlier at age 10 months and Group 3 (light blue bars) who had received their single dose of Typbar-TCV 360 days earlier at 8 months of age.

*Effect of co-administration of Typbar-TCV vaccine on IgG anti-measles antibody responses to monovalent measles (at 9 months of age) or MMR at 15 months of age.* (Figure 9C)

The baseline (day 0) GMT of anti-measles IgG antibody did not differ among the groups. The anti-measles GMT on day 28 in infants of these five groups provides the first piece of evidence for or against interference between the two vaccines. Bharat Biotech calculated 95% confidence intervals around the point estimates of GMT (Figure 9C) and around the percent of infants on a given study day whose titres of anti-measles virus IgG remained  $\geq 4$ -fold above the day 0 value (Figure 9D). The day 28 GMT of anti-measles antibody in Group 2 and 4 constitute the positive controls, i.e., the GMT observed when measles vaccine is given in the absence of co-administered Typbar-TCV. Comparison of the day 28 and day 56 anti-measles titres of Group 3 give additional data on the response to measles vaccine in the absence of Typbar-TCV. The day 28 anti-measles GMT of Group 2 and 4 must then be compared with the day 28 GMTs of Groups 1A and 1B, both of whom were given measles vaccine concomitantly with Typbar-TCV. Interestingly, the 95% CIs of these mentioned Groups all closely overlap implying no interference based on this method of analysis (Figure 9C). The anti-measles Vi responses of these groups were all near identical through day 180 when all groups received MMR, with Group 1B receiving Typbar-TCV co-administered with MMR. The measles antibody GMTs of all groups were similar on day 360 and 720 (Figure 9C).

Figure 9D displays the longevity of the anti-measles antibody responses assessed as the percent of infants in each group on each study day who exhibit anti-measles titres  $\geq 4$ -fold above their pre-vaccination baseline. No significant differences were detected among the groups at any time relevant points including days 56, 180, 360 and 720.



**Figure 9. Serum anti-Vi IgG & measles IgG titres and percentage of subjects with titres > 4-fold above Day 0 titre in infants given Typbar-TCV with or without measles-containing vaccine in an open label non-interference study\***

\*N = number of subjects for whom serum specimens were available for measurement of anti-Vi antibodies at each time point

### **Typbar-TCV: Human challenge model**

The efficacy of Typbar-TCV vaccine was assessed recently in an observer-participant-blinded study using an established controlled human typhoid infection model in naïve adult volunteers (aged 18 to 60 years, n= 103) in a non-endemic setting (the UK). Participants were randomized to receive a single parenteral dose of Typbar-TCV, Vi-PS (Typhim Vi, Sanofi-Pasteur) or a control (group ACWY meningococcal conjugate) vaccine. Both Vi vaccines contained 25µg of Vi-polysaccharide per 0.5ml dose [106]. Approximately one month post-vaccination, participants were orally challenged with  $1-5 \times 10^4$  CFUs of *S. Typhi* Quailles strain (a wild-type strain originally isolated from a chronic carrier in Baltimore, USA), preceded by the ingestion of 120ml of sodium bicarbonate buffer [107].

Different vaccine efficacy estimates of Typbar-TCV were obtained using clinical or microbiological diagnostic endpoints. Vaccine efficacy was estimated as 87.1% (95% CI 47.2, 96.9%) against a persistent fever (defined as fever  $\geq 38^\circ\text{C}$  persisting for >12 hours) followed by positive blood culture for *S. Typhi* (Vi-TT attack rate 5% vs control attack rate was 42%) compared to vaccine effectiveness of 52.3% (95% CI -4.2, 78.2%) for the ViPS against the same endpoint (an attack rate of 20%). When other endpoints were used (varying fever thresholds, or the typhoid triad of fever  $\geq 38.0^\circ\text{C}$  plus headache and abdominal pain), the effectiveness of Typbar-TCV ranged between 37.2% (95% CI, 11.8-64.7%) for bacteraemia alone and 89.5% (95% CI 20.8, 98.6%) for a clinical diagnosis.

Seroconversion was 100% in Typbar-TCV recipients and 88.6% in the ViPS recipients, with significantly higher GMTs detected one-month post-vaccination in Typbar-TCV vaccinees (GMT of 562.9 EU/ml [396.9, 798.4] versus 140.5 EU/ml [91.0, 216.9],  $P < 0.001$ ). An inverse straight-line relationship was demonstrable between the level of anti-Vi IgG titre and the probability of developing serologically defined typhoid, but with no apparent antibody titre threshold. Overall, Typbar-TCV induced satisfactory antibody response and memory, where higher levels of anti-Vi antibody correlated with increased protection. The model is limited in its generalizability in that a moderate dose of bacteria was used with neutralization of gastric acid and all volunteers were typhoid naïve and living in a non-endemic setting. The model is assumed to produce a higher attack rate than usual long-cycle transmission in an average endemic setting which may potentially overcome immune responses that might be protective in the endemic setting, and if so may underestimate vaccine efficacy. On the other hand, the inoculum size and use of bicarbonate may closely resemble the dose ingested in certain types of food vehicles contaminated by food handlers who are chronic typhoid carriers.

Vi vaccination appears not to prevent stool shedding of *S. Typhi*, with 71% shedding in the control group, 59% in the Vi-TT group and 60% in the ViPS group (non-significant difference), although the analysis was confounded by a high number of missing samples. It is unclear whether this observation would also be repeated outside of a moderate dose challenge study setting.

### ***PedaTyph<sup>TM</sup> (BioMed)***

This Vi-TT was the first TCV to be licensed in India but with limited publically available pre-licensure data to be assessed. It consists of 5µg of Vi polysaccharide from *S. Typhi* conjugated to 5µg of tetanus toxoid protein in isotonic saline.

Available evidence on the vaccine is provided by three published post-licensure studies:

- A randomized comparative trial of 400 healthy Indian children three months to five years of age who received one dose of PedaTyph (n=200) or two doses eight weeks apart (n=200). In 163 of the single dose recipients (101 children <2 years and 24 < 1 year of age) who were available for follow up, a seroconversion rate ( $\geq 4$ fold increase over pre-immunization titre) of 83% was reported at eight weeks post-vaccination, with the highest seroconversion rate in infants (seroconversion rates of 73%, 89% and 96% for children >2 years,  $\leq 2$  years and <1 year respectively) [108].
- In a follow up of the first study cohort of 400 children [108], 40 children who received either one or two doses of PedaTyph were recalled 30 months after vaccination to assess the longevity of immune response [109]. (It is worth noting that the authors also report that 10 non-vaccinated children were “recalled”, however since the previous paper did not describe an unvaccinated control arm, the selection criteria used for these 10 children is unclear). Anti-Vi IgG titres were reported to be significantly higher in vaccinated subjects (one dose or 2 doses) at 30 months post-vaccination compared to non-vaccinated subjects, and the titres in the two-dose group were reported to be higher than the single-dose group but not significant.
- A quasi-randomized, open-label trial was conducted post-licensure in 905 Kolkata children aged 6 months to 12 years who received two doses of PedaTyph 6 weeks apart and were followed with active surveillance (weekly telephone calls plus monthly school visits) for 1 year, along with 860 unvaccinated control children [110]. Among the vaccinees, 61.8% were older than 5 years, 29.1% were 3 to 5 years, and 9.1% were 6 months to 2 years of age. The control children had a similar age distribution: 61.8% older than 5 years, 29.1% 3 to 5 years, and 12.7% 6 months to 2 years of age. Notably, no cases of blood culture–confirmed typhoid fever were recorded among the 905

vaccinees during one year of surveillance versus 11 confirmed cases among the 860 unvaccinated control children, indicating a vaccine efficacy of 100% (95% CI, 97.7,100 [P < 0.001]).

In subjects older than 2 years of age, PedaTyph is recommended to be administered intramuscularly in a two-dose schedule with 4 to 8 weeks between the doses. A booster is recommended every 10 years by the manufacturer, although no data are available to support the booster recommendation. For children 3 to 23 months old, two doses of vaccine are recommended 4 to 8 weeks apart followed by a booster at 24 to 30 months of age. The manufacturer also recommends a booster every 10 years thereafter in persons immunized at this young age [4].

Recognizing the important limitations regarding information about the studies described above (and apparent non-rigorous study design) in the published papers, efforts were made to seek additional data for the SAGE Working Group's evidence review. Despite WHO efforts, no additional data were obtained from the manufacturer to facilitate in-depth review of the trial data (including age-stratified data) for this vaccine. The available published data were included in the meta-analysis by Cochrane (see Annex C).

#### ***Immunobridging of currently licensed TCVs to NIH Vi-rEPA vaccine***

The WHO regulatory guidelines on the quality, safety and efficacy of typhoid conjugate vaccines [111] notes that there is no established immunological correlate of protection for conjugated Vi vaccines, and that antibody persistence data may be viewed in terms of the percentages of vaccinees that have anti-Vi IgG concentrations above a predefined threshold for a specified period of time. These guidelines also noted that there are no established or standardized assays for assessing functional antibody responses to Vi-containing vaccines. Based on the assay used in the Vi-rEPA efficacy trial in Viet Nam, a threshold value of 4.3 µg/ml anti-Vi antibody measured by ELISA [112] was suggested to be associated with a high level of sustained protection lasting approximately 4 years after vaccination. The WHO guidelines therefore recommended that, in the absence of an international standard, TCV sponsors who wish to apply this threshold value to the results of their own assays should perform a calibration against the assay used in the Vi-rEPA efficacy trial.

An independent expert review was sought by the Working Group to perform an immunobridging of the licensed TCVs to the Vi-rEPA vaccine, the only TCV with efficacy established. A review of the history of establishing the proposed protective threshold and of the underlying serological methods concluded that, due to methodological and/or documentation gaps, it was impossible to bridge data generated with the new TCVs and analysed by the current NIH ELISA protocol to immunogenicity data generated in the original

Vi-rEPA trial in Vietnam. Thus no quantitative bridging to the Vi-rEPA vaccine could be conducted to support these recommendations. The general consensus is that efforts should now concentrate on generating efficacy data for new TCVs, with consideration for nested immunogenicity studies as an integral part, in order to help establish a correlate of protection. Further, ongoing efforts should be accelerated to develop approved international standards to permit comparisons between data generated by different laboratories as the pipeline of additional TCV candidates progresses.

### ***Safety of TCV***

In its December 2016 review of safety data for typhoid vaccines [97], the GACVS noted that the first Vi conjugated vaccine (US NIH Vi-rEPA) had a safety profile similar to that of the polysaccharide vaccine after evaluation in randomized control trials of >11 000 subjects in Viet Nam. In the available published data on PedaTyph, based on evaluation of safety in approximately 2 200 subjects (including 1 765 subjects in a Phase IV field effectiveness trial), the most frequent adverse events described were local, non-specific reactions and fever. No safety signals were reported.

More detailed data were presented to GACVS for Tybbar-TCV based on evaluation of immunogenicity and safety in approximately 1 000 subjects drawn from pre-licensure and post-licensure studies of the co-administration with measles containing vaccines (MCV), and a comparator study with Typhim Vi (with a total of 470 vaccine recipients in the 2 studies). Post-marketing surveillance data collected in the private sector in India (with more than 3 million doses of the vaccine distributed up to that point in time) were also presented. Overall, GACVS found that the adverse event profile was similar to the specific comparator vaccines in respective age groups for each study, and no safety signals were reported. However, GACVS noted that safety follow-up was largely passive and the data available were limited. Post-marketing surveillance, based on approximately 3 000 reports only received from paediatricians in the private sector in India, showed fever, pain and swelling reported in approximately 1–10% of vaccinees in any age group; no serious adverse events were reported to the manufacturer.

Of note, GACVS concluded that while the safety profile of the licensed Vi-TT vaccines appeared similar to ViPS, there were limitations to the available data. GACVS therefore made recommendations for further safety monitoring of TCV including the need for a stronger post-marketing surveillance; ensuring robust safety evaluation of TCV in planned effectiveness studies, including any potential safety risks in special population groups (e.g. malnourished children, immunocompromised individuals and, where applicable, pregnant women); the use of Brighton Collaboration case definitions and active monitoring of SAEs of interest; and, where feasible, analysis of non-specific effects of vaccination.



The results of the Cochrane systematic review and meta-analysis of serious adverse events associated with TCV are included in Annex C.

## **5. MATHEMATICAL MODELLING OF THE IMPACT OF VACCINATION STRATEGIES ON THE TRANSMISSION OF TYPHOID**

Researchers from Yale established a model describing the transmission dynamics of typhoid fever to evaluate the following vaccination strategies: a one-time campaign in 6 to 15-year old school children, routine vaccination at 6 years of age and routine vaccination at 6 years plus a catch-up campaign at 6–15 years [113]. Typhoid vaccination was incorporated into the model with the following assumptions: Ty21a VE 48%, with waning immunity comparable to that from natural infection, TCV VE 95% during 1st year, ViPS VE 68% during 1st year, duration of immunity of 19 years for TCV (with wide CI) and 3 years for ViPS vaccine. The dynamic model assumes loss of immunity to subclinical infection, differences in the risk of clinical disease for primary versus subsequent infection, a chronic carrier state, and a balance between a short cycle transmission and a long cycle transmission. The model provided a good fit to typhoid fever data from Vellore, India (2000-2011, derived from passive surveillance) and captures well both the level and age distribution of disease.

A one-time campaign is predicted to decrease the incidence of typhoid fever immediately, with a decrease greater than expected due to the direct effect of the vaccine alone. After a period of 5 to 10 years, the incidence of typhoid fever rebounds to the pre-campaign levels for the ViPS vaccine, with a slightly slower rebound for Ty21a and TCV. The model shows that routine vaccination would lead to a more gradual but sustained decline in typhoid fever incidence for the Ty21a and TCV vaccines, but a slight rebound in incidence is still predicted for ViPS. Routine vaccination with catch-up would lead to both an immediate and sustained decline in incidence with the Ty21a and TCV vaccines, but incidence would return to near pre-vaccination levels with the ViPS vaccine after a period of 10-15 years, even with routine vaccination continuing. In settings where incidence peaks in older age groups, the model shows that vaccination of school-aged children would be adequate, while in settings with an early peak in age distribution vaccination should start early.

Uncertainties in the model included prevalence and relative infectiousness of asymptomatic carriers, the rate of waning immunity to clinical disease, the reporting fraction of clinical cases, the importance of short cycle versus long cycle transmission, implications of AMR emergence for typhoid fever dynamics, and the strength, duration and nature of vaccine-induced immunity.

A model comparison exercise, involving four modelling groups, was recently initiated (under the TyVAC) and will help to address some of the current model uncertainties. It is expected that this model comparison will lead to guidance to country policy makers preparing for decisions on potential vaccination programs on an appropriate model to address questions in their specific settings.

## **6. COST-EFFECTIVENESS ANALYSIS OF TYPHOID CONJUGATE VACCINES**

Researchers from Yale have conducted a cost-effectiveness analysis (CEA) comparing routine vaccination at 9 months of age to routine vaccination at 9 months with catch-up vaccination scenarios targeting individuals up to 5 years, 15 years, 25 years and for all ages [68]. This model was applied to different urban and rural settings with varying incidence, cost of illness, cost of vaccine delivery and found that routine vaccination is preferred over no vaccination at willingness-to-pay (WTP) thresholds per DALY of  $\geq 1$  I\$/DALY in Delhi, India and Dong Thap, Viet Nam;  $\geq 5000$  I\$/DALY (less than the GDP per capita) in Kolkata, India;  $\geq 3000$  I\$/DALY in Kibera, Kenya (slightly less than the GDP per capita), and  $> 8000$  I\$/DALY in Lwak; Kenya. However routine vaccination alone was not the preferred strategy in any setting. The model was influenced by the number of doses required in children, and the probability of inpatient or outpatient treatment. However, the difference between settings was found to exert a major influence, due to differences in incidence, cost of illness, and cost of the vaccine. The researchers conclude that at a price of USD 2 or less per dose, routine vaccination with TCV is likely to be cost-effective in high incidence settings and in most medium incidence settings depending on the willingness to pay. Catch-up campaigns would be economically justified particularly in high incidence settings and at higher willingness-to-pay thresholds. Further details of this CEA model are available in the published paper provided on the SAGE website [68]. Further work is ongoing to develop CEAs for Gavi-eligible countries using vaccine prices between USD 2.5 and USD 5 per dose.

Another group of researchers in Stanford University, using a dynamic transmission model, showed that routine immunization of infants through EPI would be cost-effective in moderate incidence settings at a price of USD 2 per dose. In higher incidence settings ( $> 110/100,000$  person years) routine vaccination plus school-based catch-up campaigns would be required [114].

## 7. KEY WORKING GROUP CONCLUSIONS

### 7.1 Assessment of the potential benefits of the new generation typhoid conjugate vaccine

#### ***Typbar-TCV***

Overall (across all ages) there is moderate-certainty evidence from clinical trials that Typbar-TCV results in improved GMTs and seroconversion rates compared to ViPS vaccine. Among subjects 2-45 years of age, Typbar-TCV elicits significantly higher titres of IgG Vi antibody at 6 weeks after a primary immunization and 6 weeks after a second immunization than unconjugated Typbar. With respect to the duration of elevated antibody titres at 3 and 5 years after a single immunization, the GMT of anti-Vi and the proportion of individuals with titres >4-fold over their baseline was significantly higher among recipients of the conjugate vaccine. The proportion of subjects with IgG antibody exhibiting an AI >60 was significantly higher in Typbar-TCV recipients compared to Typbar recipients. The anti-Vi IgG GMT attained 42 days after administration of a second dose of Typbar-TCV closely resembled the GMT recorded at 42 days after the initial dose of conjugate vaccine.

Tested for the first time in infants 6-11 months and toddlers 12-23 months of age, Typbar-TCV was not only well tolerated but a single dose was impressively immunogenic eliciting high titres of IgG anti-Vi antibody that endured up to 5 years in a proportion of young children. Responses in infants 6-11 months were as robust as responses in toddlers age 12-23 months.

Additional data on avidity and IgG subclasses provide further confidence in the quality of the antibody response and potential for a strong booster response.

The Oxford human challenge study using Typbar-TCV in a population of immunologically naïve adult volunteers produced an estimate of efficacy of 87.1% (95% CI 47.2-96.9%) based on an endpoint of persistent fever followed by positive blood culture, thus reflective of real life parameters under which a typhoid fever case would be confirmed. The challenge was seen as very stringent by the Working Group, and possibly in excess of that usually observed in the field, as measured by “attack rate”. While the human challenge study is seen as a proof-of-concept study rather than an efficacy trial, the results are similar to those of the non-commercialized Vi-rEPA vaccine from a well-designed efficacy trial. That trial provided strong evidence of long-term protection up to 46 months in children aged 2-5 years (for both anti-Vi IgG and a VE of 89% (95% CI 76, 97) over a follow up period comprised of 27 months of active surveillance and

19 months of passive surveillance, the latter being again closer to real-life conditions. Efficacy for the separate periods of follow up was estimated at 92% and 82% respectively.

### ***PedaTyph***

The quality of evidence for this vaccine was assessed as very low due to apparent methodological weaknesses in the trials and lack of additional data for in-depth review. While the Working Group recognises this is the only trial for which effectiveness data were reported for younger children, there are significant questions concerning the study design.

No conclusions can therefore be made about the potential use of this vaccine, unless further data are obtained for review to inform policy decisions.

In summary, the assessment of the quality of evidence for TXCV concluded that efficacy data are limited. However, the Vi-TT (Typbar-TCV) data from the Oxford human challenge study are compelling as is the evidence generated earlier with a Vi-rEPA vaccine in a high incidence setting in Viet Nam. A formal bridging of the data generated with the two licensed TCVs to immunogenicity data in the original Vi-rEPA trials in Viet Nam was not possible due to changes in assay standards established for the latter, which are impossible to reconcile because of the loss of the original serum samples.

There is moderate quality evidence on the effectiveness of TCV in persons >2 years of age in comparison to ViPS. There are no comparative data for any TCV versus Ty21a vaccine.

Additional data to be generated from planned field studies of effectiveness, including, (i) evaluation of a Typbar-TCV introduction programme in Navi Mumbai, India and (ii) studies in Africa and Asia by the Typhoid Vaccine Acceleration Consortium (TyVAC) [115] will likely change this assessment. These data are not expected to be available in the next 2-3 years. Experience with other conjugate vaccines points to a reasonable expectation of higher levels of clinical protection than the currently recommended ViPS and Ty21a vaccines.

## **7.2 Assessment of potential harms of typhoid vaccines**

Taking into consideration the GACVS review of overall safety data for licensed typhoid vaccines with no signal of serious safety events, the human challenge study data on SAEs following Typbar-TCV and ViPS vaccine, and the GRADing of evidence on SAEs, the Working Group concluded that based on a limited amount of data, no safety concern has been identified for the licensed typhoid vaccines.

The Working Group took note that there is no evidence of a potential risk of hypo-responsiveness occurring with ViPS, although it has been reported for other polysaccharide vaccines.

Theoretically, a lower force of infection after vaccination could potentially lead to a shift of disease to older age groups and constitute a negative effect of vaccination if older individuals were more likely to become chronic carriers. There have been suggestions in the literature that older individuals previously not exposed may be more likely to develop severe disease, however this evidence is not considered robust.

In summary, the Working Group considered the evidence for safety of TCV as acceptable, taking into account all available evidence including the lack of safety signals from the TCV trials and the good safety profiles of the ViPS and Vi-rEPA vaccines. Nonetheless, the Working Group reiterates the GACVS recommendations for further safety evaluation.

## **7.3 Duration of protection**

Available evidence on Typbar-TCV suggests protection may persist for 5 years or more after primary immunization, and there is some indication from the available data that natural boosting may occur with the Typbar-TCV. Following a single dose of Vi-rEPA, antibody persistence of up to 8 years in 2-5 year old children was observed. Serological data on PedaTyph are limited to 1 year follow up of subjects from a trial with a non-rigorous design. Evidence on the duration of protection from the Oxford human challenge study is limited to 1 month follow up in naïve adult volunteers.

## **7.4 Need for booster doses**

The currently available data suggest no indication of a need for booster doses for children or adults residing in typhoid-endemic areas. However, the data indicate that the immune response is boostable through repeated vaccination, and possibly through natural exposure.

Data from the Vi-rEPA trial in infants (with doses given at 2, 4 and 6 months plus a “booster” dose 6 months later) were considered by the Working Group as weak immunological evidence of boosting. Further, there

are differences with each conjugate vaccine, and infants will respond differently from older children and adults.

## 7.5 Balance of benefits and harms

There are potential benefits of vaccination in view of the current AMR challenges which could change the dynamics of typhoid fever epidemiology and treatment. In this scenario, the potential for vaccination to reduce mortality and morbidity would be increased by reducing the typhoid fever AMR burden.

Mathematical modelling of the impact of vaccination on transmission predicts that a one-time campaign (modelled in 6-15 year old school children) could decrease the incidence of typhoid fever immediately, with a decrease greater than expected due to the direct effect of the vaccine alone, while routine vaccination would lead to a more gradual but sustained decline in incidence.

There is no evidence currently to suggest potential geographic or age shifts for typhoid fever infection after vaccination. The suggestion that older individuals who contract typhoid fever are at risk for increased severity of disease, or increased development of the carrier state, needs to be further explored.

## 7.6 Programmatic considerations for vaccination

### *Typhoid vaccine product characteristics*

**Vi polysaccharide vaccine** is licensed for individuals aged  $\geq 2$  years to be administered subcutaneously or intramuscularly as a single dose; the target value for each single human dose is about 25 $\mu$ g of Vi antigen. It is stable for 6 months at 37 °C, and for 2 years at 22 °C. The recommended storage temperature is 2–8 °C. The WHO prequalified ViPS, Typhim Vi produced by Sanofi Pasteur, is marketed in a multi-dose vial (20 doses liquid formulation comprising 25  $\mu$ g of Vi antigen with  $\leq 1.250$  mg phenol as preservative per 0.5 ml dose) with vaccine vial monitor (VVM) type 30 and estimated cold chain volume per dose of 1.58. As such it is noted as being prone to wastage and more suitable for campaign settings ([http://www.who.int/immunization\\_standards/vaccine\\_quality/pq\\_238\\_typhoid\\_20dose\\_sanofi\\_pasteur/en/](http://www.who.int/immunization_standards/vaccine_quality/pq_238_typhoid_20dose_sanofi_pasteur/en/)).

**Ty21a vaccine** is licensed for use in individuals aged  $\geq 5$  years of age. It is currently available in a formulation consisting of enteric coated capsules for oral administration every other day in a 3-dose regimen (4-dose regimen in Canada and the US). Ty21a requires storage at 2-8 °C and retains potency for approximately 14 days at 25 °C.

**Typbar-TCV** is licensed for intramuscular administration of a single dose in pre-school and school-age children and adults aged  $\geq 6$  months to  $\leq 45$  years of age. It is marketed as a single dose (0.5 ml) vial or pre-filled syringe and as multi-dose (2.5 ml) vials. Typbar-TCV consists of 25 $\mu$ g of Vi polysaccharide per 0.5 ml dose, and in its multi-dose presentation each 0.5 ml dose contains 5mg of 2-Phenoxyethanol. The manufacturer-recommended storage temperature is 2-8°C.

### ***Vaccination of children <2 years of age***

The evidence from unpublished data on typhoid fever occurrence in children <2 years of age provides strong considerations for implementation of TCV vaccination in that age group. In general, the available data confirm that in high incidence settings, typhoid fever with severity sufficient for an outpatient visit or hospital admission is common in the 0-4 years age group with a large proportion of disease occurring between 6 months and 2 years of age. About 10% of disease is considered to occur in children below 1 year of age.

Recommendations for one dose of TCV at 9 months of age with MCV1, or at 15-18 months of age with MCV2, are both valid, recognizing that in many places the appreciable burden of typhoid disease starts to appear at 12 months of age. The Working Group took note, however, that at both time points several other vaccines are already scheduled. A potential preference for TCV to be given in the first year of life should be considered.

TCV use in children <2 years of age should include requirements for robust post-licensure surveillance of effectiveness and safety.

Data on co-administration of TCV with measles-containing vaccines (measles and MMR) show no evidence of interference with the immune response to measles vaccine. At the time of report writing, the results of analysis on the immune response to mumps and rubella components of the MMR are not yet available.

### ***Typhoid vaccine use in outbreaks***

Previous evidence of the impact of Vi vaccination in controlling typhoid fever outbreaks (for example in China and Tajikistan) formed the basis for the current WHO recommendation on vaccine use for the control of outbreaks [69]. There is little additional documented experience on the use of vaccines for typhoid fever outbreak control or in humanitarian emergencies. Further, the impact of vaccination in the context of other control interventions such as improved water and sanitation services has not been studied systematically. In Fiji, a mass typhoid vaccination campaign using ViPS vaccine was conducted in cyclone-affected and

high-risk areas in 2010; >64,000 ViPS doses were administered covering 7% of the total Fiji population and approximately 10,000 doses were used to respond to a concurrent outbreak [38]. Annual typhoid fever incidence was reported to have decreased during the post-campaign year (2011) relative to preceding years (2008–2009) in three subdivisions where a large proportion of the population was vaccinated while the incidence increased or remained unchanged in 12 subdivisions where little to no vaccination occurred.

## **7.7 Delivery strategies**

The currently available data from modelling indicate that routine immunization with TCV would lead to a gradual but sustained decrease in typhoid fever cases while routine vaccination with catch-up would lead to both an immediate and sustained decline in incidence. Further, cost-effectiveness analysis has shown that at a price of up to USD 2 per dose, routine vaccination with TCV is likely to be cost-effective in high incidence settings and in most medium incidence settings depending on the willingness to pay. Catch-up campaigns would be economically justified (preferred) in high incidence settings and at higher willingness to pay thresholds. In the short-term to medium-term the indication for, and feasibility of, specific delivery strategies – for routine and catch up vaccination - will need to be carefully weighed by national authorities in each country.

Currently, no reliable risk prediction tools are available to support implementation of typhoid vaccination programmes using a risk-based approach. However, efforts are under way to develop risk prediction models. Further support to accelerate the development of such tools is highly warranted. For typhoid fever endemic countries considering a risk-based approach, it should be noted that identification of high-risk groups is likely to be more feasible for most countries at the first sub-national level while implementation of a high-risk approach at the district (or similar) level is likely to be challenging for most countries. Equity issues and integration of vaccination with other typhoid fever control interventions will also need to be considered.

In summary, where reliable data are available to assess the level of typhoid fever incidence with confidence, the vaccine delivery strategy should take into account the local epidemiological and programmatic considerations. In particular, in countries with reliable epidemiological evidence of high incidence in well-defined sub-populations, a vaccination strategy based on risk assessment (high incidence population groups) should be considered. This may be particularly important for large countries where resources are limited.



In countries with substantial typhoid fever burden but where surveillance does not allow characterisation of typhoid fever incidence among sub-populations, a universal (country-wide) strategy should be considered, and may prove more feasible and cost-effective.

### ***Catch-up vaccination***

There is a potential case for catch-up vaccination at the time of introduction of the vaccine. With a high incidence in preschool and school aged children, routine introduction plus catch-up could possibly achieve an immediate impact and an indirect herd effect.

There is weak overall evidence currently of the additional benefits and impact on disease from catch-up vaccination beyond the obvious “the more immune individuals the better”. An indirect effect of TCV use has not yet been studied and it has been suggested that this effect might be outweighed by transmission via chronic carriers. However, available modelling data should be used to estimate the potential effect of catch-up vaccination. Ongoing work by Pitzer et al [68] extending the Yale model for the analysis of 54 Gavi-eligible countries will be valuable. Options to be evaluated include routine vaccination plus country-wide catch-up vaccination or routine vaccination plus catch-up vaccination in targeted (high-risk) areas.

In addition to the overall considerations for a delivery strategy (as discussed above), decisions on catch up vaccination will need to take into account vaccine supply, expected impact (e.g., reduction of incidence in a shorter time period with a possible indirect effect), cost (usually much higher than routine), and other operational issues, including transport, cold chain, and logistics. Further research is recommended to obtain empirical data to support decisions at country-level on catch-up vaccination, including target age ranges.

## **8. DRAFT POLICY RECOMMENDATIONS**

### ***Recommendation for individuals 2 years and above***

Given the continued high burden of typhoid fever and the increasing antimicrobial resistance of *S. Typhi*, and in view of the currently available evidence on safety, efficacy, feasibility, and affordability of at least one licensed typhoid conjugate vaccines and of the previously recommended ViPS and Ty21a vaccines, SAGE re-emphasizes the importance of the programmatic use of typhoid vaccines for controlling endemic disease.

Specifically, countries should consider the routine use of typhoid conjugate vaccine or ViPS vaccine or Ty21a vaccine in individuals aged 2 years and above. The evidence reviewed for at least one licensed TCV

(Typbar-TCV) demonstrate that it is likely offering longer and higher protection than ViPS and Ty21a, and supports a recommendation for its public health use. These vaccines should be given irrespective of the intensity of other control strategies.

### ***Recommendation for children below 2 years***

Given the high proportion of typhoid fever that is sufficiently severe to require outpatient or inpatient care in children <2 years in many areas, SAGE recommends the use of TCV in children <2 years of age, administered as a single dose at any time between 6 months to 23 months of age in endemic countries. The evidence reviewed for at least one licensed TCV (Typbar-TCV) demonstrate that it is likely offering longer and higher protection than ViPS and Ty21a, and supports a recommendation for its public health use. The decision on the age of TCV administration should be based on the local epidemiology of typhoid fever, geographic heterogeneity, and taking into account programmatic considerations of the routine childhood immunization programme.

There are opportunities to administer one dose of TCV at 9 months of age with MCV1, or at 15-18 months of age with MCV2, recognizing that in many places the appreciable burden of typhoid fever starts to appear at 12 months of age.

### ***Recommendation for vaccine use in outbreaks and humanitarian emergencies***

Given the epidemic potential of typhoid fever, and observations on the effectiveness of vaccination in interrupting outbreaks, typhoid fever vaccination is recommended for outbreak control. Typhoid vaccines may be considered in humanitarian emergencies depending on the risk assessment in the local setting. However, it should be emphasized that the mainstay of typhoid fever prevention in such settings is often the provision of clean water and chlorination of water supplies, along with promotion of hygiene measures. The WHO has published guidance for the risk assessment of typhoid and other vaccine-preventable diseases in humanitarian settings as a framework for decision making on the use of vaccines in those settings [116].

### ***Recommendations for special groups***

SAGE recommends vaccination of the following specific groups of epidemiological relevance, by virtue of being at high risk or important for transmission, in line with the above age-appropriate recommendations. When ViPS or Ty21a is used, SAGE emphasizes the current recommendations for revaccination.

- **Clinical microbiology laboratory staff** with a recognized risk of occupational exposure to *S. Typhi*.

- **Professional food handlers:** where possible, preference for use of a Vi negative vaccine, such as Ty21a should be considered in order to protect the possibility for serological identification of a chronic carrier status among vaccinated persons. However, professional food handlers should not go unvaccinated due to lack of Ty21a vaccine. The value of not vaccinating this group (where Ty21a is not available) needs to be carefully weighed within the existing national policies.
- **Travellers from non-endemic to endemic areas:** Typhoid vaccination may be offered to travellers to destinations where the risk of typhoid fever is high. Where available, licensed combination Typhoid-Hepatitis A vaccines may be used for travellers.

### General recommendations

- All typhoid vaccination programmes should be implemented in the context of other efforts to control the disease, including health education, water quality and sanitation improvements, and training of health professionals in diagnosis and treatment.
- Ideally, cost-effectiveness analyses should be part of the decision-making and planning process to initiate programmatic use of typhoid vaccines.
- SAGE recommends post-licensure monitoring of effectiveness of TCV (including serological and clinical endpoints) and robust monitoring of safety in line with the GACVS recommendations.
- SAGE recommends that countries monitor the occurrence of AMR strains of *S. Typhi* in endemic and epidemic disease and contribute to the global database on antimicrobial resistance.

## 9. TYPHOID CONJUGATE VACCINES UNDER DEVELOPMENT

A number of additional TCV candidates are currently in varying stages of clinical development as summarized in Table 2 based on the information available at time of writing this report. A review of these candidates was outside the terms of reference of this Working Group.

Table 2

Developer/Manufacturer	Type of TCV (carrier protein)	Target age and/or schedule (if known)	Clinical development stage	Licensure timeline	Plan to apply for PQ
Lanzhou Institute of Biological Products (China) <sup>1,3</sup>	Vi-rEPA		Phase III randomized double-blind controlled study (subjects 2-55 years) conducted in	Submitted to DCG(I) (China NRA) for marketing authorization for initial licensure in $\geq 2$ years	Not confirmed

			China		
Zydus Cadila (India) <sup>1,3</sup>	Vi-TT	Single dose 25ug Vi; ≥ 6 months of age	Phase III non-inferiority trial with Typbar-TCV™ completed in India	Submitted to DCG(I) (India NRA) for marketing authorization	Not confirmed
Biological E (India) <sup>1,2</sup>	Vi-CRM <sub>197</sub>	Single dose 25ug Vi; ≥ 6 months of age	Phase I (Q2 2017)	Target NRA licensure 2018	Yes
Eubiologics (Republic of Korea) <sup>1,3</sup>	Vi-CRM197	Children < 2 years of age, and adults	Preclinical/Phase I		Not confirmed
Incepta (Bangladesh) <sup>1,3</sup>	Vi-DT	Children < 2 years of age, and adults	Preclinical		Yes
PT Biofarma (Indonesia) <sup>1,3</sup>	Vi-DT	Children < 2 years of age, and adults	Phase I trial (Q2 2017)		Yes
SK Chemicals (Republic of Korea) <sup>1,3</sup>	Vi-DT	Children < 2 years of age, and adults	Phase II (dose scheduling in children <2 years) planned to start in Q4 2017		Yes
DAVAC (Viet Nam) and Finlay Institute (Cuba) <sup>1,3</sup>	Vi-DT		Preclinical		Not confirmed
Walvax (China) <sup>1,3</sup>	Vi-TT		Preclinical		Not confirmed
<p>Vi-CRM197: Vi polysaccharide derived from <i>Citrobacter freundii</i> sensu lato (i.e., derived from a member of the <i>C. freundii</i> complex but not <i>C. freundii</i>) conjugated to cross-reactive material 197, a nontoxic mutated form of diphtheria toxin.</p> <p>Vi-DT: Vi polysaccharide derived from <i>S. Typhi</i> conjugated to diphtheria toxoid</p> <p>Vi-rEPA: Vi polysaccharide derived from <i>S. Typhi</i> conjugated to recombinant exoprotein A of <i>Pseudomonas aeruginosa</i></p> <p>Vi polysaccharide derived from <i>S. Typhi</i> conjugated to tetanus toxoid</p> <p>Sources: <sup>(1)</sup>Manufacturer information provided to WHO; <sup>(2)</sup>Goel A. Progress in the development of a Vi-CRM197 conjugate vaccine. 10th International Conference on Typhoid and other Invasive Salmonellosis. April 4-6, 2017. Kampala, Uganda; <sup>(3)</sup>Sahastrabudhe S. Overview of typhoid conjugate vaccine pipeline: current status and future plans. 10th International Conference on Typhoid and other Invasive Salmonellosis. April 4-6, 2017. Kampala, Uganda</p>					

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### Annex A: Summary of clinical trials of Ty21a and ViPS vaccines

Table A1. Efficacy results of randomized controlled clinical trials of Vi polysaccharide vaccine							
Study (Year)	Formulation	No. of study participants	Ages (Years)	Control vaccine	Follow-up period	Protective efficacy for blood culture confirmed typhoid fever (95% CIs)	Typhoid fever incidence rate in control group (per 100,000)
Kathmandu Valley, Nepal (1986-1988)	1 dose of Vi (25 µg)	6,907	5-44	Pneumococcal polysaccharide	17 months	72% (42-86%)	926
E. Transvaal, South Africa (1985-1988)	1 dose of Vi (25 µg)	11,384	6-14	Meningococcal A/C polysaccharide	21 months	64% (36-79%)	773
Quan County, Guangxi Province, China (1995-1997)*	1 dose of locally-produced Vi (30 µg)	131,271	3-50 (92% school-age)	Saline placebo	36 months	55%	
					19 months	69% (28-87%) (72% in school children)	63-78

Sources: Levine 1999; Ivanoff et al, 1994; Simanjuntak, 1991; Hessel et al, 1999; Klugman et al. 1987; Acharya et al, 1987; Yang et.al., 2001; Acosta et. al., 2005

\*Note: An earlier efficacy study of Vi in China (1994-95) was a double-blinded, randomized, saline placebo control study among 81,000 5-55 year olds in Boaying County in Jiangsu Province. The efficacy at 12 months was 71% (95% CI 33-88%) (published in Chinese: Wang ZG, Zhou WZ, Shi J. Efficacy and side effects following immunization with Salmonella typhi Vi capsular polysaccharide vaccine. Zhonghua Liu Xing Bing Xue Za Zhi 1997;18(1):26-9.).

Table A2. Post licensure cluster-randomized effectiveness trials of Vi polysaccharide vaccine in children 2-16 years – Kolkata, India <sup>1</sup> and Karachi, Pakistan <sup>2</sup>			
	VIPS	Hepatitis A	Adjusted vaccine efficacy (95% CI)
<b>Kolkata</b>			
# of subjects (2-4 years)	1097	1995	
Typhoid fever cases	5	27	80% (53, 91)
Incidence/10 <sup>5</sup> person days	0.64	3.54	
# of subjects (5-14 years)	4282	4584	
Typhoid fever cases	21	54	56% (18, 77)
Incidence/10 <sup>5</sup> person days	0.69	1.67	
<b>Karachi</b>			
# of subjects (2-4 years)	3154	3324	
Typhoid fever cases	16	13	-38% (-192, 35)
Incidence/10 <sup>3</sup> persons	3.0	2.3	
# of subjects (5-16 years)	10,084	10,669	57% (6, 81)
Typhoid fever cases	14	36	
Incidence/10 <sup>3</sup> persons	0.8	1.9	

<sup>1</sup>Sur et al. NEJM 2009;

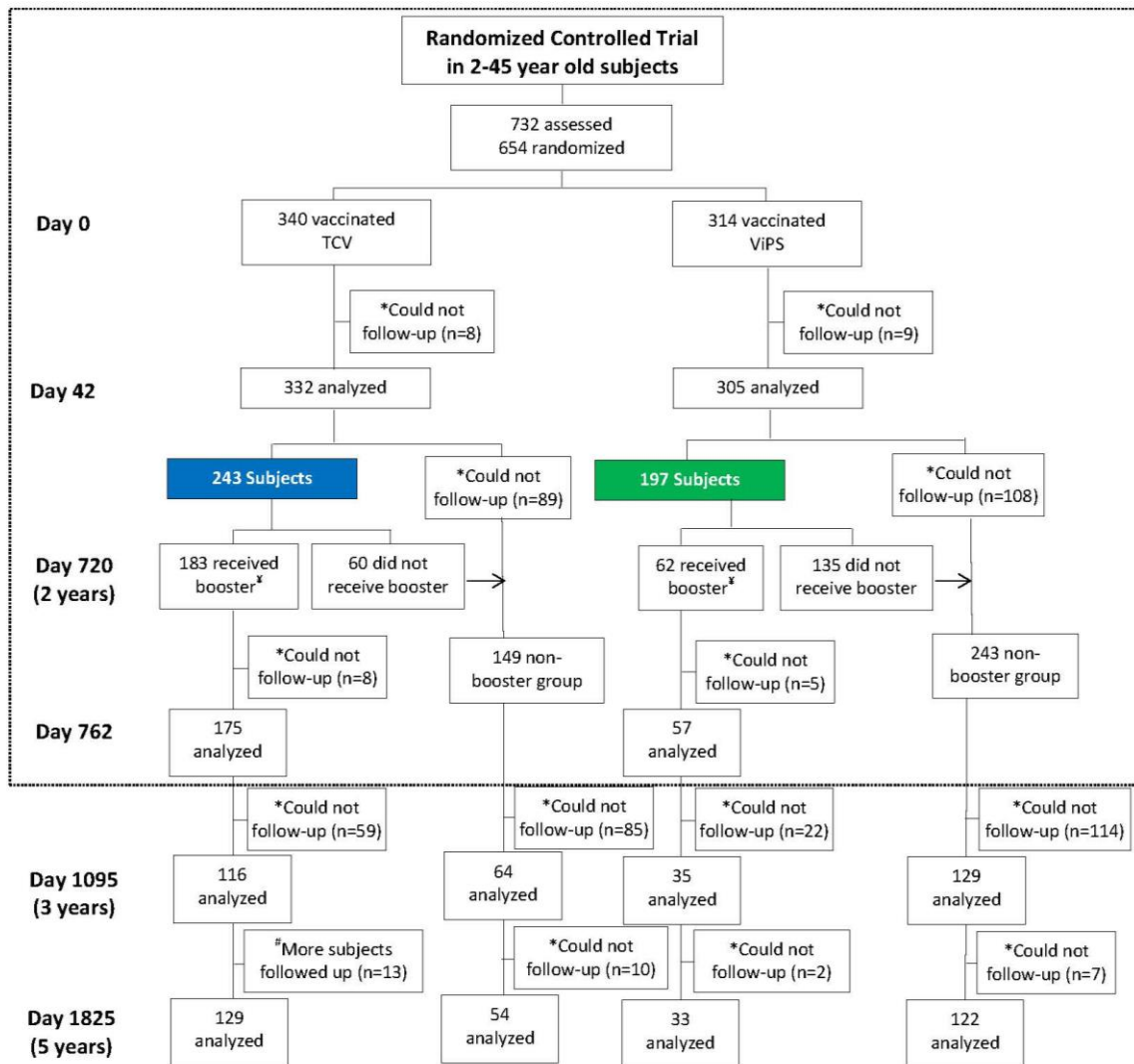
<sup>2</sup>Mi Khan et al. Vaccine 2012

Table A3. Results of randomized controlled clinical trials of Ty21a							
Study (Year)	Formulation	No. of study participants	Ages (Years)	Control vaccine	Follow-up period	Protective efficacy for blood culture confirmed typhoid fever (95% CIs)	Typhoid incidence rate in control group (per 100,000)
Alexandria, Egypt (1978-80)	Liquid given with tablet of NaHCO <sub>3</sub> *	32,388	6-7	Placebo	36 months	96% (77-99%)	50
Area Occidente, Santiago, Chile (1983-86)	3 doses of enteric-coated capsules given (1-2 days between doses)	140,000	6-19	Placebo (plus 4 vaccine groups that varied in formulation and time interval between doses)	36 months	67% (47-79%)	110
	7 years				62%		
Area Sur Oriente, Santiago, Chile (1986)	3 doses of enteric-coated capsules (1-2 days between doses)	81,321	6-19	Placebo	3 years	33% (0-57%)	100
	3 doses liquid suspension (1-2 days between doses)				3 years	77%	
					5 years	78%	
Sumatra, Indonesia (1986-1989)	3 doses of enteric-coated capsules (7 days between doses)	20,543	3-44	Placebo	30 months	42% (23-57%)	810
	3 doses liquid suspension (7 days between doses)					53% (36-66%)	

\* This formulation was not commercialized.

## Annex B: Flowcharts of clinical trials of Tybbar-TCV

B1: CONSORT diagram of Phase 3 Randomized Controlled Trial - Safety and immunogenicity of Tybbar-TCV versus Tybbar vaccine in children and adults aged 2-45 years of age



\* Could not follow-up: Subjects could not be reached for follow-up visits.

# Additional subjects reached for follow up as compared to day 1095 (3 years).

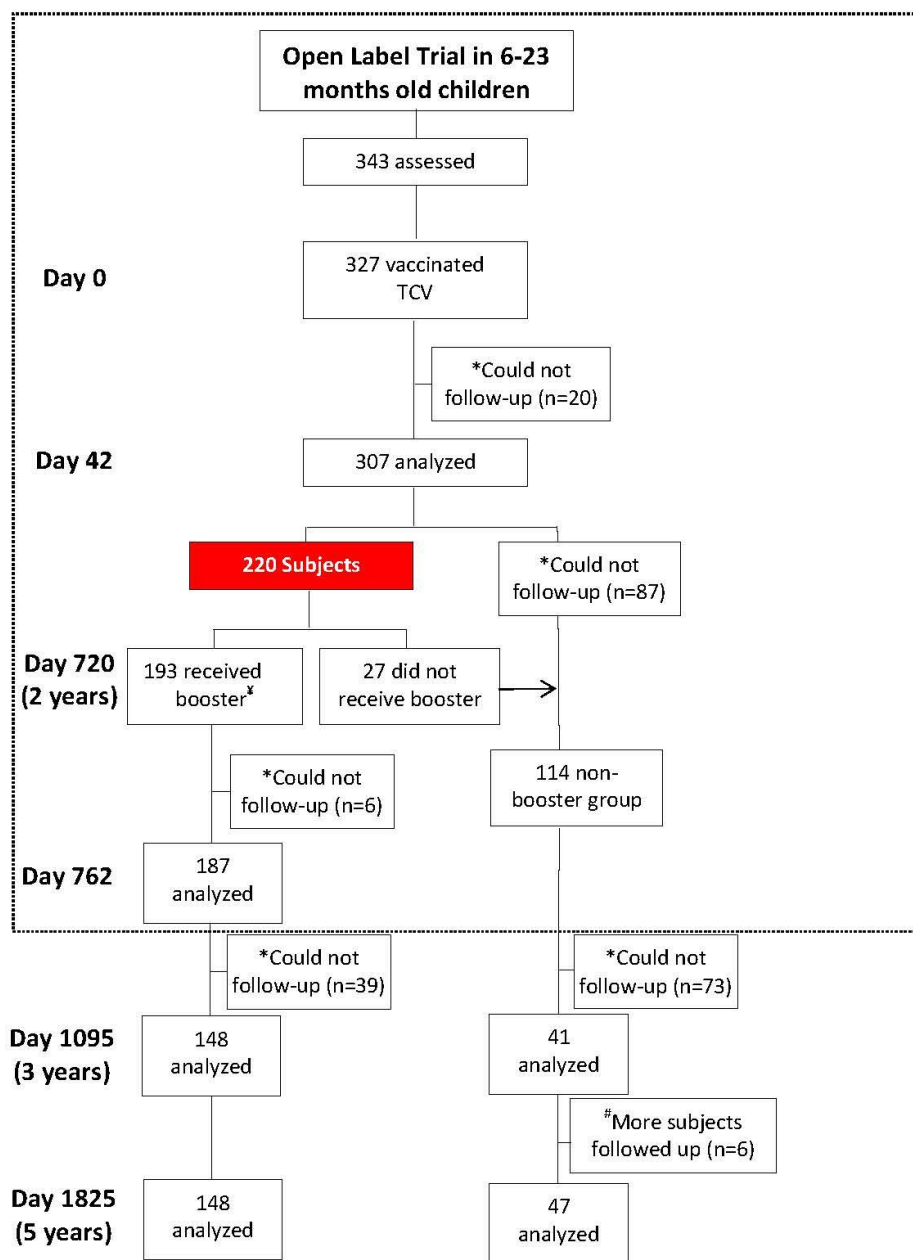
‡ Booster dose: Subjects received a second dose of the same vaccine that they received on day 0.

■ 243 subjects “could be reached” for the scheduled visit at day 720. 183 subjects received a booster (Day 720) and had samples analyzed as the **booster group** (at subsequent time points). Remaining 60 subjects, together with 89 subjects not followed up, did not receive a booster and were analyzed as the **non-booster group** (at Days 1095 and 1825 only).

■ 197 subjects “could be reached” for the scheduled visit at day 720. 62 subjects received a booster (Day 720) and had samples analyzed as the **booster group** (at subsequent time points). Remaining 135 subjects, together with 108 subjects not followed up, did not receive a booster and were analyzed as the **non-booster group** (at Days 1095 and 1825 only).

Source: Bharat Biotech International Limited

B2: Flowchart of Phase 3 Open Label Trial - Safety and immunogenicity of Typbar-TCV versus Typbar vaccine in infants aged 6-23 months



\* Could not follow-up: Subjects could not be reached for follow-up visits.

# Additional subjects reached for follow up as compared to day 1095 (3 years).

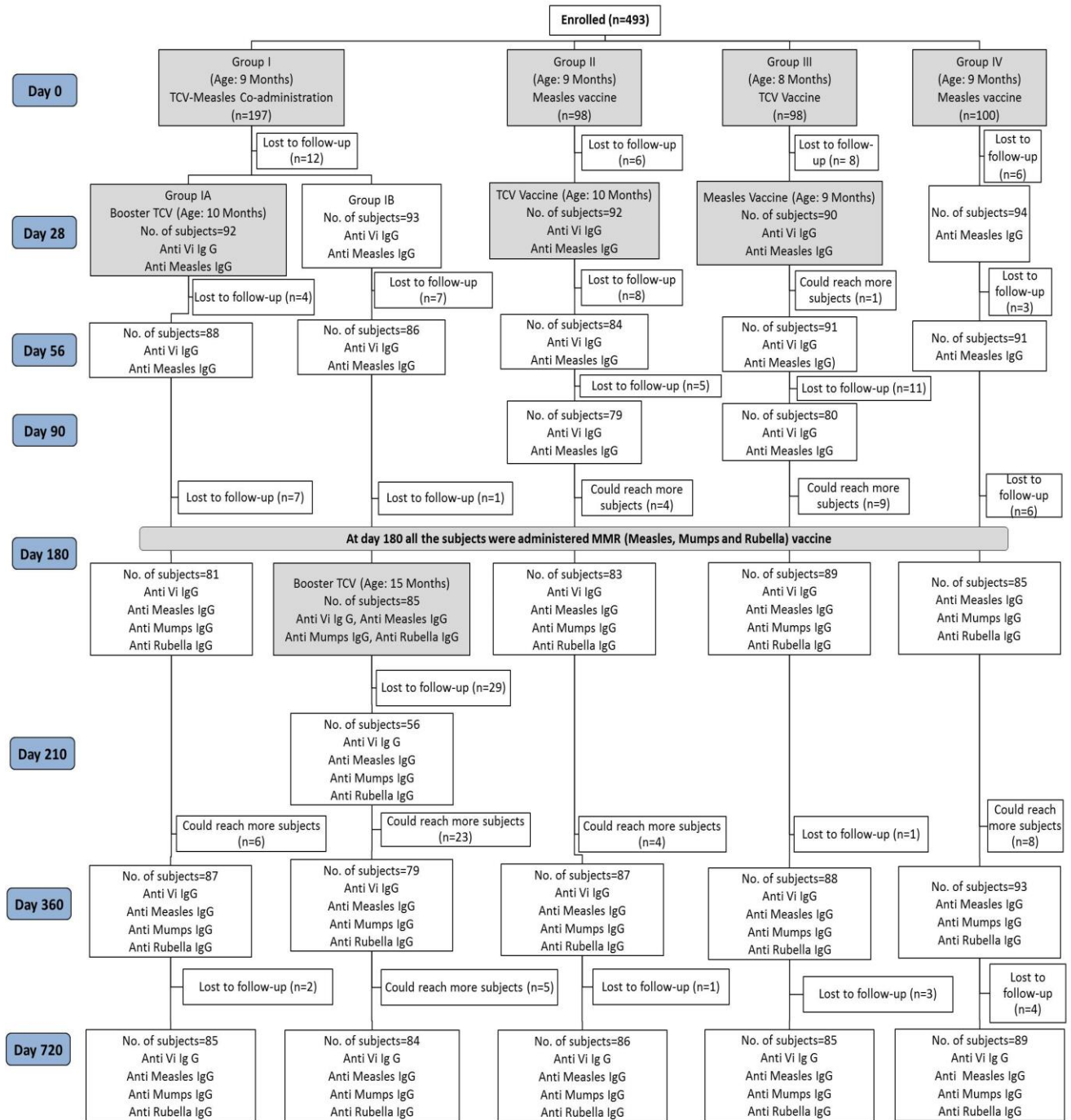
‡ Booster dose: Subjects received a second dose of the same vaccine that they received on day 0.

■ 220 subjects “could be reached” for the scheduled visit at day 720. 193 subjects received a booster (Day 720) and had samples analyzed as the **booster group** (at subsequent time points). Remaining 27 subjects, together with 87 subjects not followed up, did not receive a booster and were analyzed as the **non-booster group** (at Days 1095 and 1825 only).

Source: Bharat Biotech International Limited

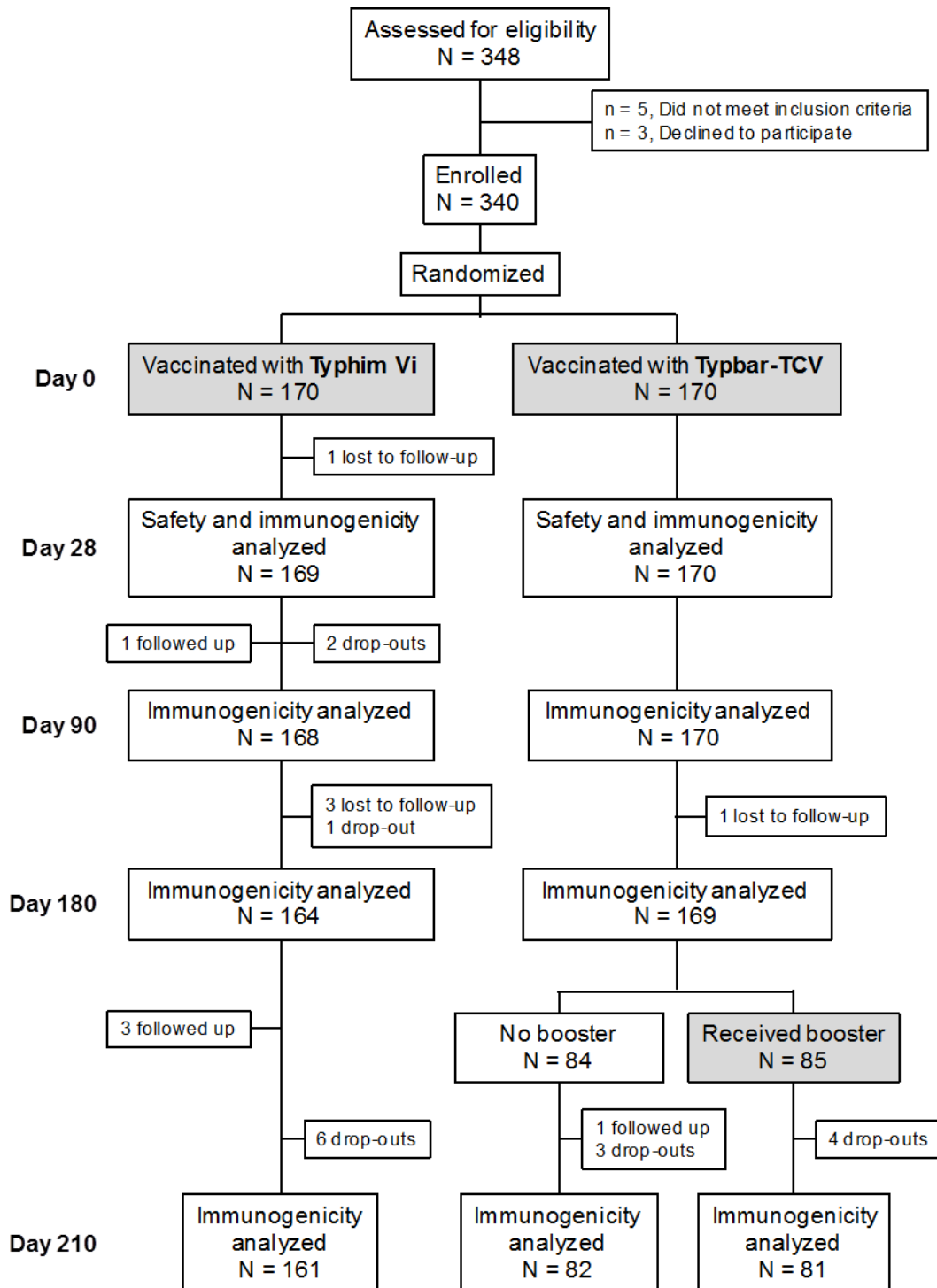


B3: CONSORT diagram of co-administration of measles vaccine with Typbar-TCV at ~9 months of age versus either vaccine alone and of Typbar-TCV co-administered with measles-mumps-rubella vaccine at 15 months of age



Source: Bharat Biotech International Limited

B4: CONSORT diagram of randomized controlled trial of the reactogenicity and immunogenicity of Typbar-TCV versus Sanofi Pasteur ViPS (Typhim Vi™) in subjects 2-15 years of age



Source: Bharat Biotech International Limited

## Annex C: GRADE tables

### C2: Systematic review and meta-analysis of immunogenicity, efficacy and safety data of Vi-TT typhoid conjugate vaccines

Source: Cochrane Response and Cochrane Infectious Diseases Group

#### Summary of Findings 1.2: Vi-TT typhoid conjugate vaccines (2 doses) versus placebo, no intervention or control vaccine in children and adults<sup>1,1</sup>

Patients: 6 month to 12-year old children; 18-60 year old adults (efficacy and immunogenicity)

Setting: India, UK (efficacy), Vietnam, UK (immunogenicity)

Comparison: Vi-TT typhoid conjugate vaccine (Peda Typh™, 2 doses (6 week interval) or Typbar-TCV®, 1 dose) versus placebo, no intervention (normal vaccination course) or control vaccine (MENVEO®, 1 dose)

Outcome	Plain language summary	Vaccine type and doses	Absolute effect		Relative effect (95% CI) No of participants & studies	Certainty of the evidence (GRADE)
			Control	Vi-TT		
<b>Incidence of typhoid fever</b> in adults follow-up: <1 month	We do not know about the effects of 1 dose Typbar-TCV on incidence of typhoid fever compared with placebo at <1 month follow-up; evidence was of very low certainty.	Typbar-TCV 1 dose	419 per 1000	54.5 per 1000 (13 to 222)	RR 0.13 (0.03 to 0.53) 68 participants in 1 RCT	⊕○○○ VERY LOW <sup>2,3</sup> due to serious indirectness and imprecision
<b>Incidence of typhoid fever</b> in children follow-up: Year 1	We do not know about the effects of 2 doses PedaTyph on incidence of typhoid fever compared with normal course of vaccination; evidence was of very low certainty.	Peda Typh 2 doses	13 per 1000	0.8 per 1000 (0 to 13)	RR 0.06 (0.00 to 1.01) <sup>1</sup> 1625 participants in 1 cluster RCT	⊕○○○ VERY LOW <sup>3,4,5</sup> due to imprecision, indirectness, and risk of bias
<b>Ratio of GMTs</b> in adults follow up: <1 month	We do not know about the effects of 1 dose Typbar-TCV on GMTs compared with placebo at <1 month follow-up; evidence was of very low certainty.	Typbar-TCV 1 dose	Mean: 7.8 EU	Mean: 579.7 EU	Ratio 73.91 (43.89 to 124.47) 72 participants in 1 RCT	⊕○○○ VERY LOW <sup>2,3</sup> due to serious indirectness and imprecision
<b>Seroconversion</b> in adults follow up: <1 month	We do not know about the effects of 1 dose Typbar-TCV on seroconversion compared with placebo at <1 month follow-up; evidence was of very low certainty.	Typbar-TCV 1 dose	0/33 (0%)	37/37 (100%)	RR 67.11 (4.28 to 1051.38) 72 participants in 1 RCT	⊕○○○ VERY LOW <sup>2,3</sup> due to serious indirectness and imprecision
<b>SAEs (RCTs)</b> in children follow up: up to 1 month	<u>Evidence from RCTs</u> We do not know about the effect of 2 doses PedaTyph on SAEs compared with no treatment in children; evidence was of very low certainty.	Peda Typh 2 doses	0/860 (no treatment)	0/905	RR not estimable* 1765 participants in 1 RCT	⊕○○○ VERY LOW <sup>4,5,6</sup> due to imprecision, indirectness, and risk of bias
<b>SAEs (RCTs)</b> in adults follow up: up to 1 month	<u>Evidence from RCTs</u> We do not know about the effect of 1 dose Typbar-TCV compared with control vaccine on SAEs in adults; evidence was of very low certainty.	Typbar-TCV 1 dose	0/34 (MENVEO)	1/41 <sup>a</sup>	RR 2.50 (0.11 to 59.46) 75 participants in 1 RCT	⊕○○○ VERY LOW <sup>2,3</sup> due to serious indirectness and imprecision

<p><b>SAEs (NIRCS)</b> in children and adults follow-up: 3 months</p>	<p><b>Evidence from non-randomised comparison:</b> We do not know about the effect of 1 dose Tybpar-TCV on SAEs; evidence was of very low certainty.</p>	<p>Typbar-TCV 1 dose</p>	<p>One SAE was reported among 327 participants in a non-randomised arm of an RCT.<sup>b</sup></p>	<p>⊕⊕⊕⊕ <b>VERY LOW<sup>6,7,8</sup></b> due to non-randomised comparison, imprecision and indirectness</p>
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CI= confidence interval; EU= enzyme-linked immunosorbent assay (ELISA) unit; GMT= Geometric mean titre; NRCS= non-randomised comparative study; MENVEO= Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine; RCT= randomised controlled trial; RR= risk ratio; Vi-TT = typhoid Vi antigen coupled to tetanus toxin carrier protein

\* Effect could not be estimated because no events were reported

<sup>1</sup> Primary trial is not cluster adjusted. This estimate uses a small assumed intra-cluster correlation co-efficient of 0.0015. (Alternatively, assuming a large intra-cluster correlation co-efficient of 0.1 would give RR 0.85, 95% CI 0.04, to 20.08).

<sup>2</sup> Downgraded two levels for serious indirectness: evaluated by only one trial in adults in the UK; human challenge study design uses high levels of bacterial inoculum and controls timing of infection relative to vaccination.

<sup>3</sup> Downgraded one level for imprecision: small sample size.

<sup>4</sup> Downgraded one level for indirectness: evaluated by only one cluster trial in one setting (Kolkata, India) in children under 12 years.

<sup>5</sup> Downgraded one level for risk of bias: unblinded, unadjusted cluster trial with baseline difference between intervention and control groups.

<sup>6</sup> Downgraded one level for imprecision: no events were reported.

<sup>7</sup> Non-randomised comparisons start at moderate level evidence.

<sup>8</sup> Downgraded one level for indirectness: evaluated by only one trial in one setting (India).

<sup>a</sup> One hospitalisation for per-rectum bleeding and altered bowel habit, diagnosed with inflammatory bowel disease. Deemed not related to vaccination - onset of symptoms occurred prior to vaccination.

<sup>b</sup> Lower respiratory tract infection in an 18-month-old girl, resolved upon treatment, assessed by trialists as unrelated to vaccination.

**Forest plots 1.2: Vi-TT typhoid conjugate vaccine versus placebo, no intervention or control vaccine in children and adults**

**Patients:** 6 month to 12-year old children (efficacy); 18-60 year old adults (immunogenicity)  
**Setting:** India (efficacy), Vietnam (immunogenicity)  
**Comparison:** Vi-TT typhoid conjugate vaccine (Peda Typh™, 2 doses (6 week interval) or Typbar-TCV®, 1 dose) versus placebo, no intervention (normal vaccination course) or control vaccine (MENVEO®, 1 dose)

Outcome	Forest plot				Certainty of the evidence (GRADE)		
	Study or Subgroup	Vi-TT Events	Control Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI		
Incidence of typhoid fever with 2 doses PedaTyph in infants and children (0.5 to 12 years) or 1 dose Typbar-TCV in adults follow up: <1 month (Pollard GBR); Year 1 (Mitra 2016 IND)	1.1.1 Typbar-TCV	2	37	13	31	0.13 [0.03, 0.53]	⊕○○○ VERY LOW
	Pollard 2017 GBR*	0	637	9	716	0.06 [0.00, 1.01]	
	1.1.3 PedaTyph	0	637	9	716	0.06 [0.00, 1.01]	
Ratio of GMTs with 1 dose Typbar-TCV in adults follow up: <1 month	Time point	Vaccine: Vi-TT vs. MENVEO		Ratio of GMT (95% CI)		N	⊕○○○ VERY LOW
	Study name	Vi-TT	Control	Vi-TT	Control	Age	
	<1 mth	1	124	1	124	15+ yrs <sup>A</sup>	
Seroconversion with 1 dose Typbar-TCV in adults follow up: <1 month	Time point	Vaccine: Vi-TT vs. MENVEO		MH RR (95% CI)		Events Vi-TT	⊕○○○ VERY LOW
	Study name	Vi-TT	Control	Vi-TT	Control	Events Control	
	<1 mth	1	1050	4	67	37/37	
		Favors Control		Favors Vi-TT			



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SAEs (RCTs)	Vi-TT vs no treatment: only 1 study (Mitra 2016 IND) included for this comparison. Tabulated in Appendix 1.2 (A.1.2.3)	⊕000 VERY LOW
	Vi-TT vs control vaccine: only 1 study (Pollard 2017 GBR) included for this comparison. Tabulated in Appendix 1.2 (A.1.2.4)	
SAEs (NRCS)	Vi-TT: only 1 study (Mohan 2015 IND) included. Tabulated in Appendix 1.2 (A.1.2.5)	⊕000 VERY LOW

A<sub>1</sub> = 18-60 yrs, \*human challenge study, unpublished data

**Summary of Findings 1.4: Vi-TT typhoid conjugate vaccines versus typhoid Vi-polysaccharide vaccine (ViPS) in children and adults**

Patients: 2 to 60-year old children and adults

Setting: India, United Kingdom

Comparison: Vi-TT typhoid conjugate vaccine (Typbar-TCV<sup>®</sup>, 1 dose) versus typhoid ViPS vaccine (Typhim Vi<sup>®</sup> or Typbar<sup>®</sup>, 1 dose)

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) No of participants & studies	Certainty of the evidence (GRADE)
		ViPS	Vi-TT		
<b>Incidence of typhoid fever</b> in adults follow-up: <1 month	We do not know about the effect of 1 dose Typbar-TCV on the incidence of typhoid fever in adults compared with ViPS typhoid vaccine at <1 month follow-up because the certainty of the evidence is very low.	200 per 1000	54 per 1000 (12 to 242)	RR 0.27 (0.06 to 1.21) 72 participants in 1 RCT	⊕○○○ VERY LOW <sup>1,2</sup> due to serious indirectness and imprecision
<b>Ratio of GMTs</b> in adults follow-up: 0-<1 month	We do not know about the effect of 1 dose Typbar-TCV on GMTs in adults compared with ViPS typhoid vaccine at <1 month follow-up because the certainty of the evidence is very low.	Mean: 1440.5 EU	Mean: 579.7 EU	Ratio 4.12 (2.38 to 7.14) 74 participants in 1 RCT	⊕○○○ VERY LOW <sup>1,2</sup> due to serious indirectness and imprecision
<b>Ratio of GMTs</b> in children and adults follow-up: 1-<2 months	There probably is higher GMTs with 1 dose Typbar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine at 1 to <2 months' follow-up in children and adults.	Mean: 411 EU/mL	Mean: 1293 EU/mL	Ratio 3.15 (2.70 to 3.61) 637 participants in 1 RCT	⊕⊕○○ MODERATE <sup>3</sup> due to indirectness
<b>Ratio of GMTs</b> in children and adults follow-up: 1-<2 years	There probably is higher GMTs with 1 dose Typbar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine at 1 to <2 years' follow-up in children and adults.	Mean: 45.8 EU/mL	Mean: 81.7 EU/mL	Ratio 1.78 (1.53 to 2.08) 440 participants in 1 RCT	⊕⊕○○ MODERATE <sup>3</sup> due to indirectness
<b>Seroconversion</b> in adults follow-up: 0-<1 month	We do not know about the effect of 1 dose Typbar-TCV on seroconversion rate in adults compared with ViPS typhoid vaccine at <1 month follow-up because the certainty of the evidence is very low.	886 per 1000	1000 per 1000 (877 to 1000)	RR 1.13 (0.99 to 1.28) 72 participants in 1 RCT	⊕○○○ VERY LOW <sup>1,2</sup> due to serious indirectness and imprecision
<b>Seroconversion</b> in children and adults follow-up: 1-<2 months	There probably is a slightly better seroconversion rate for 1 dose Typbar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine at 1-<2 months follow-up in children and adults.	931 per 1000	968 per 1000 (940 to 1000)	RR 1.04 (1.01 to 1.08) 637 participants in 1 RCT	⊕⊕○○ MODERATE <sup>3</sup> due to indirectness
<b>Seroprotection</b> in children and adults follow-up: 1-<2 years	There probably is a better seroconversion rate for 1 dose Typbar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine at 1-<2 years follow-up in children and adults.	533 per 1000	74.1 per 1000 (6.40 to 865)	RR 1.39 (1.20 to 1.62) 440 participants in 1 RCT	⊕⊕○○ MODERATE <sup>3</sup> due to indirectness

<p><b>SAEs (RCTs)</b> in children and adults follow up: up to 3 months</p>	<p><b>Evidence from RCTs:</b> There probably is little or no difference in SAE rate for 1 dose Typhar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine in children and adults at up to 3 months follow-up.</p>	<p>114 per 10,000<sup>a</sup></p>	<p>4.1 per 10,000 (8 to 207)<sup>b</sup></p>	<p>RR 0.36 (0.07 to 1.82) 732 participants in 2 RCTs</p>	<p>⊕⊕⊕○ <b>MODERATE</b><sup>4</sup> due to imprecision</p>
<p><b>SAEs (NRCS)</b> in children ≥2 years follow up: 2 days</p>	<p><b>Evidence from non-randomised comparative studies:</b> We do not know about the effect of 1 or 2 doses Pedatyph typhoid conjugate vaccine compared with ViPS typhoid vaccine on SAEs; certainty of evidence was very low.</p>	<p>0 / 37</p>	<p>0 / 169</p>	<p>RR not estimable* 206 participants in 1 non-randomised comparative study</p>	<p>⊕○○○ <b>VERY LOW</b><sup>5,6,7</sup> due to no randomisation, indirectness, and imprecision</p>

CI= confidence interval; EU= enzyme-linked immunosorbent assay (ELISA) unit; GMT= Geometric mean titre; NRCS= non-randomised comparative study; RCT= randomised controlled trial; RR= risk ratio; ViPS= typhoid Vi-polysaccharide vaccine; Vi-TT= typhoid Vi antigen coupled to tetanus toxin carrier protein

\* Effect could not be estimated because no events were reported

<sup>1</sup> Downgraded two levels for serious indirectness: evaluated by only one trial in adults in the UK; human challenge study design uses high levels of bacterial inoculum and controls timing of infection relative to vaccination.

<sup>2</sup> Downgraded one level for imprecision: small sample size.

<sup>3</sup> Downgraded one level for indirectness: evaluated by only one trial in 8 sites in India.

<sup>4</sup> Downgraded one level for imprecision: wide 95% CI that include both no effect and benefit for ViPS.

<sup>5</sup> Non-randomised comparative studies start at moderate certainty evidence.

<sup>6</sup> Downgraded one level for indirectness: evaluated by only one trial in 3 sites in India.

<sup>7</sup> Downgraded one level for imprecision: no events were reported.

<sup>a</sup> Four hospitalisations in ViPS groups, none assessed to be related to vaccine: polyarthropathy following typhoid challenge and antibiotic use, requiring ongoing rheumatological input; urinary retention secondary to vaginal ulceration; semi-elective tonsillectomy for investigation of tonsillar lesion; febrile convulsions in a 3-year-old, resolved.

<sup>b</sup> One hospitalisation in Vi-TT group: per-rectum bleeding and altered bowel habit, diagnosed with inflammatory bowel disease. Not related to vaccination - onset of symptoms occurred prior to vaccination



**Forest plots 1-4: Vi-TT typhoid conjugate vaccines versus typhoid Vi-polysaccharide vaccine (ViPS) in children and adults**

*Patients: 2 to 60-year old children and adults*  
*Setting: India, United Kingdom*  
**Comparison: Vi-TT typhoid conjugate vaccine (Typbar-TCV®, 1 dose) versus typhoid ViPS vaccine (Typhim Vi® or Typbar®, 1 dose)**

Outcome	Forest plot	Certainty of the evidence (GRADE)																																				
<b>Incidence of typhoid fever</b> with 1 dose Typbar-TCV in adults follow up: <1 month	<table border="1"> <thead> <tr> <th>Study or Subgroup</th> <th>Vi-TT Events</th> <th>Vi-TT Total</th> <th>ViPS Events</th> <th>ViPS Total</th> <th>Risk Ratio</th> <th>M-H, Random, 95% CI</th> </tr> </thead> <tbody> <tr> <td>Pollard 2017 GBR*</td> <td>2</td> <td>37</td> <td>7</td> <td>35</td> <td>0.27</td> <td>[0.06, 1.21]</td> </tr> </tbody> </table>	Study or Subgroup	Vi-TT Events	Vi-TT Total	ViPS Events	ViPS Total	Risk Ratio	M-H, Random, 95% CI	Pollard 2017 GBR*	2	37	7	35	0.27	[0.06, 1.21]	⊕○○○ VERY LOW																						
	Study or Subgroup	Vi-TT Events	Vi-TT Total	ViPS Events	ViPS Total	Risk Ratio	M-H, Random, 95% CI																															
Pollard 2017 GBR*	2	37	7	35	0.27	[0.06, 1.21]																																
<b>Ratio of GMTs</b> with 1 dose Typbar-TCV in children and adults follow up: 0 months to <2 years	<p><b>Time points</b></p> <p><b>Study name</b> Vaccine: Vi-TT vs. ViPS</p> <p><b>0-&lt;1 mths</b></p> <table border="1"> <thead> <tr> <th>Study</th> <th>Comparison</th> <th>Ratio of GMT (95% CI)</th> <th>N Vi-TT</th> <th>N ViPS</th> <th>Age</th> </tr> </thead> <tbody> <tr> <td>Pollard 2017 GBR*</td> <td>Typbar-TCV vs. Typhim Vi</td> <td>4.12 (2.38, 7.14)</td> <td>39</td> <td>35</td> <td>15+ yrs<sup>A</sup></td> </tr> </tbody> </table> <p><b>1-&lt;2 mths</b></p> <table border="1"> <thead> <tr> <th>Study</th> <th>Comparison</th> <th>Ratio of GMT (95% CI)</th> <th>N Vi-TT</th> <th>N ViPS</th> <th>Age</th> </tr> </thead> <tbody> <tr> <td>Mohan 2015 IND</td> <td>Typbar-TCV vs. Typbar</td> <td>3.15 (2.74, 3.61)</td> <td>332</td> <td>305</td> <td>2-15+ yrs<sup>B</sup></td> </tr> </tbody> </table> <p><b>1-&lt;2 Yrs</b></p> <table border="1"> <thead> <tr> <th>Study</th> <th>Comparison</th> <th>Ratio of GMT (95% CI)</th> <th>N Vi-TT</th> <th>N ViPS</th> <th>Age</th> </tr> </thead> <tbody> <tr> <td>Mohan 2015 IND</td> <td>Typbar-TCV vs. Typbar</td> <td>1.78 (1.53, 2.08)</td> <td>243</td> <td>197</td> <td>2-15+ yrs<sup>B</sup></td> </tr> </tbody> </table>	Study	Comparison	Ratio of GMT (95% CI)	N Vi-TT	N ViPS	Age	Pollard 2017 GBR*	Typbar-TCV vs. Typhim Vi	4.12 (2.38, 7.14)	39	35	15+ yrs <sup>A</sup>	Study	Comparison	Ratio of GMT (95% CI)	N Vi-TT	N ViPS	Age	Mohan 2015 IND	Typbar-TCV vs. Typbar	3.15 (2.74, 3.61)	332	305	2-15+ yrs <sup>B</sup>	Study	Comparison	Ratio of GMT (95% CI)	N Vi-TT	N ViPS	Age	Mohan 2015 IND	Typbar-TCV vs. Typbar	1.78 (1.53, 2.08)	243	197	2-15+ yrs <sup>B</sup>	⊕○○○ VERY LOW ⊕⊕⊕○ MODERATE ⊕⊕⊕○ MODERATE
	Study	Comparison	Ratio of GMT (95% CI)	N Vi-TT	N ViPS	Age																																
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Mohan 2015 IND	Typbar-TCV vs. Typbar	1.78 (1.53, 2.08)	243	197	2-15+ yrs <sup>B</sup>																																	

Time points	Vaccine: Vi-TT vs. VIPS	MH RR (95% CI)	Events Vi-TT	Events VIPS	Age
<b>Seroconversion/seroprotection</b> with 1 dose Typbar-TCV in children and adults follow up: 0 months to <2 years	<b>0-&lt;1 mths</b> Pollard 2017 GBR* Typbar-TCV vs. Typhim Vi	1.13 (0.99, 1.28)	37/37	31/35	15+ yrs <sup>A</sup>
	<b>1-&lt;2 mths</b> Mohan 2015 IND Typbar-TCV vs. Typbar	1.04 (1.01, 1.08)	323/332	284/305	2-15+ yrs <sup>B</sup>
	<b>1-&lt;2 yrs</b> Mohan 2015 IND Typbar-TCV vs. Typbar	1.39 (1.20, 1.62)	180/243	105/197	2-15+ yrs <sup>B</sup>
					⊕⊕⊕⊕ VERY LOW
<b>SAEs</b> with 1 dose Typbar-TCV in children and adults follow-up: 3 months	<b>Subgroup name</b> <b>Study name</b>	<b>MH RR<sup>1</sup> (95% CI)</b>	<b>Events Vi-TT</b>	<b>Events VIPS</b>	
	<b>Human challenge</b>				
	Pollard 2017 GBR*	0.39 (0.06, 2.50)	1/41 <sup>2</sup>	3/37 <sup>3</sup>	
	<b>Not human challenge</b>				
	Mohan 2015 IND	0.31 (0.01, 7.53)	0/340	1/314 <sup>4</sup>	
	Overall (I-squared = 0.0%, p = 0.903)	0.36 (0.07, 1.82)	1/381	4/351	⊕⊕⊕⊕ MODERATE
	VI-TT vs VIPS NRCS: only 1 study (Garg 2014 IND) included for this comparison. Tabulated in Appendix 1.2 (A.1.2.5)				

<sup>A</sup> = 18-60 yrs; <sup>B</sup> = 2-45 yrs # Human challenge study, unpublished data

<sup>1</sup>A 0.5 continuity correction was added to all cells of the 2x2 table

<sup>2</sup> 1 hospitalisation for per-rectum bleeding and altered bowel habit. Diagnosed with inflammatory bowel disease. Not related to vaccination - onset of symptoms occurred prior to vaccination

<sup>3</sup> 3 Hospitalisations, none assessed to be related to vaccine. Polyarthropathy following typhoid challenge and antibiotic use, requiring ongoing rheumatological input. Hospitalisation for urinary retention secondary to vaginal ulceration. Hospitalisation for semi-elective tonsillectomy for investigation of tonsillar lesion.

<sup>4</sup> 1 Hospitalisation for febrile convulsions in a 3-year-old, resolved and assessed to be unrelated to vaccination.

### Summary of Findings 1.6: Booster versus no booster Vi-TT in infants, children and adults

Patients: infants, children and adults  
Setting: India

Comparison: Booster dose of Typbar-TCV at 720 days after one initial dose, versus no booster (one initial dose of Typbar-TCV only)

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		No booster	Vi-TT booster		
<b>Incidence of typhoid fever</b>	No studies were identified for this outcome.				
<b>Ratio of GMTs (aged 2-45 years) follow up: 42 days after booster dose (approx. 762 days after 1<sup>st</sup> dose) versus 720 days after 1<sup>st</sup> dose</b>	We do not know about the effect of a booster dose of Typbar-TCV on GMTs in children and adults because the certainty of evidence is very low.	Mean: 82.7 EU/mL	Mean: 1685.3 EU/mL	Ratio 20.63 (19.05 to 22.03) 183 participants in 1 non-random cohort*	⊕○○○ VERY LOW <sup>1,2</sup> due to risk of bias and indirectness
<b>Ratio of GMTs (aged 6-23 months) follow up: 42 days after booster dose (approx. 762 days after 1<sup>st</sup> dose) versus 720 days after 1<sup>st</sup> dose</b>	We do not know about the effect of a booster dose of Typbar-TCV on GMTs in infants because the certainty of evidence is very low.	Mean: 48.7 EU/mL	Mean: 1721.9 EU/mL	Ratio 35.36 (32.18 to 38.84) 193 participants in 1 open-label trial**	⊕○○○ VERY LOW <sup>1,2</sup> due to risk of bias and indirectness
<b>Seroconversion</b>	No studies were identified for this outcome.				
<b>SAEs</b>	No studies were identified for this outcome.				

CI= confidence interval; EU= enzyme-linked immunosorbent assay (ELISA) unit; GMT= Geometric mean titre; RCT=randomised controlled trial; RR= risk ratio

\* Three-hundred and forty participants aged 2 to 45 years received one dose of Typbar-TCV in a single arm of an RCT, and a non-random sample of 183 of these participants went on to receive a booster dose at 720 days. The comparison is between 243 of the 340 participants who received one dose with serum samples available at 720 days, and 175 of the 183 participants who received the initial dose plus a booster, with serum samples available at approximately 762 days. All 175 participants analysed in the booster dose group are also included within the non-booster dose groups. Correlation equal to 0 (no adjustment for matching), and 0.5 and 0.75 were applied; correlation to 0.5 shown in summary of findings table.

\*\* Three-hundred and twenty-seven participants aged 6 to 23 months received one dose of Typbar-TCV in an open-label trial, and a non-random sample of 193 of these participants went on to receive a booster dose at 720 days. The comparison is between 220 of the 327 participants who received one dose with serum samples available at 720 days, and 187 of the 193 participants who received the initial dose plus a booster, with serum samples available at approximately 762 days. All 187 participants analysed in the booster dose group are also included within the non-booster dose groups. Correlation equal to 0 (no adjustment for matching), and 0.5 and 0.75 were applied; correlation to 0.5 shown in summary of findings table.

<sup>1</sup> Downgraded two levels for risk of bias: non-randomised comparison; analysis of the same sample participants before and after booster dose; age is a serious confounder, not controlled across groups.

<sup>2</sup> Downgraded one level for indirectness: evaluated by only one trial in India.

**Forest plots 1.6: Booster versus no booster Vi-TT in infants, children and adults**

Patients: infants, children and adults

Setting: India

Comparison: Booster dose of Typbar-TCV at 720 days after one initial dose, versus no booster (one initial dose of Typbar-TCV only)

Outcome	Forest plot	Certainty of the evidence (GRADE)																																				
Incidence of typhoid fever	No studies were identified for this outcome.																																					
Ratio of GMTs follow up: 1 month after booster dose versus 6 months after 3 <sup>rd</sup> dose	<table border="1"> <thead> <tr> <th>Study or Subgroup</th> <th>Booster Total</th> <th>No booster Total</th> <th>Ratio of Geometric means IV, Random, 95% CI</th> </tr> </thead> <tbody> <tr> <td colspan="4"><b>1.1 Age 2-45 years</b></td> </tr> <tr> <td>Mohan 2015 (correlation 0)</td> <td>175</td> <td>243</td> <td>20.63 [18.48, 23.02]</td> </tr> <tr> <td>Mohan 2015 (correlation 0.5)</td> <td>175</td> <td>243</td> <td>20.63 [19.05, 22.33]</td> </tr> <tr> <td>Mohan 2015 (correlation 0.75)</td> <td>175</td> <td>243</td> <td>20.63 [19.46, 21.87]</td> </tr> <tr> <td colspan="4"><b>1.2 Age 6-23 months</b></td> </tr> <tr> <td>Mohan 2015 (correlation 0)</td> <td>187</td> <td>220</td> <td>35.36 [30.93, 40.42]</td> </tr> <tr> <td>Mohan 2015 (correlation 0.5)</td> <td>187</td> <td>220</td> <td>35.36 [32.18, 38.84]</td> </tr> <tr> <td>Mohan 2015 (correlation 0.75)</td> <td>187</td> <td>220</td> <td>35.36 [33.08, 37.79]</td> </tr> </tbody> </table>	Study or Subgroup	Booster Total	No booster Total	Ratio of Geometric means IV, Random, 95% CI	<b>1.1 Age 2-45 years</b>				Mohan 2015 (correlation 0)	175	243	20.63 [18.48, 23.02]	Mohan 2015 (correlation 0.5)	175	243	20.63 [19.05, 22.33]	Mohan 2015 (correlation 0.75)	175	243	20.63 [19.46, 21.87]	<b>1.2 Age 6-23 months</b>				Mohan 2015 (correlation 0)	187	220	35.36 [30.93, 40.42]	Mohan 2015 (correlation 0.5)	187	220	35.36 [32.18, 38.84]	Mohan 2015 (correlation 0.75)	187	220	35.36 [33.08, 37.79]	<p>⊕○○○ VERY LOW</p>
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Seroconversion	No studies were identified for this outcome.																																					
SAEs	No studies were identified for this outcome.																																					

**Summary of findings 1.8: 1 dose versus 2 doses Vi-TT typhoid conjugate vaccine in children**

Patients: children (mean age: 4-5 years)

Setting: India

Comparison: 1 dose versus 2 doses (2 month interval) Vi-TT (Peda Typh™) typhoid conjugate vaccine

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		2 doses Vi-TT	1 dose Vi-TT		
<b>Incidence of typhoid fever</b>	No studies were identified for this outcome.				
<b>Ratio of GMTs in 2 to &lt;5 year olds follow up: 2-&lt;5 years</b>	We do not know about the effect of 1 dose compared with 2 doses PedaTyph typhoid conjugated vaccine on ratio of GMTs at 2 to <5 years follow-up in children; evidence is of very low certainty.	Mean: 17 µg/mL	Mean: 14 µg/mL	Ratio 0.82 (0.25 to 2.68) 40 participants in 1 RCT	⊕○○○ VERY LOW <sup>1,2,3</sup> due to risk of bias, indirectness, and imprecision
<b>Seroconversion</b>	No studies were identified for this outcome.				
<b>SAEs (RCTs) in infants and children (≤5 years) follow up: up to 7 days</b>	Evidence from RCTs We do not know about the effect of 2 doses compared with 1 dose PedaTyph typhoid conjugated vaccine on SAEs in children; evidence is of very low certainty.	0/200	0/200	RR not estimable** 400 participants in one RCT	⊕○○○ VERY LOW <sup>2,4,5</sup> due to risk of bias, indirectness, and imprecision

CI= confidence interval; GMT= Geometric mean titre; RCT= randomised controlled trial; RR= risk ratio; Vi-TT= typhoid Vi antigen coupled to tetanus toxin carrier protein

<sup>1</sup> Downgraded one level for risk of bias: high risk of performance and attrition bias, and non-random comparison (a non-random subsample of children from an RCT were included in follow-up).

<sup>2</sup> Downgraded one level for indirectness: evaluated by only one trial in children in one setting (India).

<sup>3</sup> Downgraded one level for imprecision: small sample size.

<sup>4</sup> Downgraded one level for risk of bias: high risk of performance and detection bias, and unclear randomisation methods.

<sup>5</sup> Downgraded one level for imprecision: no events were reported among relatively few participants, effect could not be estimated.



**Forest plots 1.8: 1 dose versus 2 doses Vi-TT typhoid conjugate vaccine in children**

Patients: children (mean age: 4.5 years)

Setting: India

Comparison: 1 dose versus 2 doses (2 month interval) Vi-TT (Peda Typh™) typhoid conjugate vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
<b>Incidence of typhoid fever</b>	No studies were identified for this outcome.	
<b>Ratio of GMTs follow-up: 2 to &lt;5 years</b>	<p><b>Time point</b></p> <p><b>Study name</b>      <b>Vi-TT: 1 dose vs. 2 doses</b>      <b>Ratio of GMT (95% CI)</b>      <b>N</b>      <b>N</b></p> <p><b>2-&lt;5 yrs</b></p> <p>Chinnasami 2013 IND      0.82 (0.25, 2.68)      20      20      2-&lt;5 yrs<sup>A</sup></p>	⊕○○○ VERY LOW
<b>Seroconversion</b>	No studies were identified for this outcome.	
<b>SAEs</b>	1 versus 2 doses Vi-TT: only 1 study (Chinnasami 2013 IND) included for this comparison. Tabulated in Appendix 1.2 (A.1.2.6)	⊕○○○ VERY LOW

<sup>A</sup>= range not reported; mean age 4.5 years at 30 months follow-up.

## Annex D: List of Working Group members and Declaration of interests

### SAGE members

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

### Experts

- Narendra Arora, International Clinical Epidemiology Network (INCLIN), India
- Zulfiqar A. Bhutta (SickKids Center for Global Child Health, The Hospital for Sick Children, Canada; Center of Excellence in Women and Child Health, Aga Khan University, Pakistan)
- John A. Crump (Centre for International Health, Department of Preventive and Social Medicine, University of Otago, New Zealand)
- Myron M. Levine (Center for Vaccine Development, University of Maryland School of Medicine, USA)
- Dafrossa Lyimo (National EPI Manager (Dar es Salaam), Tanzania )
- Florian Marks (Department of Epidemiology, International Vaccine Institute, Republic of Korea)
- Mark A. Miller (Office of the Director; and Division of International Epidemiology and Population Studies, National Institutes of Health, USA)
- Christopher M. Parry (Liverpool School of Tropical Medicine, UK; School of Tropical Medicine and Global Health, University of Nagasaki, Japan)
- Richard A. Strugnell (Department of Microbiology and Immunology, University of Melbourne, Australia)
- Dipika Sur (Consultant, Translational Health Science and Technology Institute, India)

### WHO Secretariat

- Adwoa Bentsi-Enchill (Primary focal point)
- Joachim Hombach

### Declaration of interests

All members completed a declaration of interests. The reported relevant interests (at any time throughout the work of the Working Group) are summarized below:

#### Zulfiqar A. Bhutta

- His institution (the Aga Khan University) received a grant from the former Novartis Vaccines Institute for Global Health (NVGH) to undertake a typhoid conjugate vaccine trial, for which he was Principal Investigator. This grant ceased in Sept 2012. This interest was assessed as non-personal, specific and financially significant.\*
- His institution (The Hospital for Sick Children, Toronto) received a grant from the Bill and Melinda Gates Foundation (BMGF) for research on global trends in typhoid fever. This interest was assessed as non-personal, specific and financially significant.\*

#### Myron M. Levine

- Has provided scientific advice, with no financial compensation, to a typhoid vaccine developer (Bharat Biotech) for the analysis and presentation of data on its licensed typhoid conjugate vaccine. This interest was assessed as non-personal, specific and financially insignificant.\*

- His institution (the University of Maryland) has a license agreement with Bharat Biotech for a bivalent typhoid/paratyphoid vaccine (in early preclinical development) for which M Levine is a co-inventor. This interest was assessed as personal, specific and financially significant.\*
- Through a Wellcome Trust grant to his institution (the University of Maryland), he is the Principal Investigator to develop and perform early clinical trials of a non-typhoidal *Salmonella* (NTS) conjugate vaccine for which he is a co-inventor. The University of Maryland has a technology transfer agreement with Bharat Biotech for this NTS vaccine candidate. This interest was assessed as personal, non-specific and financially significant.\*
- His institution (the University of Maryland) has a license agreement with PaxVax to commercialize an oral cholera vaccine for which he is a co-inventor. Paxvax is also the current manufacturer of the live oral typhoid vaccine Ty21a. This interest was assessed as personal, non-specific and financially significant.\*

#### **Florian Marks**

- His institution, the International Vaccine Institute (IVI), has a typhoid vaccine development program. IVI has technology transfer agreements and provides ongoing scientific and technical advice to three current developers of typhoid conjugate vaccines. F Marks is employed in the Epidemiology Department of IVI and this interest was assessed as non-personal, specific, and financially significant.\*
- His institution (IVI) has received research grants from the BMGF to conduct a multi-country typhoid fever burden studies in Africa (the Typhoid Fever Surveillance in Africa Program and the Severe Typhoid in Africa Program), for which he is Principal Investigator. This interest was assessed as non-personal, specific and financially significant.\*

#### **Mark A. Miller**

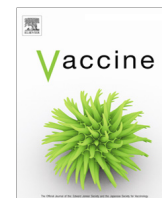
- His institution (the US National Institutes of Health) received a BMGF grant for the development of a biological reference standard for typhoid vaccines. This interest was assessed as non-personal, specific and financially significant.\*

#### **Richard Strugnell**

- He is a consultant to a planned efficacy trial for the Typbar-TCV conjugate vaccine (expected to start in mid-late 2018). This potential interest was assessed as non-personal and specific, however the financial significance could not be determined at the time of assessment as the trial was not yet funded.\*

\* According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by expert's organization, from any single vaccine manufacturer or other vaccine-related company exceeds 5,000 USD in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company in excess of 1,000 USD would also constitute a "significant shareholding".





# Cost-effectiveness analysis of typhoid conjugate vaccines in five endemic low- and middle-income settings



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## ABSTRACT

**Background:** Typhoid fever remains endemic in low- and middle-income countries. Programmatic use of existing vaccines is limited, but upcoming typhoid conjugate vaccines (TCVs) could warrant wider use. We evaluated the cost-effectiveness of five TCV delivery strategies in three urban areas (Delhi and Kolkata, India and Nairobi, Kenya) and two rural settings (Lwak, Kenya and Dong Thap, Vietnam) with varying incidence.

**Methods and findings:** We evaluated routine infant vaccination with and without catch-up campaigns among older individuals. We used a dynamic model of typhoid transmission to simulate cases, hospitalizations, deaths, disability-adjusted life-years (DALY) lost, treatment and intervention costs. We estimated cost-effectiveness (in terms of cost in international dollars (\$) per DALY averted) from the healthcare payer perspective, and assessed how it was influenced by uncertain model parameters. Compared to no vaccination, routine infant vaccination at \$1/dose was cost-saving in Delhi and Dong Thap, “very cost-effective” in Kolkata and Nairobi, and “cost-effective” in Lwak according to World Health Organization thresholds. However, routine vaccination was not the optimal strategy compared to strategies that included a catch-up campaign, which yielded the highest probability of being cost-saving in Delhi and Dong Thap and were most likely to provide a return on investment above a willingness-to-pay threshold of \$1440 in Kolkata, \$2300 in Nairobi, and \$5360 in Lwak. Vaccine price impacted the optimal strategy, and the number of doses required and rate of hospitalization were the primary sources of uncertainty.

**Conclusion:** Routine vaccination with TCV would be cost-effective in most settings, and additional one-time catch-up campaigns would also be economically justified.

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## 1. Introduction

Between 11.9–26.9 million cases of typhoid fever occur each year in low- and middle-income countries (LMICs) [1,2,48,49]. Symptoms include fever, abdominal pain, and nausea, which last between one to four weeks, and 1–2% of hospitalized cases result in death [3,4]. Improved sanitation contributed to the sharp decline of typhoid fever in industrialized countries during the early 20th century [4,5], but such infrastructure is slow to materialize in places where the disease remains endemic and antibiotic-resistance is on the rise [4,6]. Vaccination may prove a timely measure to abate the burden of disease.

Although the World Health Organization (WHO) recommends the Vi-polysaccharide (ViPS) and the live-oral Ty21a vaccines in populations at high risk for typhoid fever (including children 2–15 years old), vaccine introduction has been limited [7,8]. Newly-developed typhoid conjugate vaccines (TCVs) may prompt greater programmatic use [8,9]. Whereas existing vaccines confer 50–70% protection for 3–5 years in individuals over 2 years of age, TCVs have a higher efficacy, longer duration of protection, and are safe and immunogenic in children as young as 6 months old, making TCVs compatible with existing infant immunization programs [10–14]. In light of the recent licensure of TCVs in India and the anticipated licensure in other countries, the WHO will soon be updating their recommendations for typhoid vaccine use [15,16].

The optimal delivery strategy, economic resource implications, and cost-effectiveness of TCVs remain unknown. We sought to inform the decision-making process surrounding TCV use by

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examining whether a variety of vaccine delivery strategies aimed at children and adults might represent a comparatively efficient use of scarce resources.

## 2. Methods

We selected five settings that are distinct in their typhoid burden and costs of illness and vaccine delivery to carry out a comprehensive cost-effectiveness analysis that illustrates the interplay of various epidemiological and economic factors. Kolkata, India and Nairobi, Kenya represent high-incidence urban settings with moderate and low costs of illness, respectively, whereas Delhi, India represents an urban setting with very high incidence and a high cost of illness. Dong Thap, Vietnam represents a high-incidence rural setting with moderate cost of illness and Lwak, Kenya represents a medium-incidence rural setting with a low cost of illness (S1 Table) [17–24].

We simulated five TCV delivery strategies using a dynamic model of typhoid transmission in a theoretical open cohort of 100,000 people (with births and deaths): (I) routine vaccination at 9 months of age; and routine vaccination at 9 months plus a one-time catch-up campaign among individuals (II) 9 months to 5 years old, (III) 9 months to 15 years old, (IV) 9 months to 25 years old, (V) all ages  $\geq 9$  months. Because incidence often peaks in school-age children or young adults in low- and medium-incidence settings, we postulated that one-time campaigns could prove cost-effective in these settings [2,17].

Because vaccine prices have yet to be negotiated by the appropriate stakeholders, we assumed a price of 1 international dollar (I\$) per dose in a single-dose schedule; we examined alternative pricing and dosing schedules in scenario analyses. We assumed 80% coverage for routine vaccination and 70% coverage for campaigns.

The null comparator is a scenario with no vaccination, which is the current strategy in most LMICs [8,9,15]. Our main outcome was the incremental cost-effectiveness ratio (ICER), defined as the cost (in international dollars) per disability-adjusted life-years (DALYs) averted by each strategy over a 10-year time horizon.

The analysis was conducted in accordance with the recommendations of the Bill and Melinda Gates Foundation's (BMGF) reference case and WHO guidelines [25–27]. We adopted the perspective of the healthcare payer, therefore considering only the DALYs lost by care-seeking individuals and the direct treatment and vaccination costs accrued by the healthcare system [25,26].

### 2.1. Model structure

We modified an existing age-stratified compartmental model of typhoid transmission (“transmission model”) and added a probability model describing treatment outcomes (“treatment model”) (Fig. 1) [28]. Explicitly modeling the transmission dynamics allowed us to fully account for the decreased risk of infection that vaccination may confer on the population (herd immunity). We modeled each population using setting-specific transmission parameters, which we estimated by fitting the model to the adjusted age-specific incidence in each setting using a Hamiltonian Monte Carlo sampling algorithm (see S1 Appendix §1–3) [29].

The probability of receiving inpatient or outpatient care was parameterized using published data specific to each site; the costs and duration of disease were contingent on the type of care received [10,17–20,22–24]. DALYs were calculated as the sum of years lost to morbidity and death (discounted for severity and time) (see S1 Appendix §5) [30]. We assumed neither sanitation improvements nor enhanced capacity to treat or isolate cases would occur over the time horizon of our analysis.

### 2.2. Data

We collated data on disease incidence, progression, and mortality from the published literature to parameterize probability distributions describing uncertainty around the transmission, natural history, and costs associated with treatment of typhoid fever and vaccination campaigns (Table 1; see S1 Appendix §1, §4, and §6). We used efficacy data from a clinical trial of the two-dose Vi-rEPA conjugate vaccine to inform the probability of vaccine protection and duration of immunity (see S1 Appendix §4) [10]. The leading TCV candidate (Typbar-TCV, Bharat Biotech) was proven effective on the basis of serological surrogates of efficacy, suggesting that a single dose would provide comparable protection to Vi-rEPA [13–15]. All of the data we used to parameterize the costs of treatment and vaccination came from micro-costing studies, except for vaccine administrative costs in India, which came from the country Multi-Year Plan (see S1 Appendix §6) [31–33]. Because we did not have data itemized by each of the components of operational vaccination costs (e.g. storage, administration equipment and personnel, etc.), we assumed full operational costs rather than incremental costs; at worst, this assumption would bias our analysis against vaccine adoption.

Uncertainty distributions were assigned to each input parameter according to Briggs et al. 2006 [34]. We adjusted all costs to 2015 local currency units and converted them to international dollars [25,26]. Further details on how we resolved inconsistencies or shortcomings in the data are found in S1 Appendix §6.

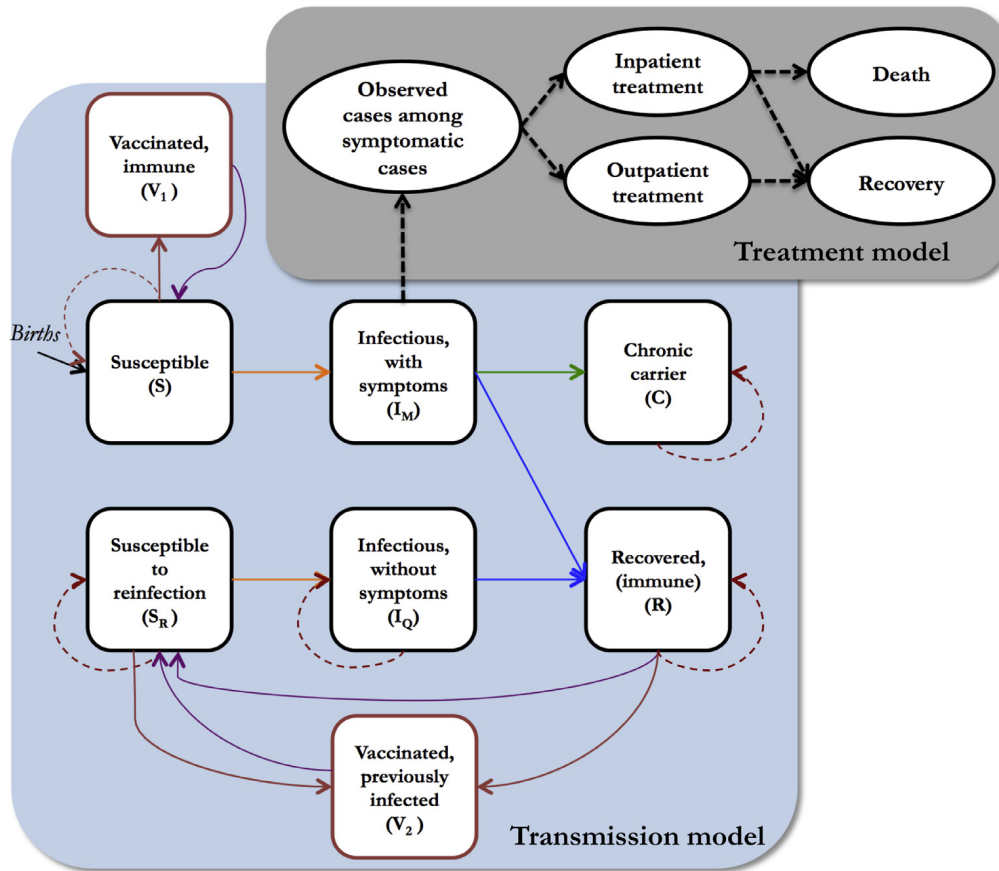
### 2.3. Cost effectiveness analysis

For each setting and intervention, we estimated the ICER at a point-estimate of the transmission, treatment, and economic model parameters. As per WHO guidelines, we defined an intervention to be “very cost-effective” if the ICER was less than the per capita gross domestic product (GDP) of the country, and an intervention was “cost-effective” if the ICER was less than three times the per capita GDP.

We then adopted a net benefits framework to evaluate the probability that each strategy was optimal across a range of willingness-to-pay (WTP) thresholds while accounting for parameter uncertainty [34,35]. Net monetary benefits (NMB) are defined as the product of the WTP threshold and the DALYs averted by the intervention, minus the cost of the intervention [34,35]. To calculate the NMB at each WTP value, we drew 1000 samples from the joint posterior distribution of model parameters. [34,35]. First, we assessed the probability that routine vaccination alone (intervention I) was the preferred strategy (had a NMB  $> I\$0$ ) compared to the status quo (no vaccination) at WTP thresholds of \$0–\$20,000 per DALY averted, which spans the range of zero to three times the per capita GDP for all countries in our analysis. We then assessed the four additional strategies that included a catch-up campaign (II–V) alongside intervention I. When comparing multiple interventions, an intervention is considered optimal at a given WTP threshold with probability equal to the proportion of samples in which the intervention in question had the highest NMB [34,35].

### 2.4. Scenario and sensitivity analysis

We performed five additional scenario analyses that evaluated the cost-effectiveness of all delivery strategies under the assumption that the cost per dose would be I\$2 or I\$5 (based on the costs of other Gavi-supported vaccines) and the current price of the Typbar-TCV vaccine in India (1800 INR) [15], and under the assumption that two doses (and thus two visits to the vaccination post) would be necessary in order to completely immunize children  $< 5$  years of age at I\$1, I\$2, or I\$5/dose. Some of the TCV



**Fig. 1.** Transmission and treatment model. The transmission model (black squares) includes: two susceptible classes—one for individuals who have never been previously infected and another for individuals whose immunity to reinfection has waned; two infectious classes—one for primary infections and another for subsequent infections, which we assume are subclinical; a recovered class, which is temporarily immune to reinfection; and a class of chronic carriers, who are assumed to remain infectious until death. We also model two vaccinated classes (red boxes)—one for individuals who have been successfully immunized and are protected from symptomatic infection, and another for individuals who had been previously infected and who are only protected from asymptomatic infection. Orange lines depict the infection process, blue lines depict the recovery process, green lines depict the process by which individuals become chronic carriers, purple lines depict waning immunity, and red lines signify the vaccination process. The dashed red lines correspond to individuals who do not respond to vaccination. The treatment model depicts a probability tree of treatment outcomes (black ovals). The dashed black lines represent probabilistic binomial samples. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 1**  
Input parameters for treatment outcomes and treatment and intervention costs. The sources for the parameters are detailed in the [Appendix](#).

Parameter	Kolkata	Delhi	Dong Thap	Nairobi	Lwak
<i>Treatment outcomes</i>					
Duration of disease in weeks: Inpatient (range)	2–4	2–4	2–4	2–4	2–4
Relative duration of disease: Outpatient vs Inpatient (range)	0.25–0.75	0.25–0.75	0.25–0.75	0.25–0.75	0.25–0.75
Disability weight	0.13 (0.025)	0.13 (0.025)	0.13 (0.025)	0.13 (0.025)	0.13 (0.025)
Probability of hospitalization	0.03 (0.015)	0.09 (0.035)	0.33 (0.0575)	0.02 (0.0125)	0.23 (0.08)
Probability of death among inpatients	0.016 (0.004)	0.016 (0.004)	0.016 (0.004)	0.016 (0.004)	0.016 (0.004)
<i>Treatment and intervention costs (2015 US\$)</i>					
Outpatient treatment costs	18.69 (1.27)	222.12 (17.48)	10.70 (4.09)	4.78 (1.88)	4.78 (1.88)
Inpatient treatment costs	928.43 (101.45)	4840.50 (755.17)	1241.32 (475)	103.87 (28.72)	103.87 (28.72)
Vaccine supplies	0.17 (0.06)	0.17 (0.06)	0.14 (0.05)	0.19 (0.07)	0.19 (0.07)
Operational costs - routine	3.55 (1.36)	3.55 (1.36)	8.33 (3.19)	3.61 (0.56)	3.61 (0.56)
Operational costs - campaign	1.67 (0.64)	1.67 (0.64)	9.02 (3.45)	3.61 (0.56)	3.61 (0.56)
<i>Fixed parameters</i>					
GDP per capita, US\$	6088.60	6088.60	6022.60	3082.50	3082.50
Life expectancy (years)	68	68	75.6	62	62
Discount rate (% per year)	3	3	3	3	3
Vaccine wastage (%)	15	15	15	15	15

Notes:  
 1. Mean (standard error) are presented for uncertain parameters, unless otherwise noted.  
 2. Abbreviations: US\$, international dollars; GDP, gross domestic product.  
 3. Whenever the literature did not report information on the uncertainty of one of our input parameters (e.g. a standard error around the mean inpatient cost), we assumed a wide uncertainty range, with the lower and upper limit 75% below/above the mean.

candidates require two doses to fully immunized children <5 years of age.

We performed sensitivity analyses to examine the robustness of our findings to parameter uncertainty. Because some of our model parameters are either not normally distributed or are correlated to other parameters, we used random forest analysis instead of the more typical ANOVA methods to estimate the relative contribution of each parameter to uncertainty in the NMB at a WTP value equivalent to the GDP per capita in each country (see [S1 Appendix §7](#) [[36,37](#)]).

### 2.5. Role of the funding source

This study was funded by the Bill and Melinda Gates Foundation (BMGF); therefore, we conducted the cost-effectiveness analysis in accordance with the BMGF reference case. An advisory board hosted by BMGF provided input on which delivery strategies to evaluate; otherwise, the funders had no role in the study design, data collection and analysis, preparation of the manuscript, nor the decision to submit for publication.

## 3. Results

Our transmission model provided a good fit to the observed incidence of typhoid fever by age across the five settings ([S5 Figure](#)). The predicted incidence rate did not differ significantly from the observed incidence rate after adjusting for blood culture sensitivity and the observed participation rate ([Table 2](#)).

The hospitalization rate had a notable impact on the DALYs lost over 10 years ([Table 2](#)). For instance, although we calculated the lowest number of cases for Lwak, the number of DALYs lost was lowest in Kolkata due to its low hospitalization rate, and by extension of our assumptions, its low mortality rate; the difference in deaths between settings (0.02% of cases in Nairobi vs 0.46% of all cases in Dong Thap) derived from the difference in hospitalization probabilities across sites, since we assumed that the probability of death was conditional on hospitalization and was equal across settings. The costs of treatment showed a different trend. Kolkata, which experienced the lowest number of DALYs lost, had higher costs of treatment than Lwak or Nairobi. Delhi had by far the highest costs, outpacing the cost of treatment in Dong Thap by nearly an order of magnitude ([Table 2](#)).

### 3.1. Vaccine impact and net costs

Our transmission model predicted a significant decrease in typhoid incidence resulting from any of the TCV delivery strategies ([S6 Figure](#)). Interventions that coupled routine vaccination with one-time catch-up campaigns yielded additional DALYs averted ([Table 2](#)). The largest decline in cases would occur in the ten years following vaccine introduction ([Fig. 2](#)). In the third decade after vaccine introduction, older age groups were predicted to experience a slight increase in typhoid incidence in some settings; this occurred because vaccination delays the time to infection but cannot completely prevent all cases. However, this did not undermine the gains from vaccination, as the overall cases averted over 30 years were still significantly greater than zero ([Fig. 2](#)).

The net costs of vaccination varied considerably among the five settings ([Table 2](#)). The costs of treatment in Delhi were high enough that the investment in vaccines was predicted to pay for itself. In Kolkata and Dong Thap, TCV introduction might save money, whereas in Nairobi and Lwak, vaccination would come at a cost.

### 3.2. Cost-effectiveness

Routine vaccination alone was predicted to be cost-saving in Delhi and Dong Thap, “very cost-effective” in Kolkata and Nairobi, and “cost-effective” in Lwak when compared to no vaccination ([Table 2](#)). In planning scenarios in which a catch-up campaign would be considered, however, routine vaccination (intervention I) was dominated in Kolkata, Delhi, and Dong Thap ([Table 2](#)).

Accounting for parameter uncertainty, routine vaccination had a 100% and 96% chance of being cost-saving (compared to no intervention) in Delhi and Dong Thap, respectively ([Fig. 3](#); [S7 Figure](#)). In Kolkata and Nairobi, routine vaccination was cost-effective at thresholds of more than I\$3300 and I\$2330 respectively—below the WHO threshold for “very cost-effective” interventions in India and Kenya. In Lwak, however, routine vaccination was optimal at thresholds of more than I\$6200—above the threshold for “very cost-effective” interventions but below the threshold for “cost-effective” interventions in Kenya.

Compared to other delivery strategies, however, routine vaccination alone (intervention I) never showed the highest probability of being cost-effective ([Fig. 3](#)). In Delhi, the most ambitious intervention (V) was unequivocally the most likely to be cost-saving. In Dong Thap, interventions III–V were equally likely to be cost-saving (when WTP = I\$0), and intervention V was optimal even at low WTP thresholds. In Nairobi and Kolkata, the status quo had a <50% probability of being optimal at values of I\$440 and I\$2300, respectively, and above that the optimal intervention depended on the WTP, but routine vaccination (intervention I) was a sub-optimal strategy at all WTP values. In Lwak, the status quo had a >50% probability of being optimal at WTP values below I\$5360; above this threshold, when vaccination is considered, the optimal strategy would include a catch-up campaign among children up to 15 years (intervention III) or 25 years of age (intervention IV).

### 3.3. Scenario analysis

Higher vaccine prices generally increased the WTP threshold at which interventions would become optimal except in Delhi, where the most ambitious intervention remained cost-saving ([S8 Figure](#), [S10 Figure](#)). Routine vaccination would most likely be “cost-effective” at I\$5/dose in Kolkata and Nairobi, but not in Lwak ([S8 Figure](#)). However, routine vaccination including a catch-up campaign (interventions II–V) would still be the preferred strategy in all sites, depending on the WTP threshold ([S10 Figure](#)). If two doses are required for children <5 years of age, the optimal strategy would be no vaccination up to a WTP threshold (which varied by setting and vaccine cost) above which interventions IV or V would be optimal in all settings but Lwak; less ambitious strategies would not confer sufficient benefits to justify the costs of administering two doses ([S11 Figure](#)). Routine vaccination alone (intervention I) was unlikely to be cost-effective in Lwak under a two-dose schedule ([S9 Figure](#)).

### 3.4. Sensitivity analysis

In all settings but Dong Thap, the number of doses contributed most to uncertainty in the NMB (as evaluated at a WTP equal to one GDP per capita) for routine vaccination, followed by the hospitalization rate ([Fig. 4](#)). In Dong Thap, the hospitalization rate and the probability of death were the most influential parameters. When we considered the NMB of delivery strategies II–V ([S12 Figure](#)), the most influential parameters did not change remarkably.

Interestingly, some of the vaccine-related parameters about which we had the least amount of data (vaccine price and probability of protection) did not rank highly in importance. However, the operational costs of vaccination (for which we applied a wide



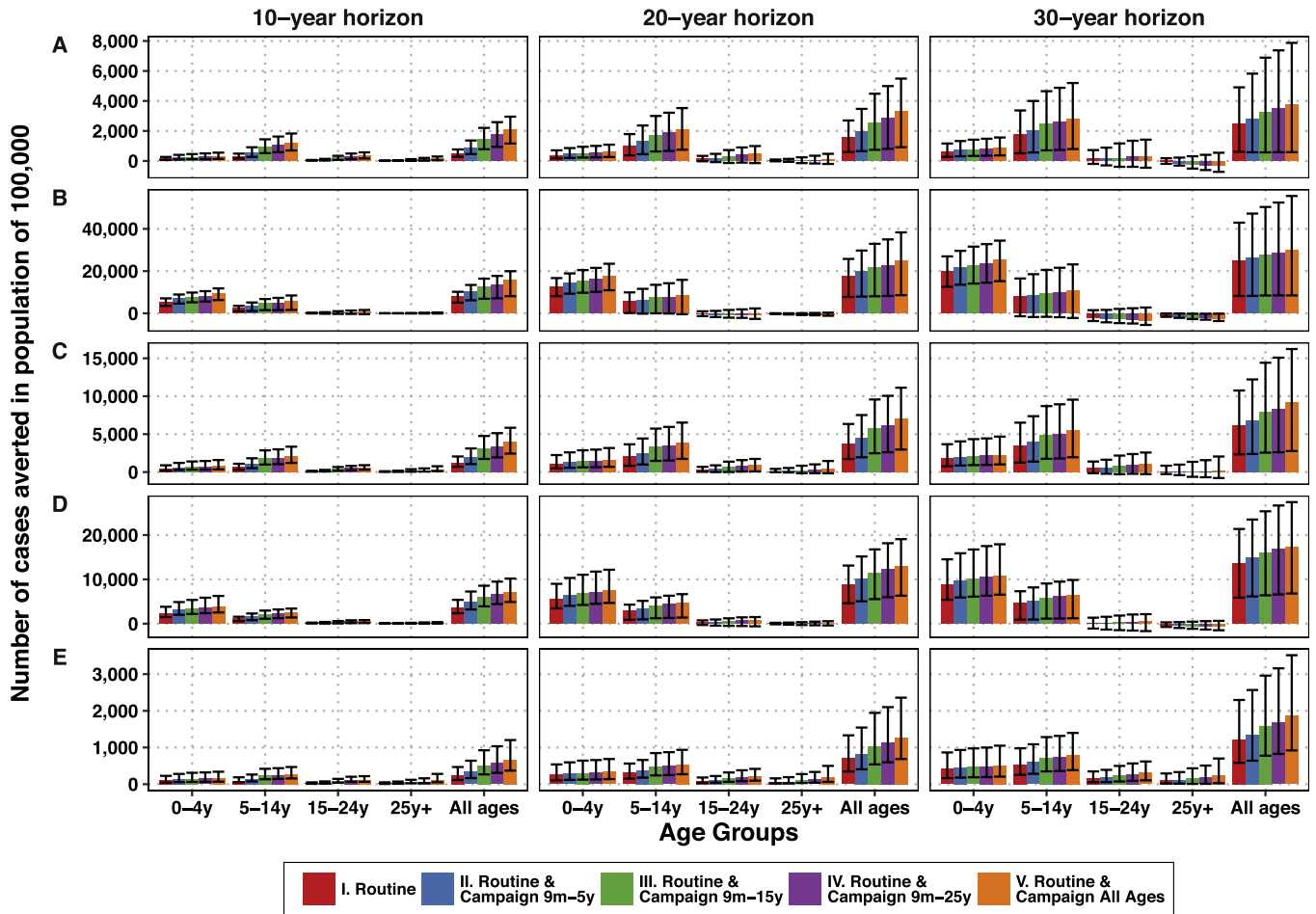
**Table 2**

Impact of various vaccination strategies against typhoid fever on typhoid disease and economic burden. Summary of model predictions in an open cohort of 100,000 people over 10 years after the beginning of the intervention.

	Kolkata	Delhi	Dong Thap	Nairobi	Lwak
<i>Typhoid disease and economic burden</i>					
Incidence (cases per 100,000 person-years)	157 (127, 190)	754 (583, 957)	196 (149, 253)	247 (208, 291)	28 (18, 42)
Adjusted incidence (per 100,000 person-years)	280 (213, 373)	2844 (2008, 4060)	534 (382, 750)	1143 (833, 1612)	125 (66, 246)
Model-predicted incidence (per 100,000 person-years)	287 (218, 383)	2153 (1723, 2306)	542 (392, 743)	880 (676, 1195)	98 (60, 164)
Total cases	2870 (2180, 3834)	21,528 (17,233, 23,059)	5420 (3917, 7434)	8798 (6759, 11,948)	976 (596, 1644)
Hospitalizations	72 (14, 202)	1930 (842, 3904)	1742 (1051, 2796)	167 (41, 457)	233 (85, 511)
Deaths	1 (0, 3)	31 (12, 68)	28 (14, 52)	3 (1, 8)	4 (1, 9)
DALYs lost	75 (21, 200)	2008 (839, 4230)	1807 (871, 3359)	178 (61, 472)	180 (59, 444)
YLD lost	10 (3, 27)	80 (27, 197)	25 (9, 59)	31 (10, 82)	4 (1, 12)
YLL lost	64 (12, 195)	1920 (750, 4164)	1780 (855, 3339)	143 (32, 438)	176 (56, 438)
Discounted DALYs lost	36 (12, 91)	840 (365, 1738)	716 (349, 1316)	92 (33, 216)	83 (27, 202)
Discounted YLD lost	9 (3, 23)	68 (23, 168)	21 (8, 51)	26 (8, 70)	4 (1, 10)
Discounted YLL lost	27 (5, 82)	765 (298, 1663)	694 (331, 1292)	61 (14, 186)	80 (25, 194)
Discounted cost of treatment (in thousands I\$)	102 (53, 210)	11,579 (6803, 20,618)	1784 (680, 3961)	50 (24, 97)	23 (9, 57)
<i>Impact of vaccination on typhoid disease and economic burden</i>					
Cases averted					
Intervention I (Routine vaccination at 9m)	527 (292, 798)	8114 (5302, 10,094)	1275 (719, 1993)	3642 (2397, 5332)	254 (127, 498)
Intervention II (Routine & campaign 9m-5y)	926 (495, 1394)	10,723 (6649, 13,419)	1979 (1087, 3061)	5010 (3285, 7142)	353 (181, 663)
Intervention III (Routine & campaign 9m-15y)	1528 (843, 2234)	12,822 (7552, 16,134)	3201 (1851, 4795)	5971 (3948, 8472)	526 (289, 926)
Intervention IV (Routine & campaign 9m-25y)	1818 (1024, 2626)	13,872 (8107, 17,484)	3506 (2061, 5144)	6646 (4,456, 9342)	589 (329, 1035)
Intervention V (Routine & campaign all ages)	2128 (1298, 3012)	16,182 (8963, 19,698)	4049 (2521, 5896)	7124 (4,921, 9972)	680 (391, 1206)
Hospitalizations averted					
Intervention I (Routine vaccination at 9m)	13 (3, 40)	723 (277, 1572)	409 (212, 738)	67 (16, 190)	60 (19, 141)
Intervention II (Routine & campaign 9m-5y)	22 (5, 70)	959 (361, 2095)	631 (331, 1115)	92 (22, 260)	84 (27, 193)
Intervention III (Routine & campaign 9m-15y)	37 (7, 115)	1138 (436, 2455)	1021 (545, 1725)	111 (26, 310)	124 (41, 279)
Intervention IV (Routine & campaign 9m-25y)	44 (9, 136)	1229 (461, 2656)	1120 (598, 1859)	124 (29, 339)	139 (47, 311)
Intervention V (Routine & campaign all ages)	52 (11, 159)	1425 (530, 3110)	1308 (717, 2123)	133 (32, 368)	162 (55, 365)
Deaths averted					
Intervention I (Routine vaccination at 9m)	0 (0, 1)	12 (4, 27)	7 (3, 14)	1 (0, 3)	1 (0, 2)
Intervention II (Routine & campaign 9m-5y)	0 (0, 1)	16 (5, 36)	10 (4, 21)	1 (0, 5)	1 (0, 3)
Intervention III (Routine & campaign 9m-15y)	1 (0, 2)	18 (6, 44)	16 (7, 33)	2 (0, 5)	2 (1, 5)
Intervention IV (Routine & campaign 9m-25y)	1 (0, 2)	20 (6, 47)	18 (8, 36)	2 (0, 6)	2 (1, 6)
Intervention V (Routine & campaign all ages)	1 (0, 3)	23 (7, 54)	21 (10, 41)	2 (0, 6)	3 (1, 7)
Discounted DALYs averted					
Intervention I (Routine vaccination at 9m)	6 (2, 18)	310 (118, 666)	161 (71, 338)	37 (13, 90)	22 (6, 56)
Intervention II (Routine & campaign 9m-5y)	12 (3, 32)	418 (155, 926)	258 (114, 532)	52 (18, 126)	31 (8, 79)
Intervention III (Routine & campaign 9m-15y)	19 (5, 52)	503 (184, 1126)	423 (190, 837)	62 (22, 152)	46 (13, 117)
Intervention IV (Routine & campaign 9m-25y)	23 (6, 61)	543 (199, 1226)	462 (214, 904)	70 (24, 169)	51 (15, 129)
Intervention V (Routine & campaign all ages)	27 (8, 72)	624 (229, 1410)	531 (254, 1030)	75 (26, 182)	59 (18, 143)
Averted cost of treatment (in thousands I\$, discounted)					
Intervention I (Routine vaccination at 9m)	17 (9, 39)	4252 (2605, 7218)	397 (153, 843)	20 (10, 39)	6 (2, 14)
Intervention II (Routine & campaign 9m-5y)	31 (17, 65)	5777 (3526, 9524)	634 (252, 1277)	28 (14, 53)	8 (3, 19)
Intervention III (Routine & campaign 9m-15y)	54 (31, 108)	7004 (4395, 11,252)	1069 (431, 2166)	34 (18, 61)	12 (5, 28)
Intervention IV (Routine & campaign 9m-25y)	65 (38, 127)	7608 (4934, 11,794)	1175 (477, 2392)	38 (20, 68)	14 (6, 32)
Intervention V (Routine & campaign all ages)	77 (44, 145)	8918 (5801, 13,185)	1364 (551, 2736)	41 (21, 73)	16 (6, 39)
Cost of intervention (in thousands I\$)					
Intervention I (Routine vaccination at 9m)	39 (23, 65)	72 (42, 121)	128 (68, 234)	107 (86, 134)	144 (115, 177)
Intervention II (Routine & campaign 9m-5y)	50 (33, 78)	91 (60, 140)	183 (111, 290)	151 (128, 179)	184 (156, 220)
Intervention III (Routine & campaign 9m-15y)	85 (61, 119)	131 (92, 186)	338 (199, 534)	219 (190, 258)	266 (227, 312)
Intervention IV (Routine & campaign 9m-25y)	120 (87, 168)	162 (115, 226)	424 (240, 695)	280 (241, 330)	317 (271, 373)
Intervention V (Routine & campaign all ages)	208 (148, 301)	241 (170, 333)	693 (380, 1179)	386 (327, 462)	421 (357, 498)
Net costs of intervention (compared to no intervention; discounted, in thousands I\$)					
Intervention I (Routine vaccination at 9m)	20 (-5, 49)	-4136 (-7742, -2176)	-246 (-829, 17)	87 (57, 116)	137 (109, 173)
Intervention II (Routine & campaign 9m-5y)	19 (-23, 49)	-5631 (-10,498, -2932)	-422 (-1307, -15)	123 (86, 155)	176 (145, 212)
Intervention III (Routine & campaign 9m-15y)	31 (-41, 74)	-6736 (-12,717, -3454)	-684 (-2066, 18)	185 (140, 227)	252 (212, 301)
Intervention IV (Routine & campaign 9m-25y)	56 (-32, 114)	-7251 (-13,747, -3645)	-697 (-2147, 75)	241 (188, 295)	301 (252, 359)
Intervention V (Routine & campaign all ages)	131 (20, 229)	-8355 (-15,969, -4112)	-617 (-2302, 377)	343 (276, 422)	403 (338, 482)
<i>Cost-effectiveness of vaccination against typhoid fever</i>					
Incremental cost-effectiveness ratios (I\$/DALYs averted)					
Intervention I vs. no vaccination (status quo)	3172	Cost-saving	Cost-saving	2390	6931
Comparison of five interventions (I\$/DALYs averted); the optimal intervention in terms of cost-effectiveness is italicized for each setting					
Intervention I (Routine vaccination at 9m)	Dominated	Dominated	Dominated	Weakly dominated	Weakly dominated
Intervention II (Routine & campaign 9m-5y)	Weakly dominated	Dominated	Dominated	2368	Weakly dominated
Intervention III (Routine & campaign 9m-15y)	1263	Dominated	Dominated	6138	6092
Intervention IV (Routine & campaign 9m-25y)	6238	Dominated	Cost-saving	8989	9960
Intervention V (Routine & campaign all ages)	20,442	Cost-saving	1655	23,628	17,007

**Notes:**

- Abbreviations: I\$, international dollars; YLD, years lost to disability; YLL, years of life lost; DALYs, disability-adjusted life years (the sum of YLD and YLL; see [S1 Appendix §5-6](#)).
- Median model output and 95% credible intervals are presented.
- "Incidence" represents the crude incidence (per 100,000 person-years) observed in the study. "Adjusted incidence" represents the crude incidence in each study after adjusting for the observation process, which included adjustments for the reported proportion of patients meeting the case definition who agreed to participate in the study and had blood drawn for diagnosis and blood culture sensitivity (see [S1 Appendix §2](#)). "Model-predicted incidence" represents the incidence predicted by the dynamic model ([Fig. 1](#)).
- Costs of treatment and of the intervention are discounted.
- The status quo and the intervention were modeled in an open cohort, taking into account births and deaths.
- Interventions were considered "very cost-effective" and "cost-effective" if the ICER was below one and three times the national gross domestic product (GDP) per capita (I\$6088.60 in India, I\$6022.60 in Vietnam, and I\$3028.50 in Kenya).



**Fig. 2.** Model predictions for the cumulative number of cases averted over 10, 20, and 30 years following vaccine introduction in four age groups and in the whole population for (A) Kolkata, (B) Delhi, (C) Dong Thap, (D) Nairobi, and (E) Lwak. Note that the scale of the y-axis varies for each location. The colored bars represent the mean model predictions, while the black error bars represent the uncertainty from the transmission model parameters. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

variance in the absence of reported data) figured prominently in Kolkata and Lwak. We omitted Delhi from sensitivity analyses because parameter uncertainty had no bearing on the conclusions regarding the optimal strategy.

#### 4. Discussion

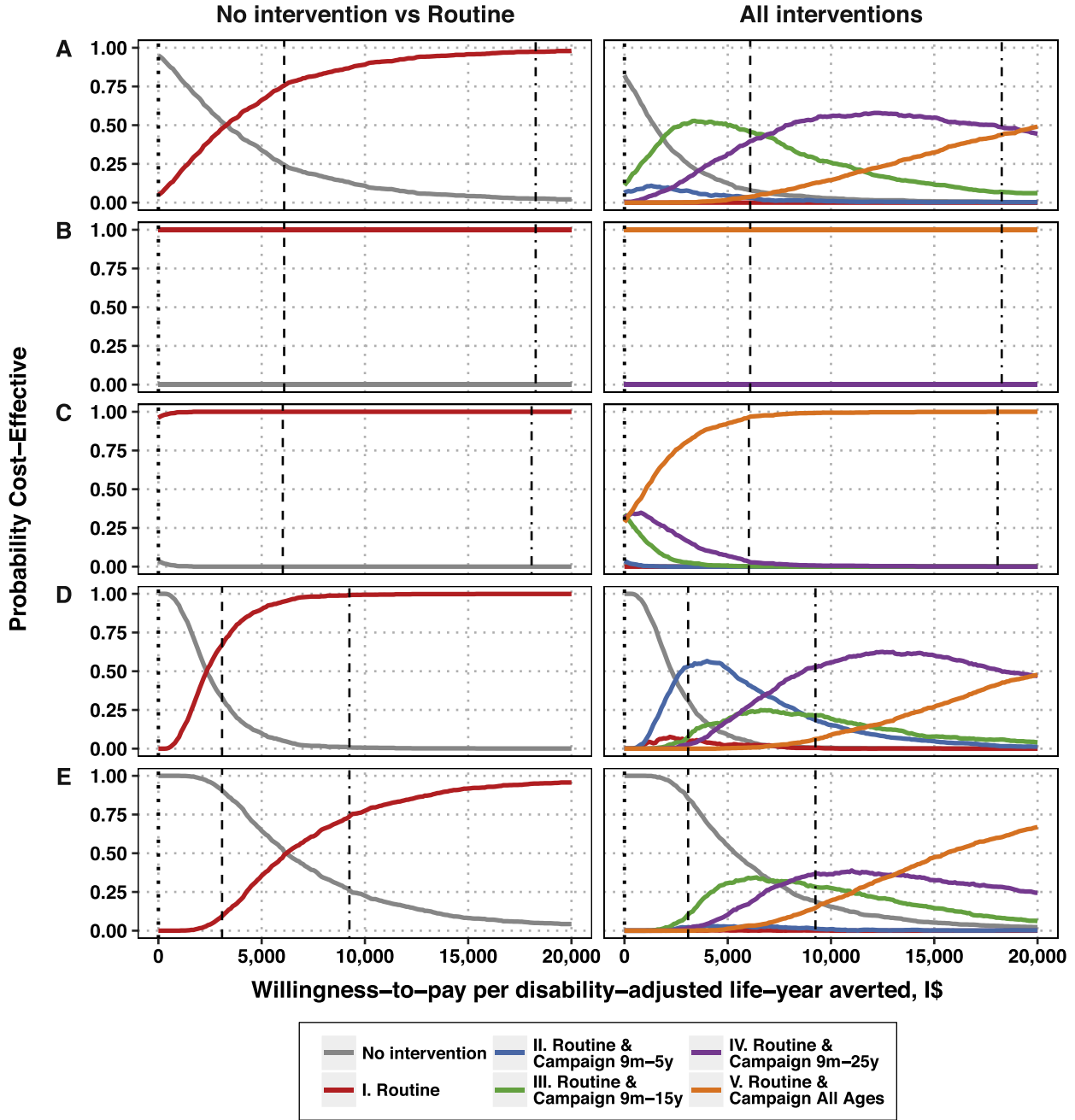
Our analysis is the first to evaluate the cost-effectiveness of TCV delivery strategies. Most strikingly, we found that although routine infant vaccination alone (intervention I) was likely to be cost-effective (or even cost-saving) compared to the status quo, it was not the optimal intervention when compared to strategies that include one-time catch-up campaigns (interventions II–V). In Delhi and Dong Thap, the most ambitious intervention (V) was cost-saving or optimal at WTP levels well below the WHO threshold for very cost-effective interventions, even when accounting for sizeable uncertainty in model parameters. In Kolkata and Nairobi, where incidence is moderate, no strategy was consistently predicted to be superior, but routine vaccination alone (intervention I) was consistently dominated by more ambitious strategies.

Previous cost-effectiveness analyses have recommended the introduction of ViPS vaccines in Delhi and Kolkata [38,39], but since ViPS is not licensed for children <2 years of age, those analyses did not consider infant immunization. In addition, previous analyses were based on static disease models rather than dynamic transmission models, which overlook the potential herd immunity

benefits of vaccinating older age groups who are less susceptible to clinical disease but may contribute to typhoid transmission. Herd immunity accounted for 28–43% of the cases averted in our model, depending on the setting and delivery strategy (S13 Figure), and had a substantial impact in our findings. In general, vaccination was not as likely to be cost-effective and less ambitious strategies were preferred when we did not account for herd immunity (S9 Table).

There is considerable uncertainty in the burden of typhoid fever, severity (as indicated by the probability of hospitalization in this analysis), costs associated with treatment, and vaccine costs and effectiveness. We conducted sensitivity analyses to identify the most influential parameters within each setting while accounting for high-level interactions. Some of the parameters for which we had the least amount of data to inform (e.g. treatment costs in Kenya and Dong Thap) did not have a strong influence on the NMB or the conclusions drawn from our model, but more precise estimates of the probability of hospitalization in Kolkata, Nairobi, and Lwak could yield stronger evidence for one intervention over others (S12 Figure). This approach, coupled with value of information analyses, could inform future research priorities.

Based on our scenario analysis, a one- vs two-dose schedule could have a formidable impact on the decision to introduce TCV; for instance, no strategy was cost-effective in Lwak when a two-dose schedule was required. When we examined the interaction between dosing schedules and vaccine price, strategies implementing two-dose schedules were likely to be cost-effective in



**Fig. 3.** Cost-effectiveness acceptability curves for routine vaccination at 9 months of age (left) and for all five delivery strategies under consideration (right) versus no intervention for (A) Kolkata, (B) Delhi, (C) Dong Thap, (D) Nairobi, and (E) Lwak. The dotted line shows the threshold at which an intervention is considered cost-saving, while the dashed line delineates the threshold at which an intervention is considered very cost-effective and the dot-dashed line delineates the threshold at which an intervention is considered cost-effective by the WHO criteria in each country.

Kolkata and Nairobi if the vaccine price was  $\leq$  I\$2/dose (S11 Figure). Of the vaccines currently in development or production, only Typhbar-TCV requires one dose; PedaTyph™ (BioMed) requires two doses for children <2 years old and others require two doses for children <5 years old [15].

We also evaluated a range of vaccine prices in scenario analyses, based on the prices of other Gavi-supported vaccines [40]. While the vaccine price had some impact on the preferred delivery strategy, routine vaccination with TCV was still likely to be cost-effective in all settings except Lwak when the cost per dose was I\$5 assuming a one-dose schedule (S9 Figure). However, at the current price of TCV-Typhbar on the private market in India (1800 rupees = I\$106), no strategy is cost-effective in Kolkata, Nairobi, or Lwak; once again, strategies that coupled one-time campaigns

with routine vaccination were optimal and likely to be cost-effective in Delhi and Dong Thap, where the costs of treatment were high (S14 Figure).

In resource-constrained settings, the decision to adopt an intervention is made not only with an eye towards cost-effectiveness, but also affordability [41]. Therefore, throughout our analysis, we made a number of conservative choices to bias against vaccine adoption, thereby lowering the risk of displacing existing or planned interventions that may confer a higher benefit to the population. For example, we assumed deaths only occurred among hospitalized cases. More broadly, we avoided overstating the case for TCVs by adopting the healthcare payer’s perspective, which disregards numerous sources of the economic burden such as caregiver’s time, transportation costs to the clinic, and foregone

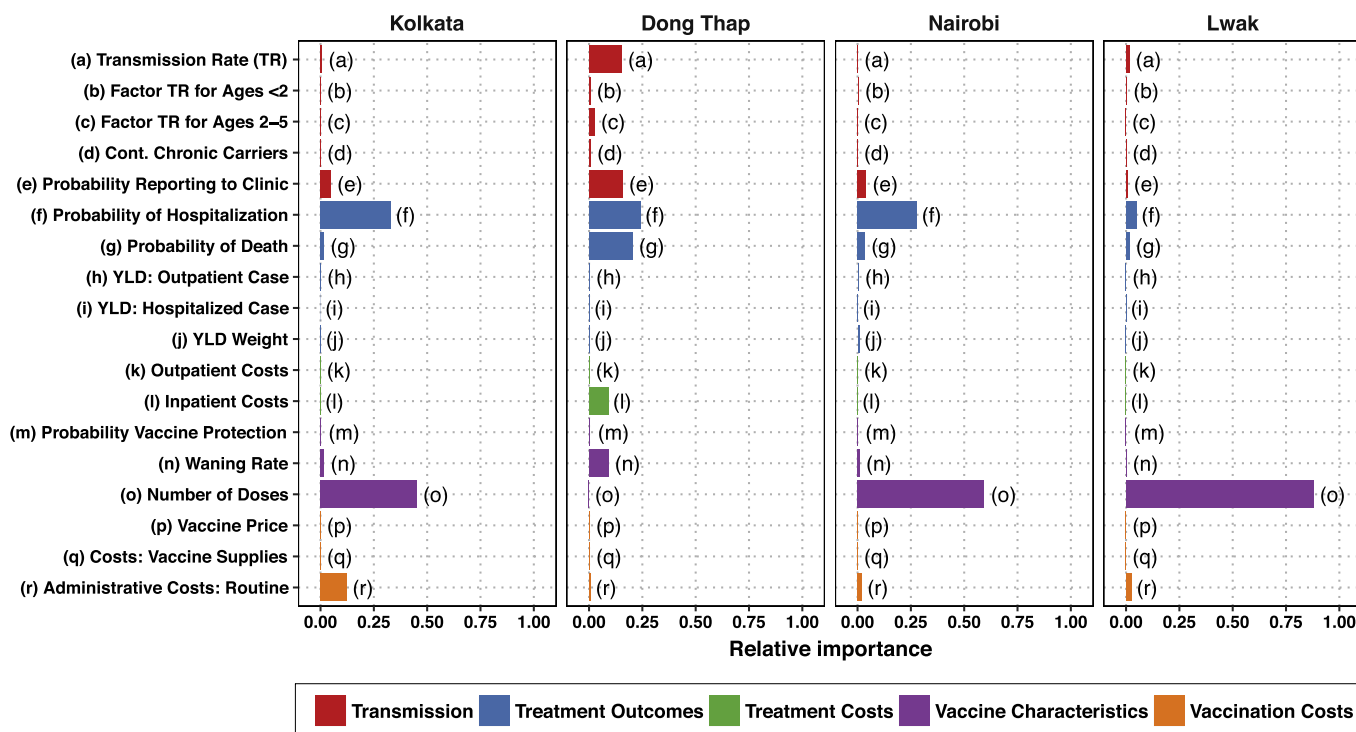


Fig. 4. Impact of uncertainty in each parameter on the net monetary benefits of routine vaccination as compared to the status quo, estimated using random forest analysis.

wages [42]. Despite these conservative choices, we found that most TCV delivery strategies were cost-effective at low WTP thresholds, and in some settings these strategies were even cost-saving.

There are three factors that we have not taken into account that may raise the willingness-to-pay of these interventions. First, three of the incidence studies were carried out in urban “slums” (in Delhi, Kolkata, and Nairobi), which may represent a higher incidence of typhoid than in the rest of the city; therefore, we recommend that all policy decisions be carried out taking into consideration the possible heterogeneity of incidence in a setting. Second, the incidence of typhoid varies over time, and has decreased in some settings in the time since the studies took place; in some instances, this may be due to improvements in water and sanitation infrastructure [43–45]. However, while improvements in clean water and sanitation often lead to decreases in typhoid transmission, the relationship is not well quantified and we do not have information on plans regarding the implementation of broad infrastructure projects and their expected impact (which would likely be small over the 10-year time horizon of our primary analysis) [43,44,46]. If the transmission rate of typhoid were to decrease over time in the comparator (no vaccination) scenario, this would raise the willingness-to-pay for any particular vaccination strategy, but the overall conclusions would be similar (S15 Figure). Third, evidence to date suggests that there are no serious adverse events caused by any of the modern typhoid vaccines [15,47]. If, however, evidence emerges as to the nature and rate of occurrence of such events, they could be incorporated as additional “costs” of vaccination, thereby increasing the cost per DALY averted for any given vaccination strategy.

In order to generalize the findings of our analysis to all LMICs where typhoid remains endemic, additional work is needed to better understand how variation in the epidemiology and costs of typhoid fever between locations (which far outpaces the variance within locations) could result in different recommendations. Furthermore, post-introduction surveillance activities would help to validate and refine model predictions of the potential long-term effects of vaccination on disease dynamics, which in turn could

help policy-makers in other locations. However, the current analysis demonstrates that TCVs are an economically viable tool to control the burden of typhoid fever in low-resource settings. Decisions regarding the recommended use of TCVs, including an updated WHO position paper and Gavi vaccine investment strategy, are imminent and must not be held hostage to the need for more data [16]. Robust analyses such as this allow for the use of uncertain or imperfect data to judiciously inform programmatic and research priorities.

#### Declaration of interests

The authors declare no conflicts of interest exist.

#### Author contributions

MA, JB, VEP conceived the study and wrote the initial draft; MA, JB performed the analyses; ADP, VEP helped with the analyses; all authors edited and approved the final draft.

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#### Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2017.05.001>.



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## Executive summary

### Introduction

The Typhoid Vaccine Acceleration Consortium (TyVAC), a partnership between the Center for Vaccine Development at the University of Maryland School of Medicine, the Oxford Vaccine Group at the University of Oxford, and PATH, an international nonprofit, aims to accelerate the introduction of new typhoid conjugate vaccines (TCVs) as part of an integrated approach to reduce the burden of typhoid in countries eligible for support from Gavi, the Vaccine Alliance (Gavi). This five-year project began in October 2016 and ends in October 2021.

### Approach

TyVAC's goal of accelerating the introduction of new TCVs requires 1) Supportive global policies, financing, and vaccine supply and 2) A supportive local environment in countries that have the necessary information, infrastructure, and financing to introduce and sustain age-specific vaccines using appropriate strategy. This goal is based on the overall assumptions that a TCV manufacturer maintains World Health Organization prequalification, an adequate supply of TCV is available during the project period, and no unforeseeable events (natural disasters, epidemics, political strife) occur that disrupt project activities or vaccine supply.

Core project activities address challenges posed by typhoid fever and demonstrate TCV introduction for optimal impact in select and varying epidemiologic and geographic settings. The overall approach is to engage local and global stakeholders to design and execute a vaccine introduction strategy based on prior successful new vaccine introductions.

### Project objectives

1. Serve as a coordinating body for typhoid-related research and control activities
2. Foster supportive global policies
3. Ensure typhoid and TCVs are recognized as global, regional, and national health priorities
4. Provide data on impact, effectiveness, appropriate vaccination strategies, and associated costs
5. Support countries in decision-making and preparation for sustained TCV introduction

### Research activities

To achieve its objectives, TyVAC is engaged in research activities to assess existing data and generate new evidence related to typhoid disease burden, antimicrobial resistance (AMR), disease modeling, demand forecasting, cost-effectiveness, health impact analyses, and regional data on TCVs. We are conducting country-level analyses to understand cost and economic value of vaccines and inform decision-makers at the national level as well as assess country preparedness and interest in TCV vaccine introduction.

## Progress to date

- **Typhoid disease burden:** John Crump leads the team collecting all existing information that describes typhoid epidemiology and typhoid vaccines. Data that has been collected has been presented to the SAGE working group.
- **Antimicrobial resistance (AMR):** Work to document AMR globally is ongoing. The development of an AMR database continues through sequencing of new *S.Typhi* isolates. A new typhoid/AMR website will soon be publically available. Gordon Dougan presented a draft paper on to the SAGE working group.
- **Disease modeling:** Systematic reviews of case fatality rates for typhoid fever, seasonal patterns of typhoid fever, and associations between climatic factors and typhoid fever incidence, that began under a pilot grant from the Yale Climate Change and Health Initiative, were completed. Manuscripts are underway.
- **Demand forecasting:** Development of the first version of a vaccine demand forecast model is complete. The model will be compared to demand forecast models prepared by Linksbridge, a consulting firm hired by the Bill & Melinda Gates Foundation to develop a demand forecast model and models prepared by the Gavi TCV sub-team.
- **Cost effectiveness:** There is ongoing work to extend cost-effectiveness modeling across all Gavi-eligible countries. Efforts to link predictions from burden (incidence) models to the dynamic model are underway. There are continuing efforts to collate data on the probability of hospitalization and costs of illness and vaccination. As requested by the SAGE working group, the team has provided evidence compiled from published studies relating to cost of illness, cost effectiveness, cost of delivery, and demand forecasting.
- **Country preparedness:** TyVAC has selected ten countries for scoping visits to determine their appropriateness and interest in TCV introduction. In six of these countries, TyVAC will assess acceptability and feasibility of TCV introduction.
- **Health impact analysis; vaccine impact studies:** Clinical trials in Nepal, Bangladesh, and Malawi will generate evidence on the impact of Vi-TCV vaccines. Table 1 below summarizes trial designs and anticipated timelines. Sites were selected because of their on-going typhoid surveillance activities, and diverse sociodemographic and typhoid epidemiology. These proposed studies are designed to complement each other and related efforts, such as data available from the vaccine manufacturer and from the Centers for Disease Control and Prevention and its partners through the planned evaluation of a programmatic introduction of the vaccine by the Indian government.
- **Cost of illness:** Completed a literature review of cost of illness and cost of vaccine delivery. Detailed work plan for cost of illness studies in Nepal and Malawi is under development.

**Table 1: Summary of TyVAC vaccine effectiveness trials**

Site	Nepal (Kathmandu)	Malawi (Blantyre)	Bangladesh (Dhaka)
Trial design	Individually randomized controlled trial	Individually randomized controlled trial	Cluster randomized controlled trial
Comparator (control) vaccine	Serogroup A meningococcal conjugate vaccine	Serogroup A meningococcal conjugate vaccine	Live attenuated Japanese Encephalitis
Sample size targets	20,000	24,000	43,350
Participant age	9 months to <16 years	9 months through 12 years	9 months to <16 years
Anticipated start date	Quarter 1 2017	Quarter 1 2018	Quarter 2 2018
Primary outcome	Determine efficacy and rate reduction of Vi-TCV in preventing blood culture-confirmed symptomatic infection by <i>S. Typhi</i>		
Study duration	30 months	36 months	30 months
Follow-up duration, post vaccination	24 months, for each participant	24-30 months, for each participant until the number of verified cases is reached	24 months, for each participant
Safety follow-up	<ul style="list-style-type: none"> <li>• Immediate reactogenicity</li> <li>• SAEs</li> <li>• A subset for reactogenicity in first 7 days</li> </ul>	<ul style="list-style-type: none"> <li>• Immediate reactogenicity</li> <li>• SAEs</li> <li>• A subset for reactogenicity in first 7 days</li> </ul>	Protocol development ongoing
Immunogenicity data	Anti-Vi antibodies on Day 0 and at 1 month (Day 28): (1000 in vaccine arm; 500 in control arm)	Anti-Vi antibodies on Day 0, 1 month (Day 28), and day 730 (600 children, 200 in each of 3 age groups: 9-11 months, 1-5 years, and 6-12 years)	Protocol development ongoing
Co-administration with other vaccines (Measles-Rubella)	N/A	Measles and Rubella antibody response in 200 children aged 9-11 months	N/A

**Research and program gaps**

Research and program gaps out of scope or not funded within the TyVAC project include:

- Studies on co-administration of TCV vaccine: There have been no studies on the immunogenicity of co-administration of TCV vaccine with vaccines commonly used in routine Expanded Programme on Immunization programs in many Gavi-eligible countries in sub-Saharan Africa, most notably yellow fever and Meningitis A conjugate vaccine
- Impact of TCV vaccine use during outbreaks
- Impact of TCV vaccine in other African countries with different epidemiology and socio-demographics than Malawi
- New typhoid surveillance studies, environmental surveillance
- Development and testing of new diagnostics

- Technical assistance or support to existing or new manufacturers
- Technical support to countries for implementation
- Post-introduction monitoring

### **Other activities**

#### **Policy and advocacy**

Building on extensive experience in advocacy and communication for vaccine introductions, TyVAC is implementing a collaborative communications strategy to raise awareness and ensure typhoid control and TCVs are recognized as global, regional, and national health priorities. Leveraging and expanding existing efforts, TyVAC partnered with the Coalition against Typhoid (CAT) to create a broad call to action, to Take on Typhoid that draws stakeholders from multiple sectors, including typhoid, vaccines, water, sanitation, and hygiene (WASH), and child health. Take on Typhoid will engage a diverse group of partners across the health and WASH sectors to promote action to reduce the burden and social impact of typhoid. The TyVAC/CAT website, nearing completion, will provide a resource with advocacy tools, data, and relevant information to promote integrated typhoid prevention and control solutions.

12-13  
September | 2017

## 14th Meeting of the SAGE Polio Working Group

Conclusions and recommendations

Note for the Record



World Health  
Organization

## **Background**

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The 14th face-to-face meeting of the SAGE Polio Working Group (WG) was held during 12-13 September 2017 at the World Health Organization HQ in Geneva, Switzerland.

The meeting was attended by the following WG members: Dr. Zulfiqar Bhutta, Dr. Peter Figueroa, Dr. Nick Grassly, Dr. T Jacob John, Dr. Elizabeth Miller, Dr. Jeffrey Mphahlele, Dr. Walter Orenstein, Dr. Kimberly Thompson, and Dr. K Zaman. Dr. Ilesh Jani, and Dr. Youngmee Jee joined over the phone. Dr. Walter Dowdle was unable to join.

Dr. Yagob Al-Mazrou chaired the meeting.

This note presents a summary of the main findings and recommendations of the meeting.

### **Context and objectives of the meeting**

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In preparation for the October 2017 SAGE meeting, the Polio WG meeting was for the following objectives:

1. To review the GPEI programme progress and update, including VDPV epidemiology and IPV supply situation
2. To develop a recommendation on the IPV catch-up campaign
3. To start discussion on “readiness criteria” for eventual bOPV withdrawal

### **Topic 1: GPEI programme update**

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The WG reviewed the 1) GPEI programme update, presented by Roland Sutter (WHO), and review of outbreak responses to VDPV type 2 events since the switch by Arshad Qudus (WHO), and 2) Risk assessment for bOPV cessation by Hil Lyons (IDM) and current planning for bOPV campaigns by Steve Wassilak (CDC).

#### **Progress toward interruption of WPV1**

The GPEI reported progress in the elimination of WPV in Afghanistan and Pakistan in the first half of 2017, with 4 WPV1 cases in Pakistan and 6 in Afghanistan (as of 6 September, 2017), which represent lower numbers than at the same time in 2016 (i.e. 13 cases in Pakistan and 7 cases in Afghanistan), but still not interruption of transmission. Despite the reductions in cases reported to date, in Pakistan there are still a number of environmental isolates (65 isolates as of 5 September 2017) and there is substantial (about 2%) genetic divergence between some of these isolates implying multiple ongoing chains of transmission.

In Nigeria, no WPV1 cases or isolates were detected in environmental surveillance since September 2016. The access in Borno State is improving, but still large parts of the state remain inaccessible, significantly affecting the quality of surveillance and Supplementary Immunization Activities (SIAs).

#### **Emergence of VDPV2 after the OPV2 withdrawal and outbreak response**

Since the tOPV-bOPV switch in April 2016, the Sabin viruses in most OPV-using countries disappeared as expected following the efforts to intensify population immunity to

transmission. After the switch, 40 VDPV2 were reported from all sources; 6 iVDPV2, 28 aVDPV2, and 6 pending classification. Excluding the iVDPVs and based on sequencing analysis, almost 50% (16/34) VDPV2 possibly emerged after switch. In addition, 6 post-switch cVDPV2 outbreaks occurred in four countries (i.e. Pakistan, Syria, Nigeria, and DRC), which falls within the range of the pre-switch estimates, but also demonstrates failure to sufficiently increase serotype 2 immunity through high quality SIAs prior to the switch. Most cVDPV2 cases were below 2 years of age in conflict affected areas or hard-to-reach population and either did not receive any OPV or were inadequately immunized. So far no international spread of cVDPV2 viruses has been documented.

The Advisory Group on the use of mOPV2 has reviewed and recommended to the Director General of WHO that mOPV2 be released from the Global Stockpile for all 6 outbreaks. 5 out of 6 outbreaks were reviewed within 3 days (except for Syria). mOPV2 has become available in the outbreak country within 7 days of DG authorization in 5/6 outbreaks (exception: Syria). First SIA took place within 14 days of confirmation of outbreak in 3/6 outbreaks (Delay in the two DRC outbreaks and in Syria).

In Pakistan, there was an outbreak in Quetta block in October 2016, responded to by two mOPV2 rounds in Quetta district, one mOPV2 round in surrounding districts, and one IPV round in the three districts of Quetta block. Following the SIAs, no cVDPV2 has been reported so far in 2017 (last isolate in Dec 2016).

In Nigeria, there were two separate cVDPV2 outbreaks; one in Borno (detected in environmental surveillance and in a WPV1 case contact) and second in Sokoto (environment and AFP case). There were three SIAs with mOPV2. The lot quality assurance sampling (LQAS) indicated that most Local Government Areas (LGAs) have achieved the target (90%) coverage in the areas evaluated. However, this may not represent all polio-infected areas due to inaccessibility, in Borno.

In DRC, there were two separate cVDPV2 outbreaks in Haut Lomami and Maniema detected in 2017. The outbreaks were responded to with two rounds of mOPV2 and one target mop-up completed. The quality of the second round (about 90% of lots accepted in LQAS) was better than the first round (about 70% of lots accepted) in LQAS.

In Syria, the first case onset was on 3 March 2017 (22 nt difference) with a total of 39 cases and 31 contacts positive for cVDPV2 as of 11 September 2017. Two rounds of mOPV2 were completed in Deir Ez-Zor and one round in Raqqa governorates respectively, under very complex security and conflict situations. The independent monitoring by Red Crescent indicated overall good quality of SIAs in Deir Ez-Zor (coverage >88%). IPV is being used in the SIA in the outbreak zone and also for vulnerable populations in Northern Syria, Turkey and Lebanon.

Pakistan and Nigeria did not report any VDPV2 outbreak related virus yet, following the mOPV2+IPV outbreak response.

### **Risk assessment for bOPV cessation and planned bOPV campaigns**



The WG reviewed an analysis by IDM on VDPV 1 and 3 risks after bOPV is withdrawn and the need for additional bOPV campaigns prior to the withdrawal. Previously, IDM predicted that the risk of cVDPV 1 and 3 emergence at the time of bOPV cessation should be relatively lower (0.5/year) than cVDPV2 (2.6/year), with high immunity against VDPV type 1 and 3, and the use of bOPV and IPV in routine immunization schedules. However, the literature on past experience suggests the paralytic burden may be higher for type 1 than type 2 once reverted. An analysis by Kid Risk (presented at the October 2016 meeting), suggests similar cVDPV risks for types 1 and 2 and highlights that the dynamic risks depend on population immunity to transmission at the time of bOPV cessation, which depends on routine immunization (RI) coverage and SIAs conducted between now and bOPV cessation.

The GPEI Supplemental Immunization Activities Options Task Team (SIAOTT), in part based on the work of the GPEI Risk Assessment Task Team (RATT) and IDM, developed four SIA options for bOPV SIAs, focusing on countries with weak routine immunization systems and substantial subnational susceptible populations. These options have different levels of maintenance SIAs and additional pre-cessation SIAs, with costs of 1.0-1.3 billion USD for the period 2018-2021. Most of the cost is due to currently endemic countries with placeholder SIA generated separately from RATT/IDM estimates. These SIA options are subject to continued modification.

The task team concluded that risk of cVDPV1 or cVDPV3 is relatively low at present due to biological properties and high population immunity, but will increase if population immunity declines, with countries with weak routine immunization systems/subnational susceptible populations representing particularly critical areas. In the context of GPEI ramp down and priority to trim expenditures, the question remains as to the appropriate maintenance level of SIAs up to bOPV cessation to prevent cVDPV outbreaks up to and after bOPV cessation.

## **Containment**

The GPEI established the Containment Working Group (WG) to support the Global Certification Commission (GCC) in its oversight role of GAPIII, and the Containment Advisory Group (CAG), which reports to the Director General of WHO, to provide scientific guidance on containment related matters. As of 14 September 2017, 29 countries reported the designation of 94 Poliovirus Essential Facilities (PEF), which plan to retain infectious and potentially infectious poliovirus materials after OPV cessation.

## **Transition planning**

The program update included mention of the polio transition and the likely serious programmatic impact of GPEI ramp-down. Many streams of work are ongoing, including country-level transition, independent monitoring and high level awareness raising, post-certification strategy development and transition planning (at WHO, UNICEF, CDC). WHO established a team to facilitate the transition work.

## **WG decisions/recommendations**

- The WG expressed concern over the continued WPV transmission in Pakistan and Afghanistan, manifested by the continued widespread detection of genetically

divergent WPV in AFP, healthy children and environmental samples. The WG concluded that the GPEI must urgently intensify its vaccination activities especially focusing on identifying and improving coverage in populations with low immunity to get over the threshold for herd immunity as soon as possible and sustain this high level of population immunity in all areas through to bOPV cessation. The WG noted the deteriorating security situations in some parts of Pakistan (e.g. Baluchistan, FATA) and Afghanistan, and urged the programme to carefully monitor and address it. The WG emphasized the importance of quality of the supervision, monitoring and evaluation in all areas, and particularly those with recent virus circulation. Lastly, the WG encouraged the programme to continue employing innovative operational measures to reach individuals in inaccessible areas.

- In the context of declining population immunity against type 2, the WG highlighted its previous recommendation that countries with co-circulation of WPV and cVDPV2 should administer at least 2 doses of mOPV2 before the next bOPV round.
- The WG acknowledged the progress towards controlling the cVDPV2 outbreak in Syria but noted serious access and security issues which must be overcome to rapidly interrupt circulation of cVDPV2 in this area.
- Considering the risk assessment of types 1 and 3 and the discussion of planned bOPV SIAs, the WG reaffirmed its previous (October 2016) recommendation that GPEI should maintain high population immunity against types 1 and 3, especially in high risk countries and sub-national high risk populations, until bOPV cessation.
- The GPEI should monitor the changes in geopolitical situation and address decline in population immunity among distressed and challenged populations.
- The WG emphasized the importance of achieving and sustaining high quality surveillance and data management through and beyond bOPV cessation.

## **Topic 2: Introduction of IPV in the routine immunization**

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The WG reviewed the IPV and OPV supply situation presented by Ian Lewis (UNICEF) and implementation of IPV in routine immunization presented by Tracey Goodman (WHO).

### **IPV and OPV supply situations**

Currently, all tier 1 and 2 countries continue to receive IPV supply. However, in some countries, the IPV supply to the private sector is also affected since the tOPV-bOPV switch. Moreover, there are 36 tier 3 & 4 countries that are not currently receiving IPV.

- 19 countries have not introduced IPV due to the supply situation.
- 17 countries that had introduced IPV with their supply through UNICEF but have experienced IPV stock-outs since April 2016 because the available IPV doses were prioritized for the tier 1 & 2 countries.

The IPV stand-alone supply available to UNICEF is expected to stabilize in 2018 but still be constrained. Both of the manufacturers are offering realistic projections on supply availability for 2018 consistent with actual quantities they have supplied in the recent past. All 36 countries without access to IPV, will have access to IPV to introduce IPV into their routine immunization in 2018, which should allow them to either restart immunization or introduce IPV into their Expanded Programme on Immunization (EPI) during the first half of 2018. In addition, 2 million doses will be set aside for outbreak response in 2018.

The GPEI planned to secure 300M, 519M and 300M doses of mOPV1, 2 and 3 respectively for the stockpile. As of today, GPEI maintains full amount for types 1 and 3, and about half (250M doses) for type 2 in bulk. The Vaccine Supply Task Team under the Eradication and Outbreak Management Group (EOMG) met in September and reviewed the GPEI stockpiles.

Lastly, the WG also reviewed the bOPV supply situations. While offered and awarded quantities meet forecasted demand including buffers, there remain risks to supply, including 1) Risks of additional market exits of manufacturers, 2) Usual risks related to production of biologicals, 3) Risks of demand reductions due to the GPEI budget pressures, which could lead to earlier departure of manufacturers and potentially insufficient bOPV supplies up through bOPV cessation, and 4) Risks of cold chain constraints. GPEI (esp. UNICEF) will continue close monitoring and ensure suppliers meet their commitments to the accepted awards. Some WG members pointed out that financial risks now appear to present a threat to the program, and discussed concerns about the concept of any attempts to stretch the GPEI budget (i.e., do less with less) to compensate for the failures to stop transmission to date.

### **Implementation of IPV in routine immunization**

To date, 4 countries have decided to move to fIPV in their routine immunization programs (India, Sri Lanka, Bangladesh & Nepal). Recently, the PAHO TAG recommended 14 countries to implement a 2 fractional dose sequential schedule (these countries represent 6% of global birth cohort), and, of those, Colombia, Nicaragua, Honduras, Ecuador, Cuba, & El Salvador will start preparations in Q4 2017. WHO is actively following up with countries in other regions (AFRO, EMRO) for introduction of fIPV in their routine immunization.

In many countries, IPV coverage has achieved a similar level as DTP3 coverage, but the performance has been variable.

In April 2017, SAGE recommended a review of the tier classification with respect to prioritization of IPV allocation. The review incorporates the size of the population with no IPV protection and the recent VDPV2 events. Imperial College developed a concept note related to the risk of a VDPV2 outbreak in all tier 3 and 4 countries based on known risk factors (e.g. estimated country-specific serotype 2 immunity in children under 3 years old, movement of people from infected areas, iVDPV reports) and suggested allocating IPV supply priorities accordingly.

In Oct 2016, SAGE recommended that when sufficient supplies of IPV become available, countries with delayed IPV introduction or stock-outs should catch-up children who did not receive IPV in RI. Currently, about 25 million children have been missed in countries denied access to IPV (i.e., delayed introductions and stock-outs as of Sept 2017). However, due to the available and projected supply, insufficient IPV doses are available to begin these catch-up activities. IPV supplies will likely increase to support some catch up in mid-2018, and sufficient supplies are likely to be available such that full catch-up of the 1 full IPV dose could become available during 2019. The GPEI requested guidance from the WG related to prioritization of the available IPV doses for catch up.

## **WG decisions/recommendations**

- The WG expressed concern that significant populations still do not have access to IPV, and welcomed the forecast that all countries will have access to IPV to include a single full dose or 2 fractional doses of IPV in their routine immunization programs in 2018.
- The WG endorsed the proposed approach to prioritize IPV allocation for the IPV introduction in tier 3 and 4 countries, based on the presented risk ranking. The WG recommended further revision of concept note and risk assessment as more information becomes available and if the GPEI wants to use the risk assessment to address other topics.
- Due to the supply constraints, the WG agreed that low-risk bOPV-using countries may currently adopt two fIPV, but not two full doses, with the first dose at or after 14 weeks, and the second dose at least 4 months after the first dose. In such cases, countries should continue bOPV in their routine schedule.
- The WG reaffirmed the previous SAGE recommendation that countries should provide catch up doses. The WG recommended that countries should provide one full dose or two fIPV doses for children in countries which delayed the introduction of IPV or had stock out due to supply shortage as soon as supply becomes available, with the following guidelines
  - IPV supply for catch-up should be allocated based on risk and readiness
  - The decision on whether to provide catch up via routine or campaign should be made based on the cost and expected increase in coverage.

## **Topic 3: Discussion on future immunization policy**

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### **IPV supply and demand forecast**

The WG reviewed the updated forecast of global IPV demand and supply. After the certification of WPV types 1 and 3 eradication (expected in 2021-22), a two full-dose IPV schedule could be implemented in all OPV-using countries. The current estimate is that the demand for the two dose schedule (about 240M if all countries adopt two full doses and about 200M if some countries adopt a fractional dose IPV schedule) is likely to be met in 2021-2022.

### **Development of antiviral drugs**

The WG reviewed the progress of antiviral development. To date, the Polio Antivirals Initiative (PAI) identified two potential candidates including Pocapavir and V-7404 with the best antiviral properties of all compounds evaluated to date. Pocapavir completed a multi-arm placebo controlled mOPV1 challenge study in 2013, demonstrating a significant reduction in the duration and magnitude of virus excretion. However, there was also evidence of treatment emergent drug resistance observed in the study. Pocapavir is currently being used to treat NPEV and poliovirus infected patients on a compassionate use basis. Two immune deficient poliovirus excretors have been treated. One patient stopped excreting after 2 days of treatment and the other patient stopped excreting susceptible virus after 2 days but continues to excrete resistant virus at last follow up. For V-7404, Pfizer completed Phase 1 single ascending dose with a conventional tablet formulation, demonstrating good tolerance but low and variable plasma concentrations.

ViroDefense is optimizing an oral spray dried drug formulation and preparing a dossier for IND submission to the FDA in Q1 2018. ViroDefense is optimizing the formulation of the combination product (Pocapavir and V-7404 called ViroD7000) and is expecting to complete the studies necessary to begin patient treatment with ViroD7000 in late 2019.

### **Readiness criteria for full OPV withdrawal**

Previously, SAGE defined the trigger point and readiness criteria for OPV2 withdrawal (October 2014). The trigger point was absence of persistent cVDPV2 and readiness criteria included:

- introduction of at least one dose of IPV vaccine in all countries;
- licensure of bOPV for routine immunization;
- establishment of a global stockpile of mOPV2 vaccine and protocols for its use;
- appropriate containment and handling of poliovirus type 2 infectious and potentially infectious materials;
- verification of eradication of wild poliovirus type 2 globally.

While some of these criteria were met, others were not met (e.g. IPV introduction in all countries, absence of persistent cVDPV2). The GPEI presented a first pass at some assumptions that would underlie bOPV withdrawal, including consideration of:

- Poliovirus type 2 (Sabin 2, VDPV2, cVDPV2) elimination (i.e., demonstrated ability to successfully stop serotype 2 OPV);
- Ability to perform surveillance to look for iVPDVs (e.g., Primary Immunodeficiency Deficiencies (PIDs) surveillance) established in high risk countries);
- iVDPV2 burden is minimized outside industrialized world;
- Certification quality surveillance has been established in areas that are currently not accessible (parts of Nigeria, Somalia, Afghanistan, etc.).

The WHO Secretariat proposed the following trigger and three readiness criteria for full OPV withdrawal (i.e., bOPV cessation)

- Trigger: Wild poliovirus serotypes 1 and 3 eradication certified by GCC
- Readiness criteria
  - Adequate population immunity, especially in high-risk communities
  - No poliovirus type 2 outside of containment
  - No persistent cVDPV1 or 3 circulation (circulation beyond the six months after the first notification)
  - Availability of sufficient IPV supply for all countries to adopt two IPV dose schedule (either IM or ID)

The WG agreed in principle that we may need to revisit readiness for bOPV withdrawal separate to withdrawal of all OPV as there could be a situation following certification of WPV1 and 3 and cVDPV1 and 3 where withdrawal of bOPV1 and 3 would be justified though certification of cVDPV2 was not yet assured and use of mOPV2 was still needed.

### **WG decisions/recommendations**

- The WG emphasized the need for continued funding for both bOPV and IPV in routine immunization and SIAs to ensure sufficient population immunity before and after the certification.
- The WG endorsed the concept of developing trigger and readiness criteria for bOPV withdrawal. It proposes to continue the discussion over the next 12-18 months. For the next WG meeting, it requested the Secretariat to
  - revise the trigger and readiness criteria, based on the WG discussions and inputs from stakeholders
  - summarize the risk assessment and surveillance quality in different countries
- The WG acknowledged the progress in the development of antiviral drugs, and encouraged the PAI to implement the proposed development plan, especially with the combination drug product (ViroD7000).

### **Topic 4: Resource requirements**

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#### **Long-term funding policy for IPV**

The WG also reviewed the future funding policy for IPV. In June 2017, Gavi's Board approved extending Gavi's support from 2018 through 2020, under the arrangements approved by Nov-13 Board and subject to polio-specific funding being available. Overall IPV cost is estimated to be US\$ 195 – 250 million for 2019-20 with approximately US\$ 90 million available in estimated unused funds and an additional donor pledge. GPEI is working on fundraising to cover the funding gap, however, uncertainty remains about IPV price since the tender is still out.

After 2020, the Gavi Board will discuss continued support for IPV post-eradication as part of the Vaccine Investment Strategy (VIS) discussion in 2018. GPEI and Gavi will continue to investigate potential funding modalities for IPV.

#### **WG decisions/recommendations**

- In the context of the polio endgame and post certification strategy, the WG emphasized the importance of securing adequate financial resources at national and international levels to sustain essential functions, such as polio vaccine stockpiles, surveillance, outbreak response and SIAs.

### **Summary and next steps for the SAGE Working Group**

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The conclusions from the WG will be presented at the October SAGE meeting for further discussions. In the future, the WG will continue to review and provide technical oversight on major areas, such as:

- Progress towards elimination of WPV and cVPDV
- Polio vaccine supply issues (both IPV and OPV)
- Risk mitigation strategy before the OPV cessation (e.g. bOPV campaigns before the cessation, detection of iVDPV cases)
- Update on iVDPV epidemiology and development of antiviral drugs
- Progress towards the final OPV withdrawal

## **CONCEPT NOTE**

### **Grading the risk of a serotype 2 vaccine-derived polio virus (VDPV2) outbreak in Tier 3 and 4 countries**

#### **Background**

In its recent meeting of April 2017, SAGE discussed the evidence on the role of IPV in stopping transmission of WPV/VDPV2. Because IPV primarily offers a complementary benefit in stopping poliovirus WPV/cVDPV transmission, the primary vaccine of choice to eliminate WPVs and respond to cVDPVs remains OPV - in any of its two current formulations, bOPV and mOPV2. However, in countries using bOPV for routine immunization, IPV has a significant role in protecting children against poliomyelitis caused by cVDPV2 through routine immunization. This use of IPV in routine immunization is especially important as population immunity for type 2 continues to decrease in the period post-switch.

After the globally synchronized switch from trivalent to bivalent OPV conducted in April 2016, Sabin virus type 2 appears to have disappeared from the both the environment and in AFP samples, outside countries with mOPV2 use. However, Nigeria detected several VDPV2 in the environment in Bauchi, Gombe and Sokoto in 2017. As a consequence, SAGE expressed concern over the ongoing circulation of VDPV2 in Nigeria.

Related to the use of IPV and the medium-term availability of vaccine for low risk countries, as defined by tier 3 and 4 criteria, the SAGE concluded:

1. IPV supply should be prioritized for use in routine immunization (especially in Tier 1 and 2 countries); and
2. WHO should review its tier classification of countries with respect to prioritization of IPV to take into account the size of the population with no IPV protection and the recent type 2 VDPV events.

#### **Risk assessment methodology**

Following the request from the SAGE, an analysis of the risk of a serotype 2 vaccine-derived poliovirus (VDPV2) outbreak was assessed in all tier 3 and 4 countries based on the following four risk factors:

##### **1. Estimated number of children under 5 years old susceptible to type 2 poliovirus**

Serotype 2 population immunity, the size of the birth cohort and routine immunization coverage were strongly correlated with cVDPV2 emergence and spread in Nigeria. In Tier 3 and 4 countries, routine immunization with a serotype 2 containing vaccine stopped in April 2016, and so routine immunization with polio vaccine is irrelevant from this point in time. The number of children under 5 years old without serotype 2 immunity in April 2017 was therefore estimated based on average serotype 2 population immunity levels in April 2016 in this age group (estimated using vaccination coverage data from children with AFP and campaign data), the number of children under 5 years old and the size of the birth cohort in each country.

##### **2. Child mortality rate as a proxy for poliovirus transmission efficiency (reproduction number)**

Some populations have historically been less likely to suffer large polio outbreaks. In Africa, a good predictor of (WPV) polio outbreaks is the under-five mortality rate, alongside other variables such as population immunity and exposure to migrants from endemic countries. This variable is likely to correlate with health care access and socioeconomic status of the population, and so is included as proxy for poliovirus transmissibility.

##### **3. Migration from countries with circulating VDPV2 (Nigeria, Pakistan, DRC and Syria in 2016-17)**

Travel to and from countries with cVDPV2 represents a risk of imported cVDPV2. Based on data from the UN Population Division, the number of permanent migrants by origin and destination (UN Population Division) can indicate the international spread of polio better than data on air travelers and tourists and other non-permanent movement (gravity models). In this model, the flow of migrants from Nigeria, Pakistan, DRC and Syria are classified as a risk for imported cVDPV2.

##### **4. Reported number of people with primary immunodeficiency shedding vaccine-derived poliovirus (iVDPV) during 2000-2012.**

Countries were scored for risk from iVDPV2 shedding using data from the WHO database on iVDPVs reported between January 2000 and April 2017.

### Scoring and outputs

Based on the above framework, countries were assigned a score for each risk factor based on their rank: top quartile scored 2 points, within the inter-quartile range scored 1, bottom quartile scored 0 points.

In the case of risk from iVDPV, scores were calculated differently: countries reporting an iVDPV case (any serotype) who continued to shed poliovirus were given a score of 2; those reporting iVDPV who had ceased shedding, died or whose status was unknown were given a score of 1; and all other countries were given a score of 0.

A total risk score was calculated by summing these scores, weighting the first risk factor (estimated number of children under 5 years old susceptible to type 2 poliovirus) more heavily by a factor of 3. Different weightings of the scores can change the overall ranking of a country.

**Based on the above methodology, countries among the Tier 3 and Tier 4 that are graded at highest risk of a serotype 2 vaccine-derived poliovirus (VDPV2) outbreak are, in order of priority: Iran, Egypt, Tanzania and Sudan.** These countries would benefit from immunization with IPV sooner than later, either through the routine programme or in a catch up<sup>1</sup> campaign if they are able to do fIPV.

#### Tier 3

	<i>Susceptibility</i>	<i>Transmission</i>	<i>Exposure</i>	<i>iVDPV</i>	<i>Total score from 12 (weighting susceptibility x3)</i>
Iran	2	0	2	2	10
Egypt	2	0	2	1	9
Sudan	2	1	1	0	8
Côte d'Ivoire	1	2	2	0	7
Burkina Faso	1	2	1	0	6
Burundi	1	1	2	0	6
Senegal	1	1	1	0	5
Eritrea	1	1	1	0	5
Nepal	1	0	1	0	4
Sierra Leone	0	2	1	0	3
Guinea-Bissau	0	2	0	0	2
Tajikistan	0	1	0	0	1
Turkmenistan	0	1	0	0	1

#### Tier 4

	<i>Susceptibility score</i>	<i>Transmission score</i>	<i>Exposure score</i>	<i>iVDPV score</i>	<i>Total score from 12 (weighting susceptibility x3)</i>
Tanzania	2	1	2	0	9
Viet Nam	2	0	1	0	7
Ghana	1	1	2	0	6
Rwanda	1	1	2	0	6
Togo	1	1	2	0	6
Zambia	1	1	1	0	5

<sup>1</sup> Catch up is defined as the immunization activity designed to reach and immunize with IPV those children that did not receive a type 2 containing vaccine since the switch date (globally considered as the 1 May 2016). If a country introduce in RI but does not conduct the catch up simultaneously, the cohort for the future catch up activity would be the cohort between 1 May 2016 until the day of national introduction in RI.



Malawi	1	1	1	0	5
Zimbabwe	1	1	0	0	4
Uzbekistan	1	1	0	0	4
DPR Korea	1	0	0	0	3
Lesotho	0	2	0	0	2
Swaziland	0	1	0	0	1
Sao Tome and Principe	0	1	0	0	1
Comoros	0	1	0	0	1
Djibouti	0	1	0	0	1
Gambia	0	1	0	0	1
Cape Verde	0	0	1	0	1
Bhutan	0	0	0	0	0
Kyrgyzstan	0	0	0	0	0
Mongolia	0	0	0	0	0
Moldova	0	0	0	0	0

Note on Tier 4 country analysis: immunity estimates were only available for Tanzania, Malawi, Gambia and Zambia. For all, other countries it was assumed that immunity is 50% and applied that to the under-5 population. Therefore, some countries that appear in the higher risk score may move to lower risk after estimation of true immunity which is expected to be higher than 50%

PAHO countries and countries that have currently vaccine have not been included in the above tables. For a full list of countries in each tier, see Annex 1

## Recommendations

1. The risk assessment model that has been used for slotting tentative timelines for supply allocation to countries. Countries at the highest risk are recommended for RI introduction as soon as supply is available. Countries are encouraged to consider fractional dose implementation and if so, supply could be slightly advanced in time.
2. The timelines are the based on the “maximum supply requirement”, this is, that is based on all countries using full dose and therefore, not conducting catch up campaigns at this time as there is not enough supply to cover routine introductions and catch up with full dose. Catch up can only be considered at present if conducted by fractional dose, due to the supply constraints mentioned.
3. Full dose catch ups will not be possible until 2019 (exact timelines to be confirmed during 2018). The SAGE WG, meeting in Geneva in September 2017, will discuss on this issue and might make additional recommendations on the catch up activities.
4. WHO and UNICEF should prepare clear communications to relevant countries to share the revised timelines and global plans and to guarantee that countries will be prepared to introduce when vaccine becomes available.

## Annex 1: Complete lists of Tier 3 and 4 countries

### Tier 3

Bangladesh	SEAR
Burkina Faso	AFR
Burundi	AFR
Cote d'Ivoire	AFR
Egypt	EMR
Eritrea	AFR
Guinea-Bissau	AFR
Iran	EMR
Nepal	SEAR
Senegal	AFR
Sierra Leone	AFR
Sudan (the)	EMR
Tajikistan	EUR
Turkmenistan	EUR
Thailand	SEAR

### Tier 4

Albania	EUR	Maldives	SEAR
Algeria	AFR	Mauritius	AFR
Antigua and Barbuda	AMR	Mongolia	WPR
Argentina	AMR	Morocco	EMR
Bahamas (the)	AMR	Namibia	AFR
Barbados	AMR	Nauru	WPR
Belize	AMR	Nicaragua	AMR
Bhutan	SEAR	Panama	AMR
Bolivia	AMR	Paraguay	AMR
Botswana	AFR	Peru	AMR
Cabo Verde	AFR	Republic of Moldova	EUR
Chile	AMR	Rwanda	AFR
Colombia	AMR	Saint Kitts and Nevis	AMR
Comoros (the)	AFR	Saint Lucia	AMR
Cook Islands	WPR	Saint Vincent and the Grenadines	AMR
Cuba	AMR	Samoa	WPR
Djibouti	EMR	Sao Tome and Principe	AFR
Dominica	AMR	Serbia	EUR
DPR Korea	SEAR	Seychelles	AFR
Ecuador	AMR	Solomon Islands	WPR
El Salvador	AMR	Sri Lanka	SEAR
Fiji	WPR	Suriname	AMR
Gambia (the)	AFR	Swaziland	AFR
Georgia	EUR	Macedonia	EUR
Ghana	AFR	Togo	AFR
Grenada	AMR	Tonga	WPR
Guatemala	AMR	Trinidad and Tobago	AMR
Guyana	AMR	Tunisia	EMR
Honduras	AMR	Tuvalu	WPR
Jamaica	AMR	Tanzania	AFR
Kazakhstan	EUR	Uzbekistan	EUR
Kiribati	WPR	Vanuatu	WPR
Kyrgyzstan	EUR	Venezuela	AMR
Lesotho	AFR	Viet Nam	WPR
Libya	EMR	Zambia	AFR
Malawi	AFR	Zimbabwe	AFR

## Cessation Risk Assessment Meeting, June 13-14, 2017: Summary

### Attendees:

BMGF: Jay Wenger, Ananda Bandyopadhyay, Apoorva Mallya, John Modlin (via phone), Arie Voorman (secretariat)

CDC: Mark Pallansch, Steve Wassilak, John Vertefeuille, Steve Cochi

UNICEF: Phil Smith, Ian Lewis

WHO: Rolland Sutter, Graham Tallis, Arshad Quddus, Hiro Okayasu, Ondrej Mach (via phone)

Imperial College: Nick Grassly, Natalie Molodecky, Isobel Blake

IDM: Hil Lyons, Mike Famulare, Steve Kroiss, Kevin McCarthy

Kid Risk: Rad Tebbens, Kim Thompson

Independent: Brent Burkholder

### Key Outcomes:

#### 1. OPV2-Cessation progress, based on data available to date

##### Summary:

- Isolation of Sabin 2 strains rapidly declined following the switch in most countries, based on available environmental and AFP surveillance data, and in the past six months most countries have not isolated any Sabin 2 or VDPV2.
- However, there have been 5 cVDPV2 outbreaks that likely originated from vaccine used before OPV2 cessation, compared to 3 or fewer cVDPV2 outbreaks which were forecast by IDM and used by the GPEI for budget and vaccine planning. These occurred largely in areas which had a high rate of VDPV emergences in the pre-cessation era, and likely had insufficient tOPV immunization prior to the switch.
  - Stopping these and possible future cVDPV2 outbreaks with an aggressive mOPV2 response should be a priority for the GPEI. Failure of the initial outbreak response will result in the need for more prolonged and possibly larger responses made more difficult by limited availability of mOPV2 and declining mucosal immunity to Type 2 poliovirus (See key point #2).
  - In addition to the 5 cVDPV2 outbreaks that likely originated from vaccine used before OPV2 cessation, 1 cVDPV2 outbreak may have originated from unauthorized tOPV use after OPV2 cessation, which highlights the need for further efforts to remove tOPV from all vaccine supply chains.
- The CRTT anticipates fewer new VDPV2 emergences in the coming year due to vaccine used in the pre-switch era. However, the number of new emergences from any source will likely be higher than originally forecast due to the need to use mOPV2 to stop serotype 2 transmission in some areas and the possibility of unauthorized tOPV use leading to cVDPV2s, and the GPEI should be prepared for at least 1 large scale mOPV2 response in a new area in addition to ongoing responses to current outbreaks.
- Maintaining a current mOPV2 stockpile of 150mds of finished mOPV2 and 500mds of bulk mOPV2 appears adequate for outbreak response over the next 2-3 years, unless the GPEI fails to use the available mOPV2 stockpile to stop outbreaks. Long-term vaccine forecasts will be developed depending on further evaluation of scenarios the program will need to be prepared for (region or country-wide responses, regional or global OPV2 re-introduction, etc).

- Based on the above review of the data, it is too early to conclude whether the program is on track to succeed in stopping all Type 2 transmission following the switch. The outcome of the current round of outbreak responses is unclear, and additional epidemiologic evaluation will be critical over the next 6-12 month period.

## Discussion

Isolation of Type-2 poliovirus declined dramatically after tOPV was withdrawn from global use in April 2016. As of Jun 13, in 2017 only 13 countries have isolated a Type-2 poliovirus (Figure 1).



Figure 1: Countries isolating Type 2 Poliovirus in 2017: Afghanistan (aVDPV2, SL2), Azerbaijan (SL2), Cameroon (SL2), Chad (SL2, aVDPV2), DRC (cVDPV2), Egypt (iVDPV2), India (aVDPV2), Mozambique (aVDPV2), The Netherlands (WVP2), Niger (SL2), Nigeria (i,aVDPV2, SL2), Pakistan (VDPV2, SL2), Syria (cVDPV2).

However, it was anticipated that VDPV2 events would be detected after cessation due to OPV2 used in the pre-cessation era. The GPEI planned for 0-3 cVDPVs outbreaks in the first year after cessation, assuming that high-quality tOPV SIAs would reduce the chances of outbreaks (Table 1). However, in this period we observed 6 cVDPV outbreaks in 4 countries: Nigeria (2), Pakistan, DRC (2), and Syria (Figure 2). These have occurred in areas with chronically poor immunity and a history of cVDPV emergences, often attributed to inaccessible/partially inaccessible populations. In Pakistan and Nigeria, co-circulation of WPV1 has complicated the outbreak response. At least 3 of these outbreaks (DRC (2), Syria) will continue into the second year after cessation, requiring mOPV2 response. It is unclear whether the outbreaks in Nigeria and Pakistan have been controlled by campaigns already conducted.

In addition, there have been 13 ambiguous or unclassified VDPV2 emergences in 8 countries and 6 iVDPVs in 5 countries attributable to pre-cessation tOPV use. The GPEI had anticipated 4 – 25 separate aVDPV emergences, most of which wouldn't require an mOPV2 response. While each isolation is concerning, the occurrence of ambiguous or unclassified VDPV2s appears roughly in line with expectations.

mOPV2 outbreak responses have either been conducted or planned in 8 countries, requiring release of 79mds of mOPV2. The target population of the responses varied from 200,000 (Mozambique) to 48 million (Nigeria and Lake Chad). These SIAs have resulted in additional SL2 isolates inside and outside the response region, as would be expected in vaccine recipients and their contacts. Isolation of SL2 has declined after the mOPV2 response mostly as expected. This fits with the projection at the last CRTT

meeting that mOPV2 would continue to be safe to use and would not persist outside the response region, at least in the first 18-24 months following cessation.

Multiple aVDPVs have been found in areas of mOPV2 response in Nigeria and Pakistan, some of which are linked but do not meet the technical criteria for cVDPV classification. These are extremely concerning and should be carefully investigated. If circulation is established, it would indicate a low-quality response which not only may have not have interrupted transmission of the original cVDPV2 virus, but possibly seeded new cVDPV. These may require further mOPV2 use in those areas, and underscore the urgent need for high quality mOPV2 responses that achieve high type 2 immunity across the entire response region. However, also note that most of these aVDPV have been found in environmental surveillance (ES); it is possible that some VDPV isolates may be expected in ES in the response region during the course of a successful outbreak response.

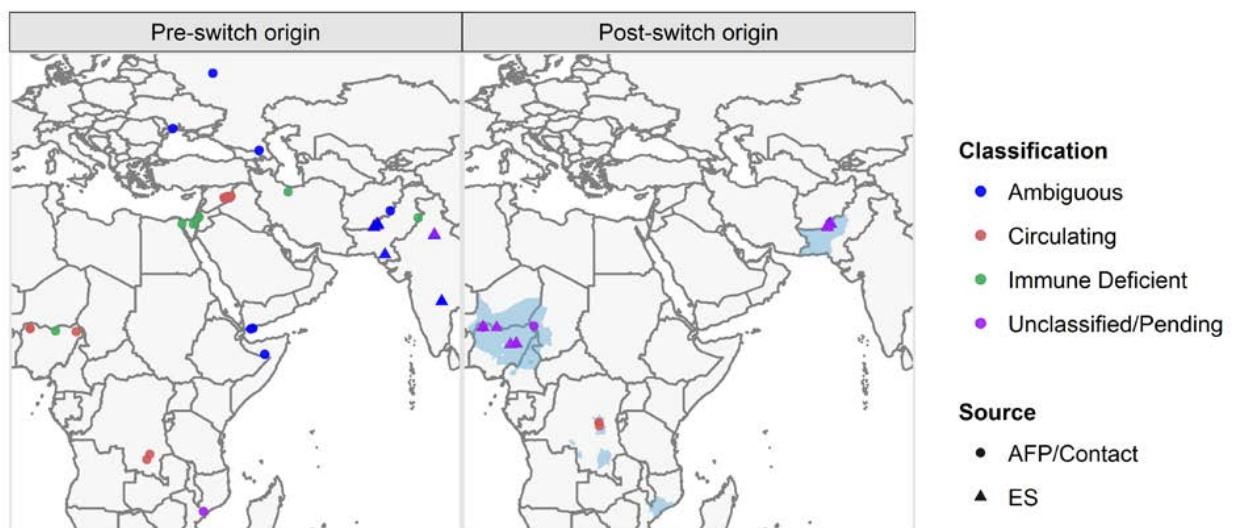


Figure 2: VDPV2 events detected post-cessation. Those with likely post-switch source are overlaid with mOPV2 response areas (blue shading).

The number of cVDPV outbreaks has been higher than anticipated in the first year following cessation, while the number of aVDPV events attributable to pre-switch tOPV use has been largely as expected. The number of VDPV2 events following mOPV2 responses was also higher than anticipated. The possibility that one cVDPV2 outbreak (Maniema, DRC) was due to illicit tOPV use post-cessation also highlights the risk of emergence elsewhere. Thus, the CRTT anticipates that both ongoing cVDPV2 outbreaks and new emergences of cVDPV will require mOPV2 vaccination responses in the second year after tOPV cessation. While a conservative estimate of the number of new outbreaks is likely above the two that were forecast, there was no consensus on a conservative upper bound. Experience from the first year after cessation is suggestive that these may be in areas of chronically poor immunization.

Vaccine and resource planning should include ongoing responses in 6 cVDPV2 outbreak zones, at least 1 large scale cVDPV2 outbreak in a new area, and additional smaller scale outbreaks. A stockpile of 150 million finished doses and corresponding financial and human resources should be sufficient for this in the short-term (for the next 2 years), but more bulk and/or semi-finished mOPV2 may be needed for longer-term contingency planning.

Table 1: Predicted vs Observed VDPV events in first year after cessation

	cVDPV outbreaks		Ambiguous or unclassified VDPV emergences		iVDPV
Virus Source	Pre-switch	Post-switch	Pre-switch	Post-switch	Pre-switch
Forecast	0 - 3	- NA	4 – 25	- NA	- NA
Observed	5 (4 countries)	1*	13 (8 countries)	14 (3 countries)	6

\*While the genetic characteristics of the cVDPV outbreak in Maniema, DRC may suggest OPV2 used post-switch, they are also compatible with a pre-switch origin.

## 2. Outbreak Response: experience and recommendations based on changing climate of risk

### Summary:

- Of the 35 events reviewed by the mOPV2 Advisory Group (AG), 6/6 cVDPVs and 4/29 VDPV2 events (Jigawa, Mozambique, Russia, Sokoto) elicited a recommendation for mOPV2 response. While it is still unclear whether responses were successful in controlling the outbreak virus, the CRTT had general comments:
  - None of the VDPV2 events have showed evidence of on-going circulation, irrespective of the response.
  - Speed, quality, and scope of the response varied widely. Some responses (Quetta, DRC) had concerning delays between AG recommendation of a response and implementation and issues related to quality.
  - Sabin 2 detection outside of the response regions was limited in most contexts, demonstrating the relative safety of mOPV2 use as an outbreak response tool.
  - Linked aVDPV2s within the response region are extremely concerning, particularly in Quetta. These highlight the risk of development of new cVDPV2s, as well as indicating a low-quality response which may have been insufficient to stop the original outbreak virus.
- For future responses, the CRTT had general comments:
  - **Circumstances for a vaccination response:** The CRTT supports the qualitative situational assessment approach used by the mOPV2 AG. cVDPV2s will continue to require an mOPV2 vaccination response. In areas where ambiguous or otherwise unclassified VDPV2s are considered a risk, resources and preparation for a high-quality response should be made for the event that circulation is established.
  - **Vaccine choice:** cVDPV2 events will continue to require an aggressive mOPV2 response. mOPV2 remains the only vaccine available that can prevent person-to-person transmission of type-2 poliovirus among un-immunized children. *Stopping the outbreak virus should outweigh concerns over the risk of using mOPV2.*
  - **Role of IPV:** The CRTT again reviewed the utility of IPV use in outbreak control in addition to mOPV2. While there was not unanimity on a position on its use, all agreed that use (if any) should be limited to special circumstances. IPV may have a role in 1) boosting intestinal immunity for OPV-exposed children and in 2) preventing paralysis. However, with mOPV2 already in use, only the very small fraction of IPV recipients who do not take to any of the mOPV2 doses but who do take to the IPV dose get protected from paralysis by IPV. Therefore, the benefit of adding IPV to VDPV2 response strategies in the current context appears to be limited the on-going supply constraints. The on-going supply constraints and risk of complicating the operational logistics of SIAs also limit its use.

- **Quality:** Good SIA quality was considered critical to control outbreaks and minimize the risk of creating new cVDPV2s (i.e. over the course of the OBR, the entire target population should be reached with high coverage). Speed remains critically important, but there was no explicit recommendation on the tradeoff between speed and quality of the first response SIA. Kid Risk stated that prior work showed that speed trumps coverage for the first round, as long as the subsequent rounds reach high quality.
- **Scope:** The scope of outbreak SIAs should be guided by the situation. However, as Type-2 immunity continues to decline, outbreak responses will generally need to be larger to prevent spread or stop possible transmission in linked populations.

## Discussion

The mOPV2 Advisory Group (AG) met approximately 59 times in the first year after cessation. cVDPV2 outbreaks required an mOPV2 response as suggested in the protocol. The majority of ambiguous or unclassified events (22/29) were considered low-risk and no vaccination response was recommended. This differs from the original protocol which had originally suggested a default mOPV2 vaccination response of 500,000 doses. However, this was not pursued in most areas since events were either relatively close to the switch (< 6 months), in areas of historically high immunity, or secondary to mOPV2 SIAs. Of those ambiguous or unclassified VDPV2 events where a response was recommended, 3 used IPV (Pakistan (Hyderabad), India (Hyderabad), and Yemen), while 4 used mOPV2 (Nigeria (Jigawa), Mozambique, Russia, and Nigeria (Sokoto)).

Those low-risk scenarios where vaccination wasn't carried out have not resulted in any further VDPV2 isolates to date. However, as new birth cohorts have no type-2 mucosal immunity and mucosal immunity in previously immunized individuals wanes, the immunity gap will be increasingly relevant. Risk assessments should consider this deteriorating immunity status when evaluating the potential for spread.

While there were fewer initial responses than planned, the scales of response in both the first and subsequent SIAs were larger than anticipated (Table 2). This was due to the Nigeria / Lake Chad response, where SIAs were conducted far outside the area of detection owing to estimated low immunity.

	Planned	Actual: Average (range)
SIA1 (n=8)	500k	1.3m (3k- 2.6m)
SIA2-3 (n=7)	2.3m	9.7m (612k-48.3m)

The diversity of outbreak responses to VDPV2s provides a considerable challenge for vaccine supply, management, and budgeting. However, modeling did not provide general rules for the appropriate scale of response. It was suggested by Imperial College that larger responses will be needed in areas of lower Type-2 mucosal immunity (Figure 3), implying that over time larger mOPV2 responses should be considered. Kid Risk results agree with this finding and also suggested the need for larger response to control outbreaks in areas with higher poliovirus transmissibility ( $R_0$ ). A failure to respond aggressively initially will ultimately create greater demand from the stockpile because it allows the outbreak to spread geographically.



## Optimal vaccination response to cVDPV2 outbreak in Pakistan and

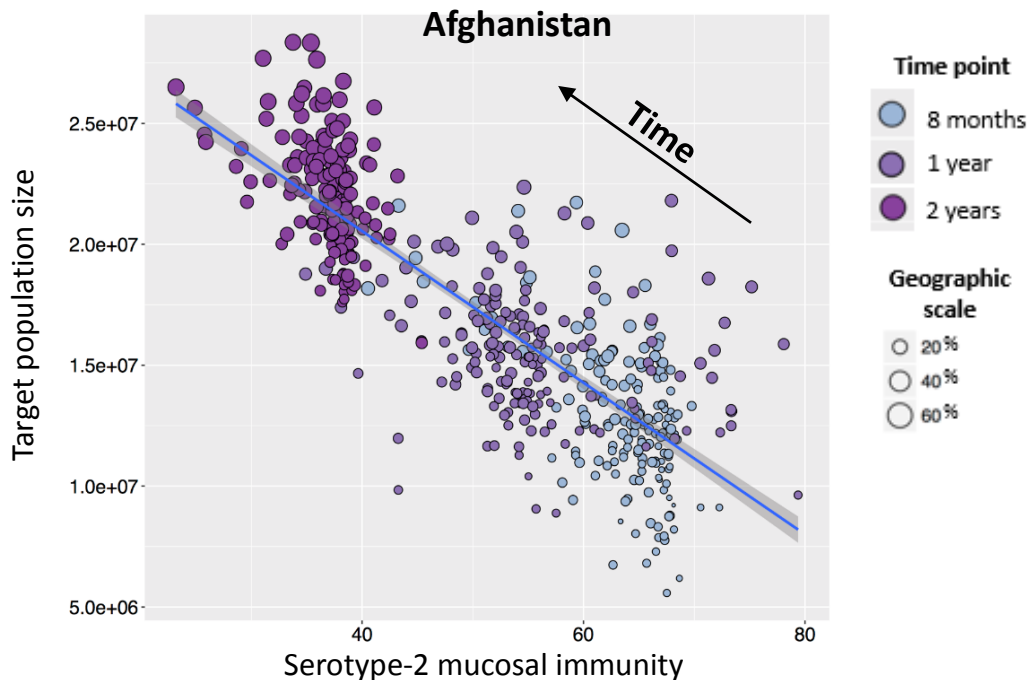


Figure 3: Optimal vaccination response size, as a function of Type-2 immunity in Pakistan. Points represent an outbreak originating in each of the 163 districts was simulated at 8, 12, and 24 months after cessation. (Imperial College London)

All groups agreed that mOPV2 is essential in controlling a cVDPV2 outbreak. While there is concern among the CRTT that mOPV2 used in outbreak response may spread and persist outside of the response area, the need to stop a cVDPV2 with mOPV2 continues to outweigh these concerns. It is the only vaccine available which can induce Type 2 mucosal immunity in naïve children, who are typically the majority of individuals who contribute to cVDPV2 transmission and are a growing demographic in the post-cessation era. IPV can boost mucosal immunity of individuals who have already been immunized with OPV2. However, groups were divided on whether IPV use would be beneficial in an outbreak response. Kid Risk and IDM have argued that the impact of IPV in outbreak response is minimal compared to mOPV2 and mOPV2 is easier to deliver. Imperial College has conducted an observational, retrospective analysis of data from Nigeria and Pakistan which suggested that the addition of IPV to tOPV may have reduced infection and disease in Nigeria, possibly by accessing populations that aren't reached in OPV-only campaigns, but not in Pakistan. However, the reported reduction in cases for Nigeria depended on the findings from a single district that only experienced cases before and not after a series of one tOPV+IPV SIA followed by multiple tOPV-only SIAs. In addition, simulations from Imperial College showed that IPV used outside the response region may help contain OPV2 used in the response. Kid Risk modeling suggests that it is better to expand the mOPV2 outbreak response areas than to use IPV around the response region.

The CRTT was unanimous that high quality of outbreak response campaigns is essential, though measurement and verification of sufficient outbreak response is difficult. The AG and WHO suggested that, while quantitative campaign quality measurements are often high, they are not always well-measured and in general don't include populations that are inaccessible or partially accessible by



vaccination programs. Some surveillance/virologic data do reflect on campaign quality. Disappearance of the outbreak virus is required to verify a sufficient response. In addition, the persistence of Sabin 2 viruses and cVDPV2 emergence following an mOPV2 use indicates a lower-quality or insufficient response. The emergence of linked aVDPV2s in Nigeria and Pakistan are thus concerning.

Kid Risk and IDM stressed that both the quality and number of SIAs should be emphasized, and expressed concern that the 2-SIA recommendation in the current outbreak response protocol does not sufficiently communicate the importance of the quality response.

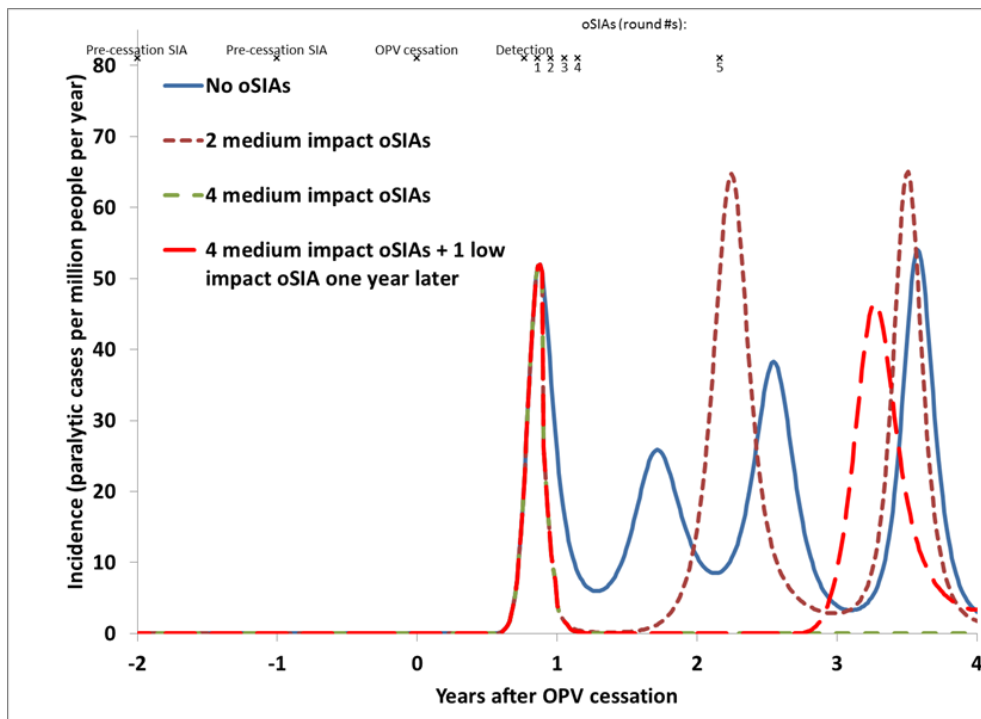


Figure 4: Importance of quality and the number of rounds in response to a cVDPV2 outbreak (Kid Risk. DOI: 10.1093/infdis/jit838.)

### 3. Conclusions on risk-mitigating and enabling activities

- **Collection and use of sequencing data:** It was agreed that genetic data should be shared among the key partner groups. An expanded data sharing agreement established by the WHO-DG should be investigated as a mechanism for greater sharing of these genetic sequences within the partnership. In addition to current sequencing data, whole-genome and/or next-generation sequencing could be useful in risk assessment.
- **Epidemiological context:** Those involved in the mOPV2 AG and outbreak response consistently recommended that existing epidemiological data could be optimized to better guide risk assessment. For instance, when dose histories are presented from NP-AFP cases, they should account for the likely type of vaccine received based on the child's age to provide serotype-specific estimates of population immunity.
- **Ad-hoc serosurveys:** It was recommended that a protocol for ad-hoc serosurveys be developed for rapid deployment. Possible uses include risk assessment for VDPV spread, measurement of immunological impact of an outbreak response campaign, or risk assessment of mOPV2 spread to surrounding areas.
- **Environmental surveillance outbreak guidelines:** A protocol for ad-hoc environmental surveillance was presented which is aimed at streamlining the process of enhancing ES following VDPV2 detection, or a subsequent response with mOPV2. The objective of such an approach is to assess evidence of continued circulation of the VDPV2, or to monitor the outbreak and/or vaccine virus circulation and new emergence following a vaccination response. Ensuring the quality of ad-hoc surveillance sites and managing increased lab and cost burden need to be explicitly addressed in the final plan. The CRTT supported continued work on this front to finalize and implement the protocol for enhanced ES for VDPV2 detection and response.
- **nOPV:** The CRTT noted the progress made in getting the new OPV2 into clinical trials, and expressed support for further clinical development to have a potentially safer alternative to mOPV2 for the long term.

### 4. Areas for future work

The CRTT discussed the following areas for further work. Another CRTT meeting will be held in 6 months (18-months post- OPV2 cessation). The primary purpose of the 18-month meeting will be to analyze SL2 and a/i/cVDPV2 evolution and persistence as mucosal immunity to Type-2 virus continues to decline and make appropriate recommendations for control/elimination of VDVP2 risks.

Several additional outstanding issues will be addressed through teleconferences prior to the 18 month meeting. These include:

- **Planning for OPV1,3 cessation.** The CRTT opened discussion on pre-bOPV cessation SIAs, vaccine management, stockpile needs, and their common characteristics with tOPV cessation. Maintenance of bOPV SIAs and intensification prior to cessation will decrease risk of cVDPV1,3 emergence and WPV1 importation outbreaks, and mOPV1,3 will need to be stockpiled in order to respond to outbreaks after cessation. However, additional work is needed for development of the strategy for bOPV cessation. Vaccine supply planning should be conservative enough to allow the possibility of both sustained bOPV SIAs and

mOPV1,3 stockpiles of a similar or larger order than mOPV2 for response activities after bOPV cessation.

- **Long-term stockpile planning** OPV needs to be available for outbreaks long after cessation, which have the potential to be large and even require OPV2 re-introduction. Several scenarios were discussed of varying size (<1 billion doses – 10 billion doses) and likelihood of each occurring. Quantifying which are most likely and what an appropriate response may be will require continued discussion at the CRTT. High-level input on long-term risk tolerance and budget will also be needed.
- **How to monitor SIA quality with virologic data.** CDC and IDM presented on the virologic characteristics of SL2 and VDPV2 emergences. Research from IDM suggested that genetic characteristics (synonymous vs non-synonymous mutation rates) could be used to inform risk assessments. Imperial College also suggested that deep-sequencing would be useful to characterize diversity of infections and number of infected individuals. How these laboratory and data analyses could be carried out and shared will be addressed in a future teleconference.
- **Indicators for countries to provide for the mOPV2 Advisory Group.** It was suggested that better use could be made of epidemiological data for the mOPV2 advisory group, and the CRTT will evaluate the currently available data and suggest a useful approach.
- **Further clarification on tradeoffs on SIA number/quality/speed.** While all modeling groups emphasized the need for sufficient quality, number, and speed of outbreak response, there was insufficient discussion around the tradeoffs between quality and speed of the first mOPV2 response, and how this relates to the immunity achieved by iteratively improving quality over multiple rounds. Prior work by Kid Risk suggested that speed trumps coverage for the first round, as long as the subsequent rounds reach high quality (Thompson et al., Risk Analysis 2006;26(6):1541-1556). Additional work will be done to make a useful recommendation on this issue.
- **Consolidated view on IPV utility in outbreaks.** While all agreed that mOPV2 would be needed to stop circulation of a VDPV2, the use of IPV was still debated. It was proposed that the CRTT come up with a consensus recommendation on IPV-use in outbreak response. The CRTT will review the model results and assess its impact on its previous recommendation to not prioritize IPV use in outbreak control.
- **Experience with mOPV2 SIA effectiveness.** The heterogeneity of speed, quality, and scope of mOPV2 SIAs should make it possible to evaluate effectiveness of different outbreak response strategies. However, it is too early to tell which have been effective in controlling the outbreak and preventing Sabin-2 persistence. The CRTT will continue to monitor outbreaks and recommend modifications in risk assessment and response strategies based on experience.



# Post-Certification Strategic Plan

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# Acronyms and Abbreviations

To be added with the final draft

## Executive Summary

To be developed with the third draft

### I. Statement of Intent

#### A. Purpose of the Plan

*The Post-Certification Strategic Plan (PCS)* provides recommendations for mainstreaming the essential functions for maintaining a polio-free world after global wild poliovirus eradication has been certified.

With certification of wild poliovirus (WPV) eradication, the global health community will mark an enormous achievement. Polio will be the second human vaccine-preventable disease (after smallpox) to be eradicated, and the first in the 21<sup>st</sup> century. Three decades ago, the World Health Assembly agreed to eradicate polio, and the Global Polio Eradication Initiative (GPEI) was founded in 1988. Since then, the GPEI has reduced the global incidence of polio by more than 99.9%, preventing paralysis and possibly death for more than 16 million people. In financial terms, polio eradication has saved more than US\$ 27 billion since 1988—and looking forward past eradication, an additional US\$ 20-25 billion is projected to be saved by 2035 through prevented treatment costs and gains in productivity.<sup>1</sup>

But a polio-free world is not just a world without polio; it's also a world made better by the effort needed to achieve eradication. This effort has taken the concentrated and coordinated work of all 194 WHO member states, private and public sector partners, over 140 laboratories within the GPEI Global Polio Laboratory Network (GPLN) that conduct disease surveillance for polio and beyond, 150,000 polio-funded frontline workers,<sup>2</sup> a network of more than 18,000 dedicated polio staff,<sup>3</sup> and millions of volunteers—including vaccinators, all of whom are critical for outbreak response, vaccination campaigns, routine immunization, and the delivery of a number of other primary healthcare services. Through this large-scale collaboration, the GPEI developed a strategy for reaching the world's most vulnerable in operationally challenging areas. But the GPEI has become more than a case study for targeting and eliminating disease; it has also broadly contributed to strengthening health systems by training public health staff, developing outreach strategies, and creating a comprehensive laboratory network linked to epidemiologic investigations of diseases that extend far beyond poliomyelitis.

<sup>1</sup> GPEI. Investment Case: Executive Summary. March 2017. <http://polioeradication.org/wp-content/uploads/2017/03/InvestmentCase.pdf>. See also Duintjer Tebbens RJ, Pallansch MA, Cochi SL, Wassilak SGF, Linkins J, Sutter RW, Aylward RB, Thompson KM. Economic analysis of the Global Polio Eradication Initiative. *Vaccine* 2011;29(2):334-343.

<sup>2</sup> GPEI. Investment Case: Executive Summary. March 2017.

<sup>3</sup> GPEI, the Bill and Melinda Gates Foundation and McKinsey & Company. Economic Case for Eradicating Polio. 2014. <http://polioeradication.org/wp-content/uploads/2016/07/EconomicCase.pdf>

While the achievement of global eradication merits recognition for the scale and scope of work it has required, the activities and functions that were critical for “getting the job done” must now be reimagined for the post-certification era in order to secure the gains of the GPEI and protect a polio-free world. As such, the Strategy Committee of the GPEI called for the development of a comprehensive plan to define the global strategies needed to sustain polio eradication after certification. The PCS fulfills this mandate by providing the technical standards for polio-essential functions that must remain in place post-certification (some for the short term, others indefinitely), as well as an organizational framework that outlines the governance and financing needed to sustain WPV eradication.

To solidify and protect the hard-won gains made through polio eradication, the PCS identifies the potential future risks jeopardizing polio eradication and defines the mitigating steps that must be taken to minimize and eliminate these risks, to the extent possible. These risk-mitigating measures are organized according to the three strategic goals:

- **Contain poliovirus sources:** Ensure potential polioviruses are properly controlled or removed
- **Protect populations:** Withdraw the oral live attenuated polio vaccine (OPV) from use and immunize populations with inactivated polio vaccine (IPV) against possible re-emergence of any poliovirus
- **Detect and respond:** Promptly detect any poliovirus reintroduction and rapidly respond to prevent transmission

Additionally, the PCS will provide a **set of enabling and cross-cutting recommendations** to ensure ongoing polio functions are either embedded in existing structures or in newly developed mechanisms to sustain the above goals. Other activities, functions, and knowledge which have been critical to achieving polio eradication may transition to support broader health programs.

## B. Plan Engagement, Audience, and Duration

The PCS is being developed through an iterative consultative process and extensive engagement with experts within and beyond the GPEI (See **Annex A** for *PCS Engagement List*). Such outreach is intended to provide stakeholders at the global, regional, and national level with opportunities to understand and provide input on the approach and elements of the strategy before its finalization. The PCS also draws upon programme-generated plans and guidelines to ensure that the strategy is data-driven and based on realistic needs, assumptions, and achievements, both past and future.<sup>4</sup>

The PCS is intended for use by core private- and public-sector partners, technical advisory groups of the GPEI and, more broadly, the future managers of global health—which will include new implementing agencies and donors outside of the GPEI. In the full course of its development, the PCS also provides broad strategic recommendations to the WHO Health Emergencies Programme (WHE), Expanded Programmes on Immunization (EPIs), and more generally for Ministries of Health (MoH).

<sup>4</sup> Such reports include: The Stockpile Requirements Plan by the Vaccine Supply Task Team (VSTT); bOPV Cessation Guidelines by the Immunization Systems Management Group (IMG); the Global Surveillance Plan by the Surveillance Task Team (STT), Environmental Surveillance Working Group (ESWG), and the Global Polio Laboratory Network (GPLN); and Outbreak Response Standard Operating Procedures by the Eradication and Outbreak Management Group (EOMG). *(Note: This will become an annex in future drafts.)*



The high-level technical standards and recommendations for mainstreaming polio-essential functions that are included in the PCS are offered as the last strategic phase of the eradication effort. To provide visibility into the strategy for polio-essential functions after global certification and to allow for the planning required, the PCS will be developed by the end of 2017. However, implementation of the high-level guidance contained in the PCS will not begin until after global certification of eradication, with the exception of specific activities that are required to start earlier in preparation of certification and bOPV withdrawal. (See **Annex B** for a summary of the prerequisites and assumptions that inform the PCS, and specifically its relation to existing workplans of the eradication effort.)

The PCS covers the period starting from an expected date of certification (2021) and extending for 10 years (2030). Depending on the epidemiology of poliovirus transmission after 2017, the GPEI, donors, and country governments will identify the need for adjustments in the end date of eradication and anticipated date of certification. Similarly, the PCS will require updates as risks to organizational, environmental, and programmatic factors change over time. While the PCS anticipates periods of revision—likely to include a year prior to certification, after bOPV cessation, and at the midterm of the PCS’s ten-year duration—it is the future owners of the PCS who will re-evaluate the plan, as and when appropriate.

## II. Background

The GPEI was launched in 1988 following a global commitment to polio eradication formalized in the Resolution from the World Health Assembly. Its founding partners—Rotary International, the World Health Organization (WHO), United Nations International Children’s Emergency Fund (UNICEF), and the Centers for Disease Control and Prevention (CDC), later joined by the Bill and Melinda Gates Foundation (BMGF)—provide the overall technical guidance, direction, and support to the implementation efforts led by countries around the world.

The current strategies for the GPEI were developed in 2012 to guide the final stages of polio eradication. The **Polio Eradication and Endgame Strategic Plan 2013-2018** (PEEPS), also referred to as the endgame strategy, defined four objectives: 1) to detect and interrupt poliovirus transmission, 2) to strengthen immunization systems and coordinate OPV withdrawal, 3) to implement poliovirus containment and certify global polio eradication; and 4) to begin transition planning for the post-eradication era.<sup>5</sup> In 2015, an in-depth **Midterm Review** validated the core strategies as appropriate to eradicate polio even as it extended the timeline by a year due to challenges posed by access and security risks in the last remaining endemic countries.<sup>6</sup>

The PCS provides a strategic vision for a key provision of transition planning, the fourth objective of the endgame strategy, particularly as it is situated in relation to broader global health strategies.

<sup>5</sup> GPEI, WHO. Polio Eradication & Endgame Strategy 2013-2018. February 2013. [http://polioeradication.org/wp-content/uploads/2016/07/PEESP\\_EN\\_A4.pdf](http://polioeradication.org/wp-content/uploads/2016/07/PEESP_EN_A4.pdf)

<sup>6</sup> GPEI, WHO. Polio Eradication & Endgame Midterm Review. July 2015. [http://polioeradication.org/wp-content/uploads/2016/07/GPEI-MTR\\_July2015.pdf](http://polioeradication.org/wp-content/uploads/2016/07/GPEI-MTR_July2015.pdf)

## 1. The Role of the PCS within Global Health Strategies

With the historic milestone of WPV eradication and the significance it holds for global health, it is important to situate the PCS within broader global public health regulations, specifically the International Health Regulations (IHR). The IHR provides a foundational premise that a “health threat anywhere is a health threat everywhere.” With globalization and the risk for the international spread of dangerous pathogens, the IHR puts forward global regulations that direct countries to detect, assess, report, and respond to public health events without interfering or interrupting international travel and trade.<sup>7</sup>

In addition to a focus on the core objectives of protection, detection, and response, the IHR calls for the multilateral, multi-sectoral coordination to strengthen country, region, and global capacity for international health concerns and health security risks. Such multi-sectoral, multilateral coordination is also central to the PCS as it provides recommendations for polio-essential functions that must be mainstreamed by agencies and countries, and ultimately resides under the umbrella of the IHR to ensure global health security.

In a post-certification world, polio will be both a pathogen that presents risks to global security and an ongoing part of routine immunization programmes. As such, the recommendations of the PCS share in the principles of the Global Vaccine Action Plan (GVAP), a framework for global equity through universal access to immunization.<sup>8</sup> The GVAP framework provided a focus on equity for the development of the PCS, particularly in relation to the risks of different countries and regions. GVAP was designed to strengthen routine immunization to meet vaccination coverage targets; accelerate control of vaccine-preventable diseases with polio eradication as its first milestone; and introduce new and improved vaccines and spur research and development for the next generation. As polio eradication fulfills one of the goals put forward by GVAP, and as the Decade of Vaccines comes to a close with a possibility of extension into the next decade, GPEI partners will engage with other GVAP stakeholders on how to best keep polio-essential functions within the future framework that succeeds the 2011–2020 plan.

## 2. The Role of the PCS within Transition Planning

The work of the PCS is also part of a larger coordinated transition planning effort that addresses the eventual changes with global certification of eradication and the closure of the GPEI.<sup>9</sup>

Transition planning has three goals:

- Goal One: Maintain and mainstream polio-essential functions after eradication has been certified, to protect a polio-free world
- Goal Two: Where feasible, desirable and appropriate, transition the capacities, processes, and assets that the GPEI has created to support other health priorities
- Goal Three: Capture and disseminate the lessons of polio eradication

<sup>7</sup> WHO. International Health Regulations, third edition. 2016. <http://www.who.int/ihr/publications/9789241580496/en/>

<sup>8</sup> WHO. Global Vaccine Action Plan 2011-2020. May 2012. [http://www.who.int/immunization/global\\_vaccine\\_action\\_plan/](http://www.who.int/immunization/global_vaccine_action_plan/)

<sup>9</sup> See GPEI. Transitioning Planning Framework. March 2017.

The PCS fulfills *Goal One* by providing global standards and guidelines to maintain polio-essential functions post-certification, specifically by identifying the financial requirements and technical assistance infrastructure needed after global certification of WPV eradication.

## IV. Certification and the Path Forward

### 1. Global Certification

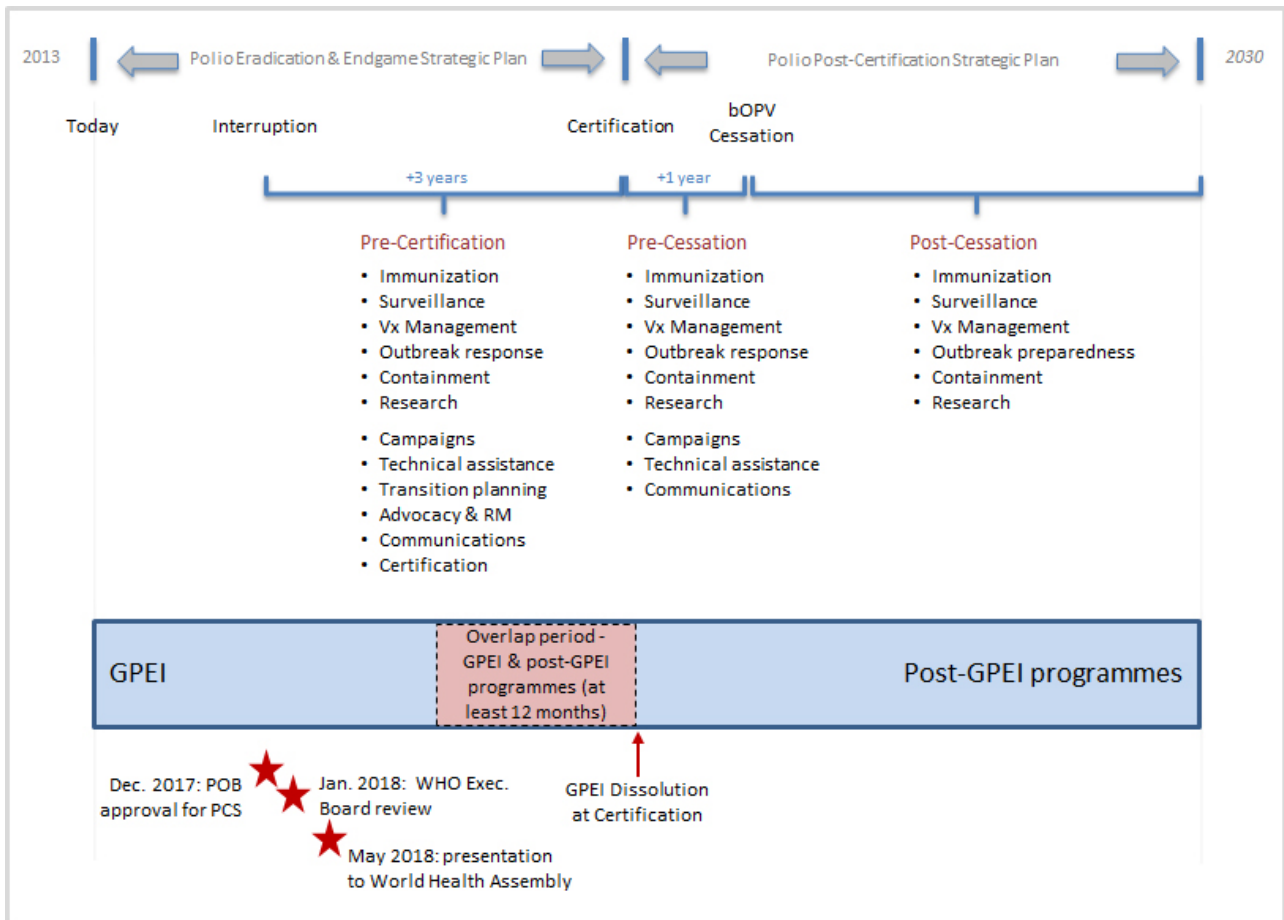
Regions can consider certification of WPV eradication only when all countries in the area demonstrate the absence of wild poliovirus transmission for at least three consecutive years in the presence of certification-standard surveillance. The Region of the Americas was first to receive certification in 1994, followed by the Western Pacific Region (2000) and the European Region (2002). The last region to be certified was the South-East Asian Region, with the last case detected on 13 January 2011 in India and regional certification granted on 27 March 2014. Regions that have yet to receive certification due to endemic transmission in Afghanistan, Pakistan, and Nigeria are the Eastern Mediterranean Region and the African Region.

Comprised of public health and scientific experts, Regional Certification Commissions (RCCs) independently verify polio eradication for all countries in the region. They are supported by National Certification Commissions (NCCs) that collect, review, and decide on national documentation through consultations. After regional certification, the Global Certification Committee (GCC) oversees the global certification process, receives and reviews regional commission reports and – if and when appropriate – will issue a report to the WHO Director-General to certify that the circulation of wild polioviruses has been interrupted globally.

Placeholder: This is a general discussion in need of requirements for global certification and the process to global certification, and messaging on how VDPV certification will be handled after WPV certification.

### 2. Post-Certification Timeline

Transition planning has already been initiated except for the endemic countries. As the last WPV cases are identified, GPEI will accelerate efforts to transition responsibilities to other groups as it prepares for the closure of its partnership. The programme has facilitated a large number of functions that have been essential to reach this stage of global eradication. As the programme moves forward, it will phase out its support for previously essential functions which are no longer needed, based on consensus among the partnering agencies around polio activities, the achievement of key indicators or outcomes, and the assessment of any related risks and mitigation strategies needed to support the work of maintaining a polio-free world. (See **Figure 1**: *Polio essential functions mapped across post-certification intervals*).



**Figure 1: Polio-essential functions mapped across post-certification intervals**

The PCS will identify elements of a governance structure that will be needed to support functions during each post-certification interval. The GPEI as an organizational entity will dissolve at certification, but many of the same agencies will still be engaged with implementing the strategies required at the global level. As part of transition planning, each partner agency has its own transition planning group. Additionally, national governments are responsible for their own country-level transition planning by developing implementation plans that include the mobilization of resources to mainstream polio-essential functions and achieve the standards laid out in the PCS.

## Virologic Monitoring of Poliovirus Type 2 after Oral Poliovirus Vaccine Type 2 Withdrawal in April 2016 — Worldwide, 2016–2017

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The Global Polio Eradication Initiative (GPEI) has made substantial progress since its launch in 1988; only 37 wild poliovirus type 1 (WPV1) cases were detected in 2016, the lowest annual count ever. Wild poliovirus type 3 has not been detected since November 2012, and wild poliovirus type 2 was officially declared eradicated in September 2015. This success is attributable to the wide use of live oral poliovirus vaccines (OPVs). Since 2001, numerous outbreaks were caused by the emergence of genetically divergent vaccine-derived polioviruses (VDPVs) whose genetic drift from the parental OPV strains indicates prolonged replication or circulation (1). In 2015, circulating VDPV type 2 (cVDPV2) outbreaks were detected in five countries worldwide (Nigeria, Pakistan, Guinea, Burma, and South Sudan), and VDPV2 single events were reported in 22 countries. These events prompted the GPEI to withdraw the type 2 component (Sabin2) of trivalent OPV (tOPV) in a globally coordinated, synchronized manner in April 2016 (2,3), at which time all OPV-using countries switched to using bivalent OPV (bOPV), containing Sabin types 1 and 3. This report details for the first time the virologic tracking of elimination of a live vaccine that has been withdrawn from routine and mass immunization systems worldwide (3). To secure elimination, further monitoring is warranted to detect any use of tOPV or monovalent OPV type 2 (mOPV2).

### The Global Polio Laboratory Network

The Global Polio Laboratory Network (GPLN) comprises 146 World Health Organization (WHO)–accredited poliovirus laboratories in 92 countries located in the six WHO regions (4). GPLN member laboratories follow standardized protocols to isolate poliovirus using sensitive and specific cell lines, conduct intratypic differentiation to identify WPVs, Sabin (vaccine) polioviruses, or screen for VDPVs, and conduct genomic sequencing. Sequencing results help monitor pathways of poliovirus transmission by comparing the nucleotide sequences of the capsid protein VP1-coding regions of poliovirus isolates. The GPLN processes approximately 200,000 specimens from cases of acute flaccid paralysis (AFP) each year and provides timely results to direct GPEI actions. The accuracy and quality of testing at GPLN member laboratories is monitored through an annual accreditation program that includes on-site reviews of work practices, performance, and proficiency testing (5).

### Surveillance Systems

GPLN laboratories provide support to different polio surveillance systems, including AFP surveillance, environmental surveillance (testing of sewage samples), and enterovirus surveillance (testing of patients with specific clinical illness caused by enteroviruses). These surveillance systems ensure sensitive and timely detection of circulating polioviruses worldwide. Whereas AFP surveillance has been the standard surveillance system for poliovirus since the beginning of the GPEI, recently, existing environmental surveillance for poliovirus has been expanded (6) in countries with endemic poliovirus transmission and in countries designated as countries at high risk for WPV importation and circulation and/or VDPV emergence. During the last 5 years, 11 laboratories dedicated to environmental surveillance were established in Bangladesh, Cameroon, Côte d'Ivoire, Senegal, South Africa, Indonesia, Jordan, Kenya, Madagascar, Niger, and the Philippines; equipment and supplies were procured by WHO and field and laboratory personnel were trained by GPLN (7). This infrastructure, combined with the existing environmental surveillance system and AFP surveillance, has been used to monitor Sabin type 2 virus circulation after worldwide OPV2 withdrawal in April 2016.

### Detection of Type 2 Polioviruses

Before OPV2 withdrawal, mass immunization campaigns using tOPV were conducted in OPV-using countries, to ensure that sufficiently high levels of immunity against poliovirus type 2 (PV2) were achieved in all countries. From January to April 2016 (before the global switch from tOPV to bOPV), 46 countries were reporting PV2 detected by GPLN laboratories from specimens from persons with AFP or their contacts and sewage samples (Table). From May to August 2016 (during the early switch period), the number of countries reporting PV2 declined to 22; from September to December 2016, eight countries reported isolation of PV2, and from January to March 2017, seven countries (Afghanistan, Cameroon, Chad, Mozambique, Niger, Nigeria, and Pakistan) reported PV2 detection.

Field investigations in response to detection of PV2 after the switch found breaches in OPV2 withdrawal with evidence of continued inadvertent use of tOPV in India (8), Pakistan, Afghanistan, Russia, Iraq, Nigeria, and Cameroon. Response

TABLE. Countries that have reported isolating poliovirus type 2 (PV2) from persons with acute flaccid paralysis or their contacts and from sewage samples, January 2016–March 2017

Countries	Human specimens				Sewage samples			
	2016			2017	2016			2017
	Jan–Apr (pre-switch)	May–Aug (early post-switch)	Sep–Dec (post-switch)	Jan–Mar	Jan–Apr (pre-switch)	May–Aug (early post-switch)	Sep–Dec (post-switch)	Jan–Mar
<b>mOPV used post-switch (six countries)</b>								
Cameroon	4	—	1	14	—	—	—	—
Chad	3	—	—	7	—	—	—	1
Mozambique	—	—	—	1	—	—	—	—
Niger	8	—	1	6	—	—	—	1
Nigeria	341	64	26	103	123	65	24	196
Pakistan	42	4	—	5	99	14	3	29
<b>No. of countries/No. of isolates</b>	<b>5/398</b>	<b>2/68</b>	<b>3/28</b>	<b>6/136</b>	<b>2/222</b>	<b>2/79</b>	<b>2/27</b>	<b>4/227</b>
<b>mOPV not used post-switch (44 countries)</b>								
Afghanistan	22	1	1	—	16	—	—	1
Algeria	1	—	—	—	—	—	—	—
Angola	1	—	—	—	—	—	—	—
Azerbaijan	1	—	—	—	—	—	—	—
Bahrain	1	—	—	—	—	—	—	—
Bangladesh	1	—	—	—	—	—	—	—
Benin	1	—	—	—	—	—	—	—
Bhutan	1	—	—	—	—	—	—	—
Bosnia and Herzegovina	1	3	—	—	—	—	—	—
Burkina Faso	15	—	—	—	—	—	—	—
Burma	2	—	—	—	—	—	—	—
Central African Republic	2	1	—	—	—	—	—	—
Republic of the Congo	1	1	—	—	—	—	—	—
Côte d'Ivoire	5	—	—	—	—	—	—	—
Democratic Republic of the Congo	54	—	—	—	—	—	—	—
Egypt	8	1	—	—	—	—	—	—
Ethiopia	15	2	—	—	—	—	—	—
Guinea	40	3	—	—	—	—	—	—
India	345	7	—	—	13	53	4	—
Indonesia	15	1	—	—	—	—	—	—
Iran	—	1	—	—	—	—	—	—
Iraq	20	—	2	—	—	—	—	—
Israel	—	—	—	—	1	—	—	—
Kazakhstan	—	—	—	—	2	—	—	—
Kenya	3	—	—	—	22	3	—	—
Madagascar	26	—	—	—	6	10	—	—
Moldova	—	—	—	—	1	3	—	—
Mali	11	—	—	—	—	—	—	—
Morocco	1	—	—	—	—	—	—	—
Nepal	2	—	—	—	—	—	—	—
Russia	7	4	2	—	3	5	1	—
Senegal	2	—	—	—	—	—	—	—
Sierra Leone	2	—	—	—	—	—	—	—
Somalia	7	2	—	—	—	—	—	—
South Sudan	10	5	—	—	—	—	—	—
Sudan	—	1	—	—	—	—	—	—
Syria	—	1	—	—	—	—	—	—
Thailand	1	—	—	—	—	—	—	—
Turkmenistan	2	—	—	—	—	—	—	—
Uganda	13	—	—	—	—	—	—	—
Ukraine	5	—	—	—	5	1	—	—
Tanzania	2	—	—	—	—	—	—	—
Yemen	5	2	—	—	—	—	—	—
Zimbabwe	1	—	—	—	—	—	—	—
<b>No. of countries/No. of isolates</b>	<b>38/652</b>	<b>16/36</b>	<b>3/5</b>	<b>0/0</b>	<b>9/69</b>	<b>6/75</b>	<b>2/5</b>	<b>1/1</b>
<b>Total all countries/All isolates</b>	<b>43/1,050</b>	<b>18/104</b>	<b>6/33</b>	<b>6/136</b>	<b>11/291</b>	<b>8/154</b>	<b>4/32</b>	<b>5/228</b>

Abbreviation: mOPV2 = monovalent oral poliovirus vaccine type 2.



to these breaches included development of guidelines for investigation and implementation of corrective actions to ensure the safe disposal of all tOPV vials. For example, in India, the National Polio Surveillance Program established a policy to replace any tOPV vial found in private clinics with two bOPV vials as an incentive for finding and reporting tOPV vials. All countries with PV2 detected in 2017 (except Afghanistan) conducted immunization campaigns using monovalent oral poliovirus vaccine type 2 (mOPV2) in response to cVDPV2 isolates detected in Pakistan and Nigeria. PV2 detected in Afghanistan was linked to the use of mOPV2 in a neighboring district of Pakistan.

During the pre-switch period (January–April 2016), PV2 was detected through both AFP and environmental surveillance; after the switch, PV2 was detected primarily through environmental surveillance (Figure 1) (Figure 2). In countries where mOPV2 was not used after the switch, few PV2 isolates were reported during September–December 2016, and 60% of the viruses detected were from sewage samples (Figure 1). Among 364 isolates detected in 2017, 228 (62.6%) were from sewage samples (Figure 1) (Figure 2).

To provide evidence concerning the origin and significance of circulating PV2, on August 1, 2016, GPLN laboratories began to refer all PV2s detected from all sources for genetic sequencing. Isolation of Sabin-like poliovirus with zero or few nucleotide differences from Sabin2 by GPLN laboratories

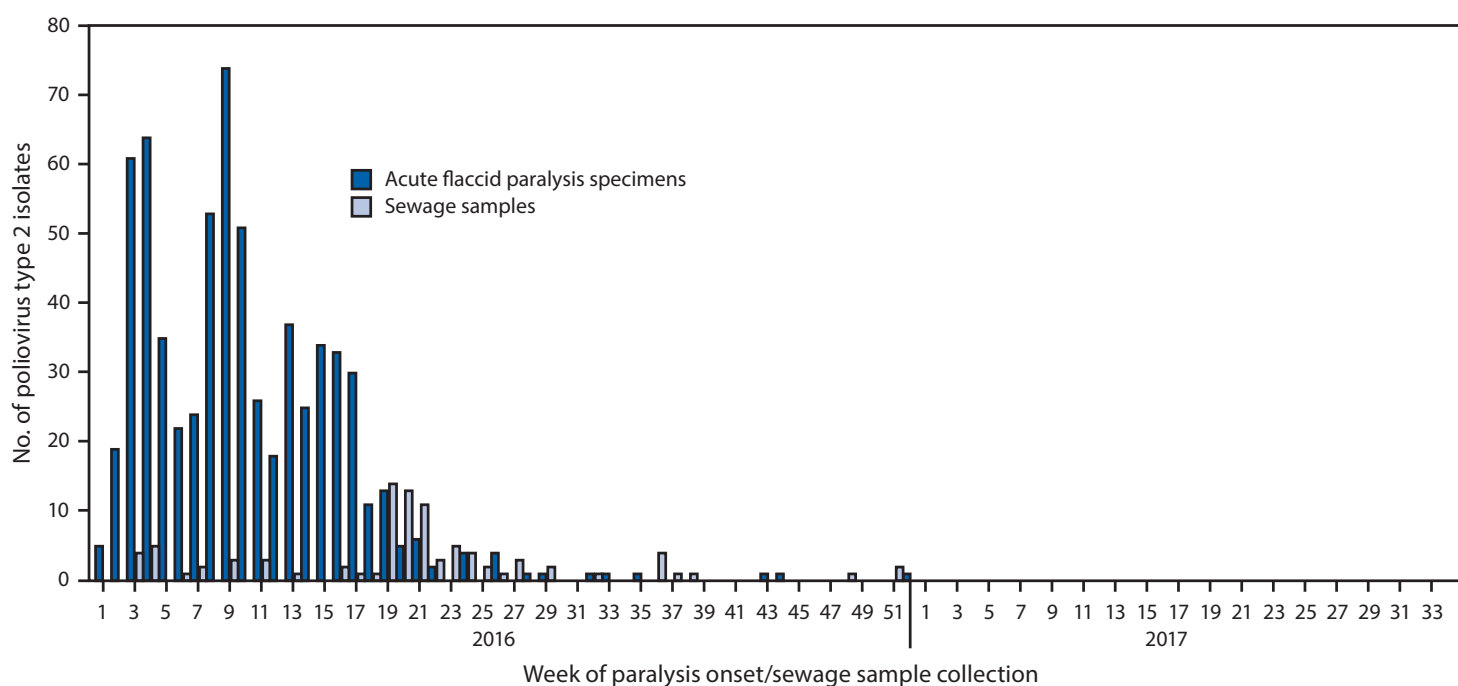
were instrumental in 1) identifying continued use of tOPV in some countries post-switch and in 2) confirmation of three post-switch cVDPV2 outbreaks caused by genetically related cVDPVs that began circulating before the switch.

### Discussion

Virologic monitoring through AFP cases and sewage samples indicate that withdrawal of a live vaccine, OPV2, used in routine immunization programs and mass immunization campaigns, was successfully accomplished by the GPEI. Some evidence of limited use of tOPV after the global tOPV to bOPV switch was found; however, 1 year after OPV2 withdrawal, PV2 has been isolated only in the few areas where mOPV2 has been used in response to detection of cVDPV2 isolates. By expanding the preexisting surveillance network to include environmental surveillance for polioviruses during the last 5 years, GPLN successfully detected VDPV2 emergences and outbreaks to allow GPEI to respond in a timely manner. AFP and environmental surveillance with laboratory testing for poliovirus by GPLN will continue to play a long-term, critical role in ensuring polio eradication (9).

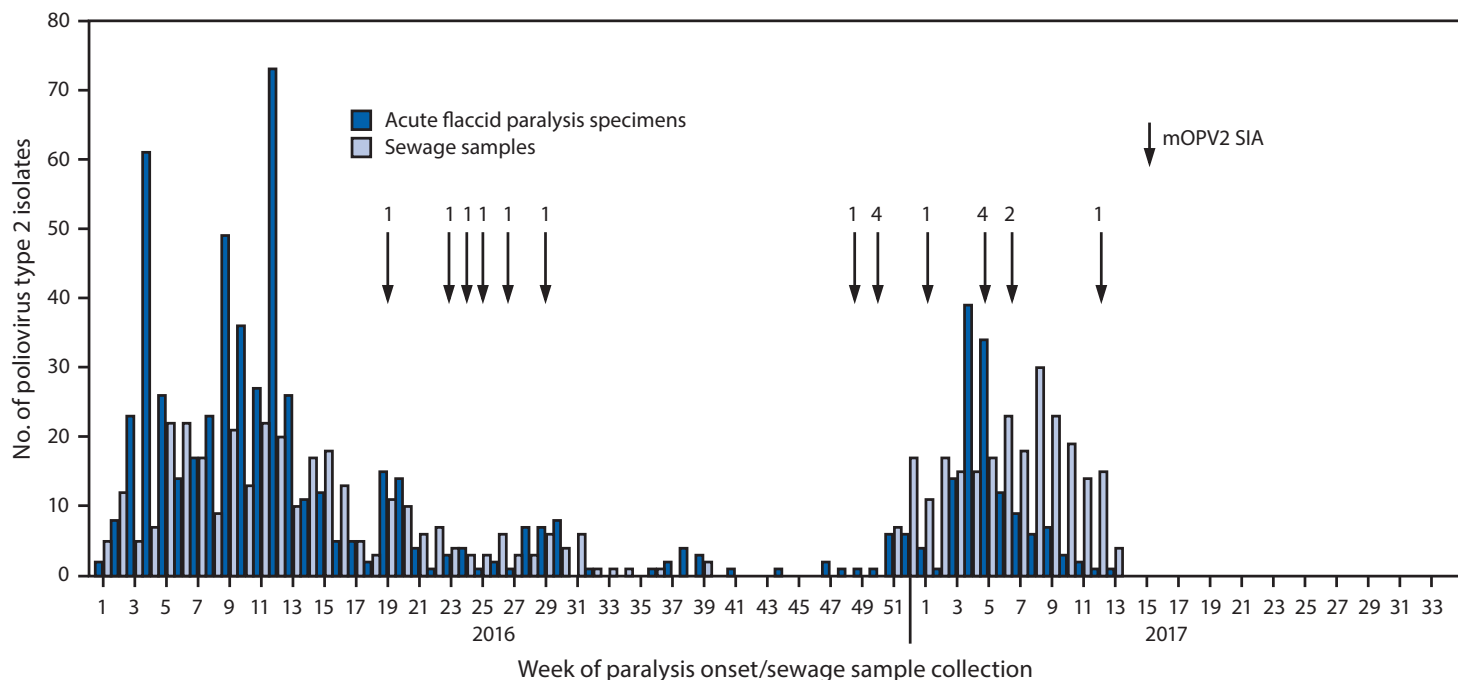
During the first year after the switch, although several emergences of VDPV2 occurred, including some in areas with low poliovirus immunity, such as Mozambique, only two new small-scale VDPV2 outbreaks were detected, in Sokoto, Nigeria, and Quetta, Pakistan, and mOPV2 was used to stop

**FIGURE 1. Number of poliovirus type 2 isolates from persons with acute flaccid paralysis or their contacts and from sewage samples in countries where mOPV2 was not used after the global synchronized switch from tOPV to bOPV — January 2016–March 2017**



**Abbreviations:** bOPV = bivalent oral poliovirus vaccine; mOPV2 = monovalent oral poliovirus vaccine type 2; tOPV = trivalent oral poliovirus vaccine.

FIGURE 2. Number of poliovirus type 2 isolates from persons with acute flaccid paralysis or their contacts and from sewage samples in countries where mOPV2 SIAs were conducted\* after the global synchronized switch from tOPV to bOPV — January 2016–March 2017



Abbreviations: bOPV = bivalent oral poliovirus vaccine; mOPV2 = monovalent oral poliovirus vaccine; SIA = supplementary immunization activity; tOPV = trivalent oral poliovirus vaccine.  
 \* Number of vaccination rounds shown for SIAs.

these outbreaks. However, it is noteworthy that ongoing persistent cVDPV2 transmission pre-switch was evidenced in Nigeria in April 2016 using environmental surveillance, and mOPV2 was used in Nigeria and in countries bordering Lake Chad (Cameroon, Chad, and Niger) to respond to this outbreak. Nigeria and Pakistan also have circulation of WPV1, and WPV1 circulation continues in Afghanistan.

Reintroduction of live PV2-containing vaccine through the use of 19 mOPV2 immunization campaigns to interrupt VDPV2 transmission in six countries (Cameroon, Chad, Mozambique, Niger, Nigeria, and Pakistan), from May 2016 to Mar 2017 has disrupted the goal of interrupting PV2 transmission globally after the switch. The GPEI has established a mOPV2 advisory group, which advises WHO about each use of mOPV2, after an in-depth review of risk assessments conducted after any VDPV2 event or outbreak detection. In countries where no type 2-containing vaccine has been used after the switch, only three countries (Russia, Iraq, and India) have reported VDPV2 detection since September 2016.

Environmental surveillance for polioviruses detected the majority of PV2 from September 2016 to March 2017. Detection and sequencing of polioviruses isolated from sewage samples is difficult because these isolates often represent

complex mixtures of viruses. Despite these challenges, further expansion of environmental surveillance is needed to maintain the high level of vigilance required to detect and respond to any type 2 poliovirus from all sources in the future, including breaches in containment in facilities retaining or still working with PV2 materials, including WPV2.

PV2s were tracked in both human specimens and sewage samples using a newly designed molecular diagnostic assay and algorithm developed by CDC (real-time reverse-transcription–polymerase chain reaction assay for intratypic differentiation of polioviruses), which was rapidly and efficiently implemented in GPLN laboratories in 2016. PV2 detection and genetic sequencing has been essential for the following: 1) providing evidence of continued use of tOPV after the withdrawal of this vaccine in April 2016; 2) identifying and following up unusual patterns of PV2 detection or circulation that signal gaps in herd immunity against PV2; and 3) classifying VDPV2s as either circulating viruses (cVDPV2s) or originating from immunodeficient persons (iVDPV2s), or of ambiguous origin (aVDPV2s) (10). The lessons learned and the innovative mechanisms used to monitor and respond to any detection of PV2 from all sources will be leveraged to monitor type 1 and 3 polioviruses after WPV1 eradication and bOPV cessation.



## Summary

### What is already known about this topic?

The Global Polio Eradication Initiative (GPEI) has made substantial progress since 1988; in 2016, only 37 wild poliovirus (WPV) type 1 (WPV1) cases were detected, the lowest number ever recorded. WPV type 2 has been eradicated, and WPV type 3 has not been detected since 2012. To reduce the risk for paralysis from infection with vaccine-derived polioviruses (VDPVs), in April 2016, all 155 oral poliovirus vaccine (OPV)-using countries switched from trivalent OPV (tOPV) to bivalent OPV (bOPV), containing vaccine virus types 1 and 3.

### What is added by this report?

After the withdrawal and destruction of tOPV, the GPEI devised mechanisms to monitor disappearance of type 2 polioviruses (PV2s) in human populations and the environment. Enhanced environmental surveillance and provision of clear guidance to the Global Polio Laboratory Network has allowed timely, accurate, and comprehensive detection of PV2 by examining approximately 208,000 stool specimens and sewage samples. Preceding the tOPV to bOPV switch (January–April 2016), 43 countries reported detection of PV2; during January–March 2017, the number of countries reporting PV2 had declined to seven.

### What are the implications for public health practice?

To prevent paralysis caused by VDPVs, elimination of vaccine viruses from the environment will be critical. Lessons learned from surveillance for PV2 after the global synchronized withdrawal of the PV2 component from vaccines have resulted in development of standardized procedures for investigation of PV2 detection in humans and the environment, and handling PV2 in diagnostic laboratories. These lessons will guide the elimination of OPV1 and OPV3 once eradication of polio has been certified.

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## Cessation of Trivalent Oral Poliovirus Vaccine and Introduction of Inactivated Poliovirus Vaccine — Worldwide, 2016

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Since the 1988 World Health Assembly resolution to eradicate poliomyelitis, transmission of the three types of wild poliovirus (WPV) has been sharply reduced (1). WPV type 2 (WPV2) has not been detected since 1999 and was declared eradicated in September 2015. Because WPV type 3 has not been detected since November 2012, WPV type 1 (WPV1) is likely the only WPV that remains in circulation (1). This marked progress has been achieved through widespread use of oral poliovirus vaccines (OPVs), most commonly trivalent OPV (tOPV), which contains types 1, 2, and 3 live, attenuated polioviruses and has been a mainstay of efforts to prevent polio since the early 1960s. However, attenuated polioviruses in OPV can undergo genetic changes during replication, and in communities with low vaccination coverage, can result in vaccine-derived polioviruses (VDPVs) that can cause paralytic polio indistinguishable from the disease caused by WPVs (2). Among the 721 polio cases caused by circulating VDPVs (cVDPVs\*) detected during January 2006–May 2016, type 2 cVDPVs (cVDPV2s) accounted for >94% (2). Eliminating the risk for polio caused by VDPVs will require stopping all OPV use. The first stage of OPV withdrawal involved a global, synchronized replacement of tOPV with bivalent OPV (bOPV) containing only types 1 and 3 attenuated polioviruses, planned for April 18–May 1, 2016, thereby withdrawing OPV type 2 from all immunization activities (3). Complementing the switch from tOPV to bOPV, introduction of at least 1 dose of injectable, trivalent inactivated poliovirus vaccine (IPV) into childhood immunization schedules reduces risks from and facilitates responses to cVDPV2 outbreaks. All 155 countries and territories that were still using OPV in immunization schedules in 2015 have reported that they had ceased use of tOPV by mid-May 2016.<sup>†</sup> As of August 31, 2016, 173 (89%) of 194 World Health Organization (WHO) countries

included IPV in their immunization schedules.<sup>§</sup> The cessation of tOPV use is a major milestone toward the global goal of eradicating polio; however, careful surveillance for polioviruses and prompt, aggressive responses to polio outbreaks are still needed to realize a polio-free world.

### Global Cessation of Use of Trivalent Oral Poliovirus Vaccine

Although the global cessation of tOPV use is essential for eliminating cVDPV2s, cessation of tOPV use carries some risks for facilitating the spread of undetected or newly emergent cVDPV2s among persons without immunity to type 2 poliovirus infections after the switch to bOPV (3–5). To stop the spread of existing cVDPV2s before the switch and to reduce risks for post-switch outbreaks (4), population immunity to type 2 poliovirus at the time of the switch was boosted through implementation of 116 supplemental immunization activities (SIAs<sup>¶</sup>) with tOPV in 42 OPV-using countries during November 2015–April 2016. Afghanistan, Nigeria, and Pakistan also conducted SIAs with IPV in selected regions before stopping tOPV use. In addition, the synchronized timing of the switch aimed to prevent exportations of type 2 polioviruses from areas continuing to use tOPV to neighboring areas that have ceased tOPV use (3,4). All 155 countries and territories that used OPV in 2015 reported that they had terminated use of tOPV by May 12, 2016 (Figure 1). To facilitate global cessation of tOPV use, all manufacturers of OPV ended production of tOPV before the switch, after several years of communications and close coordination with the Global Polio Eradication Initiative (GPEI).<sup>\*\*</sup>

\* VDPVs are classified as cVDPVs if genetically linked examples of a VDPV strain are isolated from at least two persons who are not household contacts, from one person and at least one environmental surveillance (sewage) sample, or from two or more environmental surveillance samples collected from different environmental surveillance sites or collected from the same site more than 2 months apart.

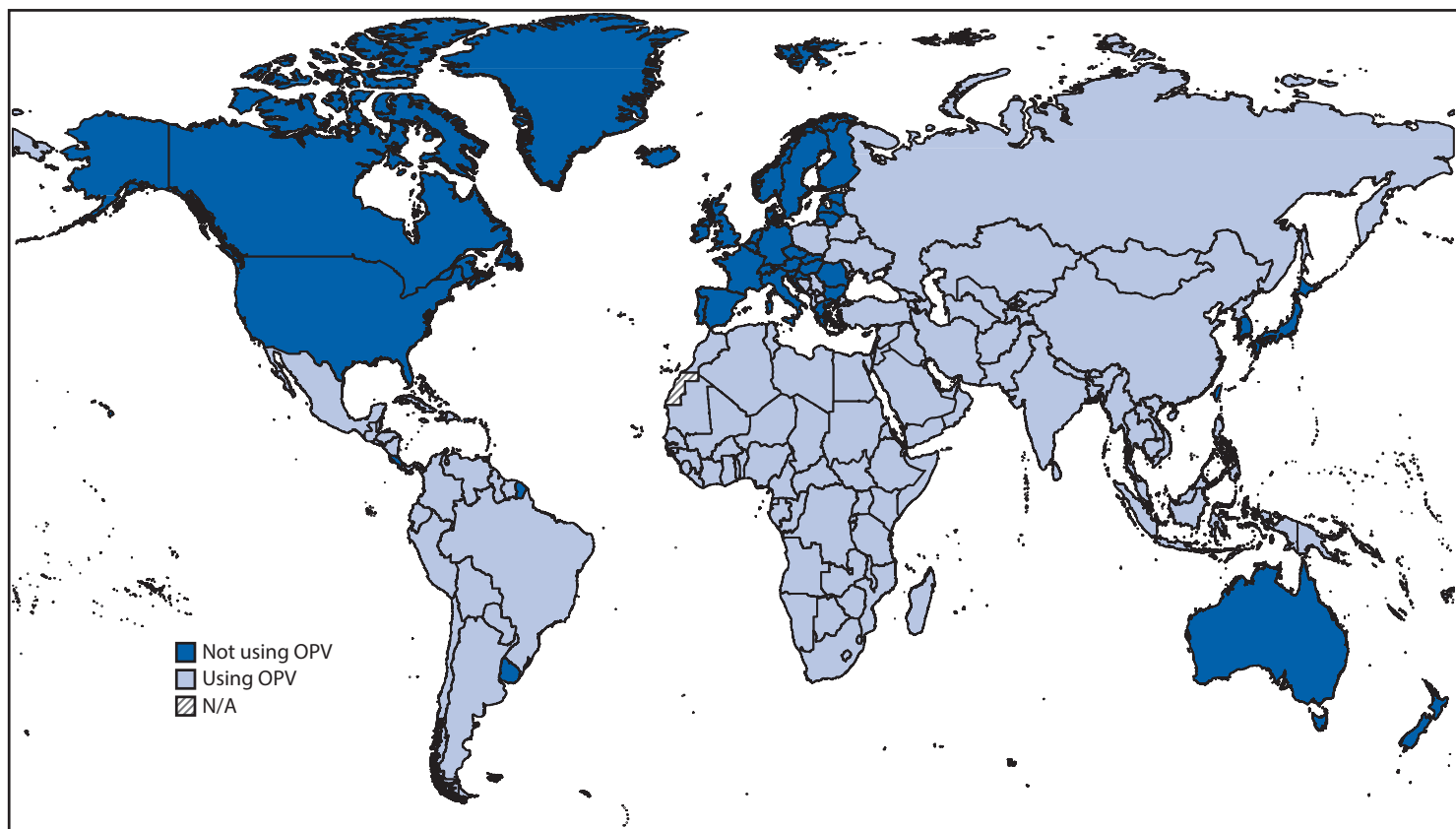
<sup>†</sup> Five countries reported ceasing all regular use of any OPV between early 2015 and March 2016. The other 150 countries and territories still using OPV in April 2016 all reported ceasing use of tOPV by May 12, 2016.

<sup>§</sup> WHO tracks progress in the introduction of new vaccines by the number of WHO member states that have introduced a given vaccine. However, because of the need for even higher precision in tracking cessation of tOPV use, seven countries and territories using OPV in 2015 that are not full WHO member states were included in efforts to track tOPV use in addition to 148 countries using OPV in 2015 that are full WHO member states.

<sup>¶</sup> Supplemental immunization activities are mass vaccination campaigns conducted over a short period (days to weeks), in this case, in which a dose of OPV is administered to all children aged <5 years, regardless of previous vaccination history. Campaigns can be conducted nationally or subnationally, in portions of a country.

<sup>\*\*</sup> The Global Polio Eradication Initiative coordinates the global effort to eradicate polio; WHO, the United Nations Children's Fund, CDC, Rotary International, and the Bill and Melinda Gates Foundation are core partners.

FIGURE 1. Countries and territories using oral poliovirus vaccine (OPV) — worldwide, 2015



Abbreviation: N/A = not available.

Source: World Health Organization Immunization Repository.

To reduce the risk for inadvertent or intentional use of tOPV after the switch, which could lead to the emergence of new cVDPV2s (5), a combination of external and in-country monitors visited >160,000 vaccine stores and service delivery points in countries and territories participating in the switch. Monitors verified the absence of tOPV from each area's vaccine supply cold chain and helped ensure that any tOPV they found in the cold chain was removed. The monitors' findings in each country and territory were reviewed by a validation committee, whose assessment of whether or not tOPV had been removed from the cold chain was provided to the national government and later transmitted to WHO. By August 31, 2016, all but two countries and territories that used OPV in 2015 had submitted validation reports to WHO.

Type 2 poliovirus strains held in research or manufacturing facilities also might cause polio outbreaks if released into a population. To prevent such outbreaks, countries should ensure that all remaining type 2 polioviruses, including WPV2s, VDPV2s, and the type 2 Sabin polioviruses used in tOPV and monovalent OPV type 2 (mOPV2), are destroyed

or appropriately contained in certified poliovirus-essential facilities in accordance with the third Global Action Plan to Minimize Poliovirus Facility-Associated Risk (GAPIII) (3,6).

If type 2 poliovirus outbreaks do occur, GPEI has developed a response protocol and assembled a global stockpile of mOPV2, managed by the United Nations Children's Fund and stored under containment conditions, to be released at the direction of the WHO Director-General. As of August 31, this stockpile contained approximately 36 million mOPV2 doses in finished vials. An additional 50 million mOPV2 doses will become available between September and December 2016, and another 50 million doses by March 2017. Hundreds of millions of doses stored in bulk form are also available for conversion into finished mOPV2 doses. GPEI has also created an IPV stockpile for use in outbreak responses. Surveillance for acute flaccid paralysis cases is supplemented by environmental surveillance for polioviruses in sewage in at least 36 countries to help identify and respond to the asymptomatic spread of type 2 polioviruses in those countries (7).

## Global Introduction of Inactivated Poliovirus Vaccine

To further reduce the risk for type 2 poliovirus outbreaks after the cessation of tOPV use, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization recommended in 2012 that all countries' immunization schedules include at least 1 IPV dose (3). IPV protects against paralytic polio from type 2 polioviruses, might facilitate interruption of transmission during cVDPV2 outbreaks by enhancing immunologic response to mOPV2 and reducing the duration and amount of viral shedding, and aids in eradicating WPV by boosting immunity to types 1 and 3 polioviruses in persons who have received bOPV or tOPV (3).

Efforts to introduce IPV in the 126 countries using only OPV at the beginning of 2013 have been hampered by challenges manufacturers have experienced in scaling up production to meet the increased demand for IPV, as well as increased need for IPV in SIAs targeting WPV1 in countries where polio is endemic and the need to stockpile IPV for outbreak response. As of August 31, 2016, among the 126 countries using only OPV at the beginning of 2013, a total of 105 (83%) had introduced IPV, resulting in 173 (89%) of 194 WHO member states using IPV. However, 20 countries have had

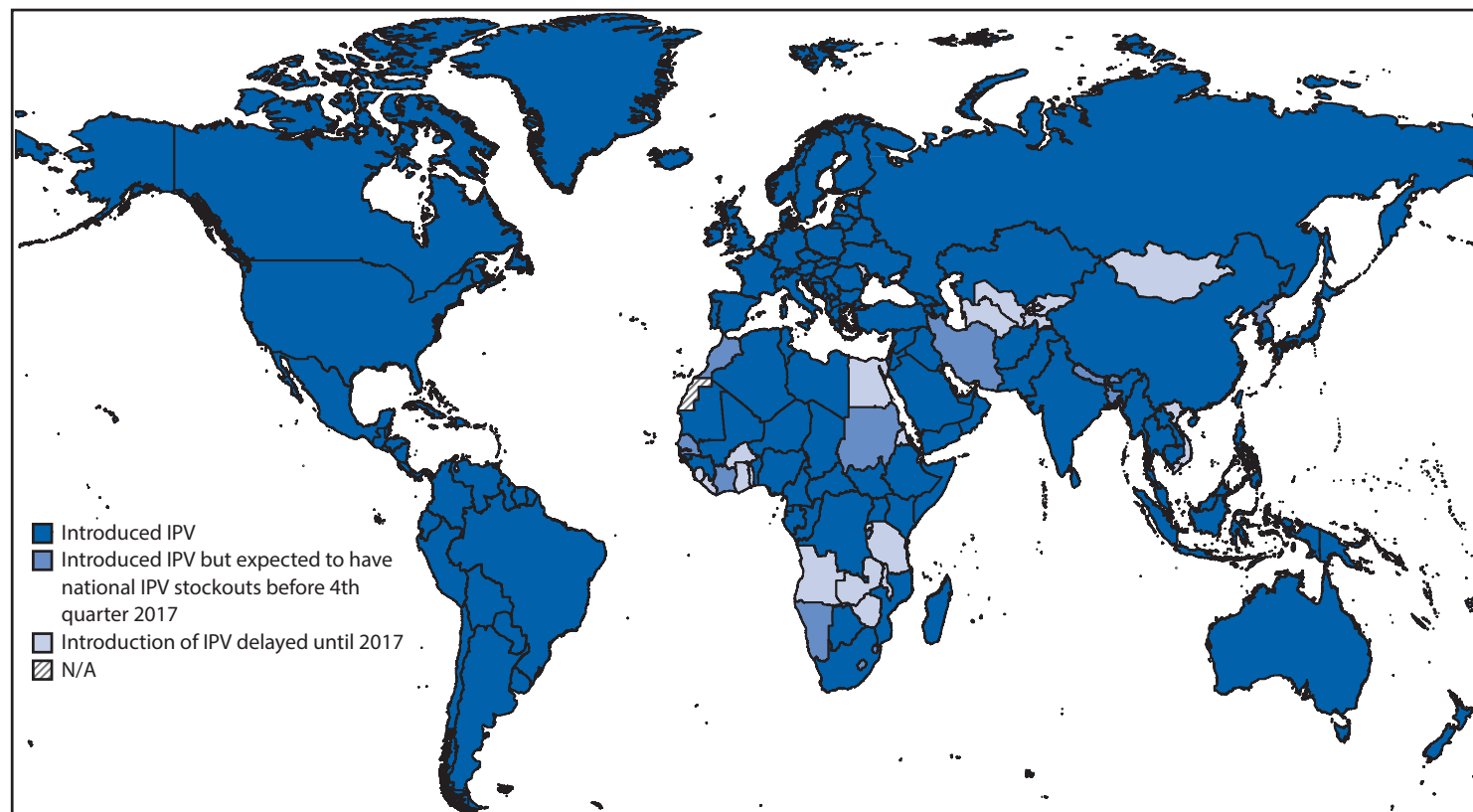
to delay introduction of IPV until adequate supplies of IPV become available, which is not likely before the fourth quarter of 2017 (Figure 2). In addition, 29 countries that previously introduced IPV are expected to run out of IPV nationwide before they receive their next supply of IPV in late 2017, and Cabo Verde has opted to postpone its introduction until 2017 to avoid a similar stock-out.<sup>††</sup>

In response to the IPV shortage, GPEI has set priorities for allocating the limited IPV supply. The highest priority countries for receipt of IPV are Afghanistan, Nigeria, and Pakistan because of ongoing indigenous WPV transmission. The second priority is the other 33 countries considered to be at high risk for cVDPV2 outbreaks. The third priority for IPV allocation is SIAs conducted in response to polio outbreaks, and the final priority is countries considered to be at low risk for polio outbreaks.<sup>§§</sup> All countries considered to be at high risk for cVDPV2 outbreaks are providing IPV to infants through routine immunization service delivery. To use limited supplies

<sup>††</sup> Eight of these countries are Pacific island countries.

<sup>§§</sup> Countries are considered to be at high risk for a cVDPV2 outbreak if they have had a cVDPV outbreak since 2000, have endemic WPV transmission, or have estimated routine immunization coverage of <80% for the third dose of a vaccine containing diphtheria, tetanus, and pertussis antigens.

FIGURE 2. Status of introduction of inactivated poliovirus vaccine (IPV), by country — worldwide, August 31, 2016



Abbreviation: N/A = not available.

Source: World Health Organization Immunization Repository.



**Summary****What is already known about this topic?**

To address the risks posed by type 2 circulating vaccine-derived polioviruses, which have caused hundreds of paralytic poliomyelitis cases since 2006, the type 2 component of oral poliovirus vaccine was scheduled for global withdrawal through a synchronized switch from trivalent oral poliovirus vaccine (tOPV) to bivalent oral poliovirus vaccine (bOPV). All countries not already using inactivated polio vaccine (IPV) have committed to introducing it as part of their efforts to reduce risks associated with potential type 2 polio outbreaks after the switch.

**What is added by this report?**

All 155 countries and territories using OPV in their immunization programs in 2015 reported that they had completely ceased use of tOPV by mid-May 2016. As of August 31, 173 (89%) of 194 WHO countries had introduced inactivated polio vaccine (IPV) into their immunization programs despite a global shortage of IPV, although 29 of those countries are expected to deplete their supplies of IPV before being resupplied in 2017.

**What are the implications for public health practice?**

The cooperation of all OPV-using countries ending use of tOPV in a synchronized fashion is unprecedented. However, although the cessation of tOPV use is a major milestone toward the completion of the global effort to eradicate polio, vigilant surveillance for all polioviruses, including type 2 polioviruses, is still needed. Any tOPV found in a vaccine storage refrigerator or freezer in the future should be destroyed consistent with the Global Action Plan to Minimize Poliovirus Facility-Associated Risk. Any type 2 polioviruses detected in the future will require thorough investigation and an aggressive response.

of IPV efficiently, SAGE has recommended that countries consider administering 2 intradermal fractional doses of IPV to children eligible for IPV, instead of 1 full intramuscular dose (8). Two fractional doses of IPV, administered at separate visits, elicit a better immune response than a single full intramuscular dose of IPV, yet each fractional dose requires only one-fifth the volume of vaccine of a full intramuscular dose. Sri Lanka and India have begun administering 2 fractional doses of IPV to children through their routine immunization services.

**Discussion**

The synchronized global switch from tOPV to bOPV has gone smoothly based on the reported cessation of tOPV use in all countries and territories by mid-May 2016. The 721 cases of polio caused by cVDPV2s during 2006–2016 highlight both why the switch was necessary and why multiple precautions were taken to prevent cVDPV2s from emerging or spreading after the switch (2). Maintaining strong surveillance and response systems that can detect polioviruses, and responding promptly and aggressively when poliovirus is detected, will be essential for preserving and building upon the gains made against polio

since 1988. The prompt detection and destruction of any tOPV vials found in the cold chain in the future, as well as of any mOPV2 vials found outside of the global mOPV2 stockpile after completion of an mOPV2 SIA, also will help to prevent new cVDPV2s from emerging in the future. Ultimately, the success of the withdrawal of tOPV and associated activities such as the tOPV and IPV SIAs held in the months before the switch and the global introduction of IPV will be measured by the number of polio cases caused by cVDPV2s that occur after tOPV withdrawal, with fewer cases indicating a greater success.

As of August 31, 2016, no new cVDPV outbreaks had been identified in 2016 (2). In April 2016, a cVDPV2 was identified in an environmental sample collected in March 2016 in northeastern Nigeria, before cessation of tOPV use, but genetic testing indicated that it is part of a known cVDPV2 lineage that was undetected after isolation from an environmental sample in early 2014 (9). Following the protocol for responding to detection of WPV2 after the switch and using the prepared mOPV2 stockpile, SIAs with mOPV2 were implemented in northeastern Nigeria after detection of the cVDPV2.<sup>¶¶</sup> An SIA with fractional dose IPV is planned for the same area later in September, and SIAs with mOPV2 are planned for the high-risk neighboring countries of Cameroon, Chad, and Niger in October and November.<sup>\*\*\*</sup> The response to the identification in August of polio cases caused by WPV1 in northeastern Nigeria should lead to further strengthening of surveillance and, through vaccination, population immunity to polio infections in that area (10).

The introduction of IPV into the immunization schedules of 105 countries since 2013 is an important achievement, particularly given the challenges imposed by the global supply shortage. Continued external support for IPV introduction in countries that have not yet been able to introduce IPV but plan to do so once the supply shortages have been resolved and strengthening of routine immunization systems that distribute and administer IPV will help to maximize the benefit of IPV for all children.

The experience developed from tOPV cessation will contribute to the success of future efforts directed at the cessation

<sup>¶¶</sup> New type 2 ambiguous vaccine-derived polioviruses (aVDPV2s), which are VDPV2s that cannot be classified as either circulating VDPV2s or immunodeficiency-related VDPV2s (iVDPV2s) after adequate investigation, had been identified in 2016 in the Democratic Republic of Congo, Egypt, India, Kenya, Nigeria, Pakistan, Senegal, and Syria, as of August 31. However, these aVDPV2s have generally had relatively few genetic changes compared with the attenuated Sabin polioviruses in OPV they are descended from, indicating they were detected relatively soon after they emerged. All of the affected countries conducted SIAs with tOPV in 2016 in preparation for the switch. Specifically in response to the detections of these aVDPV2s, a localized SIA with tOPV was held in early May in Egypt, a localized fIPV SIA was held in June in India, and a series of mOPV2 SIAs were conducted in Nigeria. In addition, a localized mOPV2 SIA and a localized fIPV SIA are planned in Pakistan.

<sup>\*\*\*</sup> As of August 31, 2016, additional VDPV2s had been identified in Ukraine and Yemen and had not yet been classified as cVDPV2s, aVDPV2s, or iVDPV2s because they were under investigation.

of all OPV use, primarily the withdrawal of bOPV. The cooperation of all OPV-using countries and territories in ending tOPV use in a synchronized manner is an unprecedented public health achievement. This synchronized withdrawal of tOPV followed over 2 years of preparation by and communications among GPEI, its partner organizations, OPV manufacturers, and country and territorial governments, and was achieved by essential work performed by immunization workers in the countries and territories that stopped use of tOPV. Active support from senior leaders of GPEI and national ministries of health was critical, as was the cooperation of all OPV manufacturers in ceasing production and distribution of tOPV and ensuring the availability and timely delivery of bOPV. Combined with the eradication of WPV, the ultimate withdrawal of all OPV from use will enable the creation of a polio-free world.

### Acknowledgments

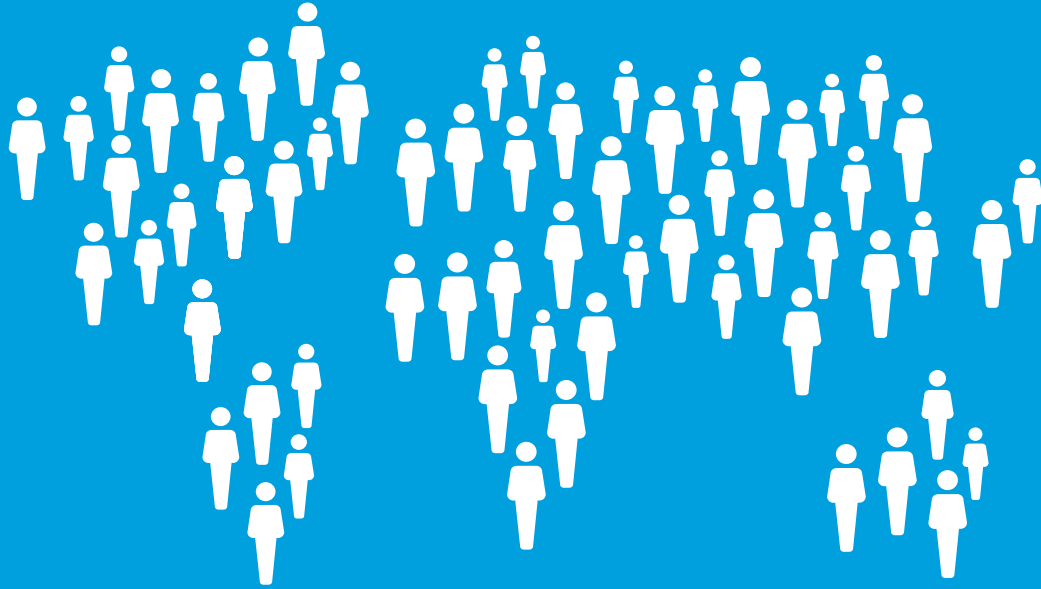
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2017  
ASSESSMENT  
REPORT OF THE  
GLOBAL VACCINE  
ACTION PLAN

STRATEGIC  
ADVISORY  
GROUP OF  
EXPERTS ON  
IMMUNIZATION

## I EXECUTIVE SUMMARY

In 2016, some progress was made towards the goals set out in the Global Vaccine Action Plan. The year saw the fewest number of cases of wild poliovirus ever reported, and three more countries were certified as having achieved maternal and neonatal tetanus elimination. Nine additional countries have introduced new vaccines. Overall DTP3 vaccination coverage increased, but by only 1% to 86%. **Progress therefore still remains too slow for most goals to be reached by the end of the Decade of Vaccines in 2020.**

Furthermore, **multiple global, regional and national issues threaten further progress**, and have the potential to reverse hard-won gains. Economic uncertainty, conflicts and natural disasters, displacement and migration, and infectious disease outbreaks all pose major challenges to immunization programmes. At the same time, there are concerning signs of complacency and inadequate political commitment to immunization – as well as a global lack of appreciation of its power to achieve wider health and development objectives.

Additional risks include growing levels of vaccine hesitancy and the worrying rise in stockouts disrupting access to vaccines – related primarily to shortcomings in vaccine procurement and distribution but also to some extent to vaccine production. The continued marked underperformance of certain countries relative to others within their region – ‘outlier’ countries – remains of grave concern.

The potential impact of the **phase-out of funding for polio eradication is also of concern**. It is vital that the polio transition remains sufficiently flexible that it does not jeopardize ongoing outbreak control efforts or critical surveillance activities and post-eradication certification processes. Furthermore, there is a significant risk that wider surveillance activities and routine immunization programmes, and hence global health security, could be compromised during the polio transition. The potentially simultaneous phasing out of polio and Gavi funding and technical support is of further concern.

These risks threaten to slow the extension of vaccines to under-served populations and heighten global inequalities in vaccine access. As the Decade of Vaccines draws to a close, there is a need to **intensify global efforts to promote immunization and to address the systemic weaknesses that are limiting equitable access** to life-saving and life-changing vaccines, particularly in outlier countries and middle-income countries.

The recommendations made in the Strategic Advisory Group of Experts on Immunization (SAGE) 2016 Assessment Report informed the development of World Health Assembly Resolution WHA70.14, approved in May 2017, and remain a high priority. In light of the risks highlighted, SAGE also calls for a broadening of the dialogue, to align immunization with emerging global health and development agendas, including the sustainable development goals, global health security, universal health coverage and the battle against antimicrobial resistance. A concerted effort is also required to address outlier countries, through a multidimensional, system-wide approach, recognizing that complex issues require multifaceted solutions and that civil society organizations have important contributions to make.

Through these and other measures, progress can continue to be made towards GVAP goals and the ground laid to exploit the full potential of immunization post-2020.



## I RECOMMENDATIONS IN BRIEF

See page 27 for more detailed versions of these recommendations.

1. **Broadening the dialogue:** The immunization community should ensure that immunization is fully aligned and integrated with global health and development agendas, including global health security, universal health coverage and the battle against antimicrobial resistance
2. **Funding transitions:** Until polio eradication is achieved, financial and technical support provided through the Global Polio Eradication Initiative, Gavi and WHO should be maintained in at least the 16 polio priority countries to ensure the success of eradication efforts and to mitigate the risks to infectious disease surveillance, routine immunization and global health security more generally
3. **Polio and communicable disease surveillance:** Countries in all regions should ensure they maintain effective poliovirus surveillance capacities through the polio endgame and beyond, and build on the polio surveillance platform to strengthen surveillance for other communicable diseases, especially measles and rubella
4. **Outlier countries:** WHO regional offices should work with countries experiencing the greatest difficulties in achieving GVAP goals to develop and implement multidimensional remediation plans, integrating existing national improvement plans
5. **Maternal and neonatal tetanus:** The immunization community should make concerted efforts to achieve elimination by 2020, in particular by exploiting compact pre-filled auto-disable devices to extend the reach of immunization
6. **Displaced and mobile populations:** WHO should synthesize existing knowledge on reaching displaced and mobile populations – including individuals escaping conflict zones or natural disasters, economic migrants, seasonal migrants, those moving to urban centres, and traditional nomadic communities – to identify good practice and gaps in knowledge
7. **Hesitancy:** Each country should develop a vaccine hesitancy management strategy and crisis response plan
8. **Civil Society Organizations:** Countries should broaden and deepen their engagement with CSOs to enhance the performance and reach of their national immunization programmes
9. **Technical capacity-building:** WHO regional offices should work with regional and global partners to support national technical capacity-building, adopting a multidimensional approach and leveraging regional and national institutional capacities and expertise as well as global tools and resources
10. **Vaccine access:** WHO regional offices and UNICEF should work with countries to identify and systematically address procurement and other programmatic issues affecting vaccine access
11. **Vaccine supply:** UNICEF, WHO and global partners should continue and expand efforts to map current and anticipated vaccine supply and demand for routinely used vaccines, with a particular focus on vaccines most at risk of supply shortages
12. **Middle-income countries:** WHO regional offices should support middle-income countries in their regions by leveraging all opportunities to promote the exchange of information, the sharing of lessons learned and peer-to-peer support



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## 1. INTRODUCTION

In 2016, SAGE published a mid-term review of the Global Vaccine Action Plan, which noted the slow speed of progress towards GVAP's eradication, elimination, coverage and other goals. The mid-term review made a number of recommendations to accelerate progress (see Box). These recommendations informed the development of World Health Assembly Resolution WHA70.14, approved in May 2017, which made a series of recommendations to Member States and WHO in order to strengthen immunization and achieve the GVAP goals.

Among other recommendations, the WHA resolution urged Member States to:

- strengthen the **governance and leadership** of national immunization programmes
- improve **monitoring and surveillance systems** to ensure that policy and programmatic decisions are based on up-to-date data to optimize performance and impact
- expand immunization services **beyond infancy**
- mobilize **domestic financing**, and
- strengthen **international cooperation** to achieve the GVAP goals.

It also requested the **WHO Secretariat** to:

- continue supporting countries to achieve regional and global vaccination goals
- scale up **advocacy efforts** to improve understanding of the value of vaccines and urgency of meeting the GVAP goals

The recommendations made in the mid-term review and reinforced by the WHA resolution remain equally relevant this year. For 2016, SAGE has built on their foundation, providing a series of recommendations that set the agenda for the remaining years of the Decade of Vaccines and begin to anticipate a successor to GVAP for 2020 and beyond.

Since progress on research and development (R&D) goals is reviewed every two years and was covered in the mid-term review, this report does not include discussion of R&D objectives. Detailed information about progress against GVAP indicators can be found in the Global Vaccine Action Plan Secretariat Report 2017.

### A SUMMARY OF 2016 SAGE RECOMMENDATIONS ON GVAP IMPLEMENTATION

- Demonstrate stronger leadership and governance of national immunization systems
- Prioritize immunization system strengthening
- Secure necessary investments to sustain immunization during polio and Gavi transitions
- Improve surveillance capacity and data quality and use
- Enhance accountability mechanisms to monitor implementation of Global and Regional Vaccine Action Plans
- Achieve elimination targets for maternal and neonatal tetanus, measles, rubella and congenital rubella syndrome
- Resolve barriers to timely supply of affordable vaccines in humanitarian crisis situations
- Support vaccine R&D capacity in low- and middle-income countries
- Accelerate the development and introduction of new vaccines and technologies

## I 2. HIGHLIGHTS OF THE YEAR

**Maternal and neonatal tetanus:** Three additional countries and one province – Equatorial Guinea, Indonesia and Niger, and the Punjab province of Pakistan (home to more than 110 million people) – achieved **maternal and neonatal tetanus elimination** in 2016. Maternal and neonatal tetanus has now been eliminated throughout the South-East Asia region. With two additional countries (Haiti and Ethiopia) being certified in 2017, elimination has now also been achieved in the Region of the Americas, leaving just 16 countries and three regions still affected as of September 2017.

**Hepatitis B control:** Immunization programmes in the Western Pacific region have **averted an estimated 7 million deaths** and 37.6 million chronic hepatitis B cases among children born between 1990 and 2014. Before hepatitis B vaccine was introduced, hepatitis B transmission was hyperendemic throughout most of the region, with an estimated prevalence among 5-year-old children greater than 8%.

**Measles elimination:** The Region of the Americas was **verified as having eliminated measles** in 2016. In addition, seven additional countries were verified free of measles in 2016, bringing the total number of countries verified as having interrupted the transmission of measles to 24 in the European region, two in the South-East Asian region, and seven in the Western Pacific region.

**Coverage in challenging contexts:** Despite the challenging situation in Syria, 240,000 children received at least one immunization in 2016. In Yemen, coverage has been remarkably stable. Such achievements speak to the resilience and dedication of immunization staff on the ground, civil society organizations (CSOs) and the support mobilized by the international donor community. Nevertheless, it remains to be seen whether this performance can be maintained given the devastating impact of conflict on health service infrastructure.

**Growing technical support:** The number of **national immunization technical advisory groups (NITAGs)** has doubled since 2010. NITAGs and regional immunization technical advisory groups (RITAGs) provide an independent source of expert advice to countries and can play a pivotal role in the development of effective national immunization programmes.

**Procurement and price transparency:** Some 144 countries submitted vaccine price information to the **Vaccine Product Price and procurement (V3P)** initiative in 2017. Incorporating data provided by UNICEF and WHO, the V3P database now covers 84% of all WHO Member States and 95% of the world's birth cohort. V3P is providing unprecedented levels of price transparency, which has facilitated negotiation and collaboration among countries in the European region, resulting in savings of up to 25% on vaccine procurement.

**Humanitarian crisis situations:** In 2016, a mechanism was established by WHO, Médecins Sans Frontières, UNICEF and Save the Children, in discussion with vaccine manufacturers, to accelerate access to affordable vaccines in humanitarian emergency situations. The **Humanitarian Mechanism** was launched in May 2017, and by September 2017 it had already been used five times to facilitate access to affordable vaccines in crisis situations.

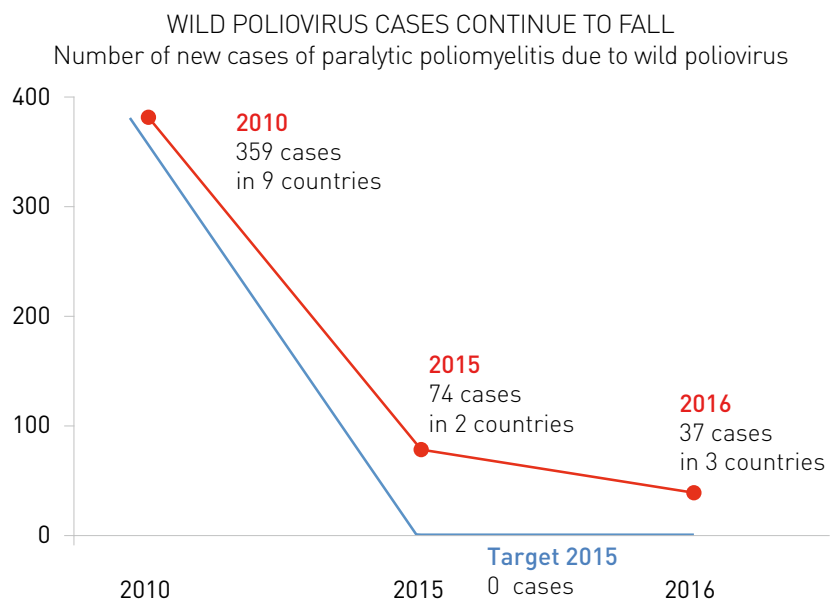
**Political commitment:** In 2016, the Ministerial Conference on Immunization in Africa laid the groundwork for the landmark **Addis Declaration on Immunization (ADI)**, including 10 commitments to achieve universal and equitable access to immunization in Africa. The ADI was endorsed by Heads of State from across Africa at the 28th African Union Summit in early 2017, signalling political support for immunization on the continent at the highest possible level.

**116.5 million**  
infants received three  
doses of DTP vaccine  
in 2016

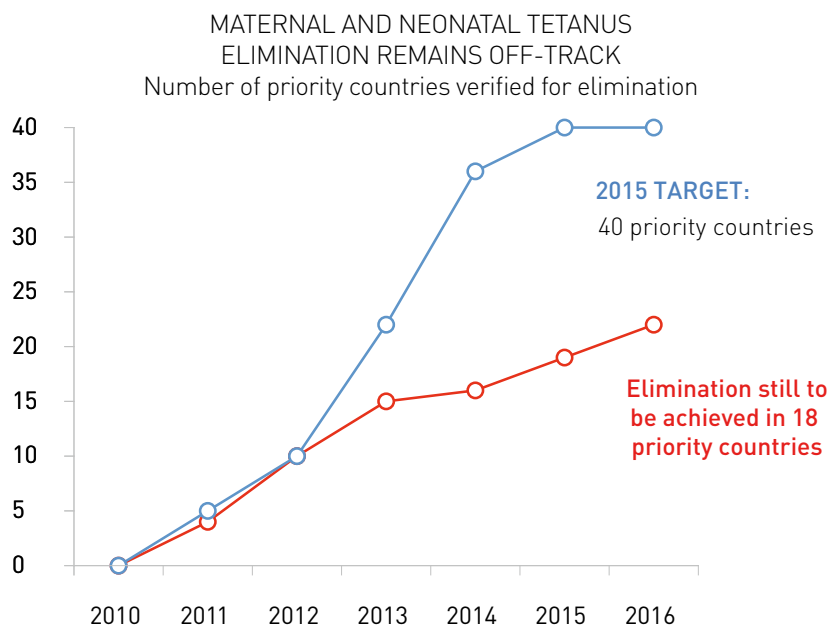
**37 cases**  
of wild poliovirus  
were reported in  
2016, the lowest  
number ever

### 3. KEY INDICATORS

Last year's mid-term review of GVAP reported that most indicators were off-track, and that a significant change of pace would be required if 2020 targets were to be achieved. The data for 2016 show improvements in some areas but in general not sufficient to provide confidence that 2020 targets will be reached. The following graphics summarize the current status of key coverage and other indicators in 2016.



The number of cases of wild poliovirus fell in 2016, to the lowest level yet recorded. Wild poliovirus continued to circulate in an area spanning parts of Afghanistan and Pakistan, and in Nigeria. The countries concerned have launched aggressive outbreak control action plans to interrupt wild poliovirus transmission, backed up in Nigeria by a broader regional outbreak response coordinated with neighbouring countries.

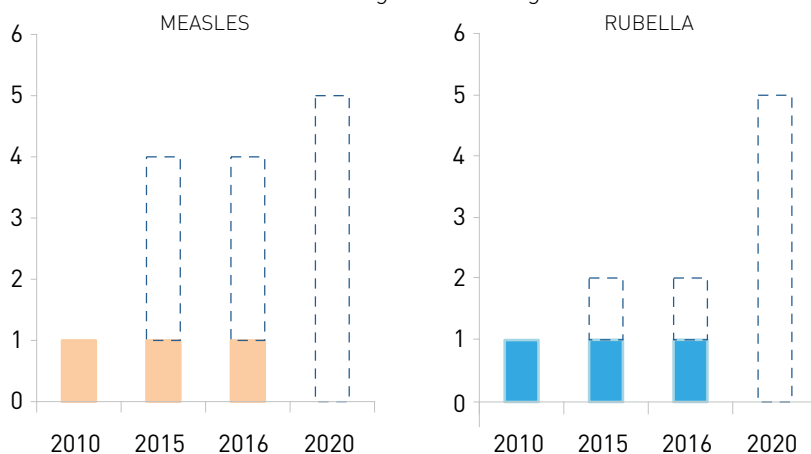


The numbers of  
neonatal tetanus  
deaths fell by 96%  
between 1998  
and 2015

Three additional countries achieved maternal and neonatal tetanus elimination in 2016 – Equatorial Guinea, Indonesia and Niger. Elimination was also achieved in the Punjab, the most populous province of Pakistan. Following Indonesia’s achievement, the entire South-East Asia region has eliminated maternal and neonatal tetanus. Two additional countries – Haiti and Ethiopia – achieved maternal and neonatal tetanus elimination in 2017, leaving 16 countries yet to reach this target as of September 2017.

### MEASLES AND RUBELLA ELIMINATION TARGETS HAVE NOT BEEN MET

Number of WHO regions achieving elimination



**2016 TARGET:**  
at least 4 WHO regions

**2016:** Only 1 region achieved measles elimination

**2016 TARGET:**  
at least 2 WHO regions

**2016:** Only 1 region achieved rubella elimination

The Region of the Americas is the only region to have achieved measles elimination. In addition, 24 countries in the European region, two in the South-East Asia region and seven in the Western Pacific region have been verified as having interrupted transmission of measles. However, between 2010 and 2016, global routine measles vaccine coverage stagnated at 85%. Globally, coverage with a second dose of measles-containing vaccine (MCV2) was 64%; just 26% of countries reached the MCV2 target of 95%. Some 41% achieved a similar MCV1 target, meaning that 20.8 million infants did not receive their first dose of measles-containing vaccine.

The establishment of Regional Verification Commissions and National Verification Committees for measles elimination has helped to refine understanding of the barriers to elimination and build stronger national commitment to elimination goals. Regional Verification Commissions have been established in the Region of the Americas and in the European, South-East Asian and Western Pacific regions; planning for the establishment of Regional Verification Commissions for the African and Eastern Mediterranean regions began in 2016.

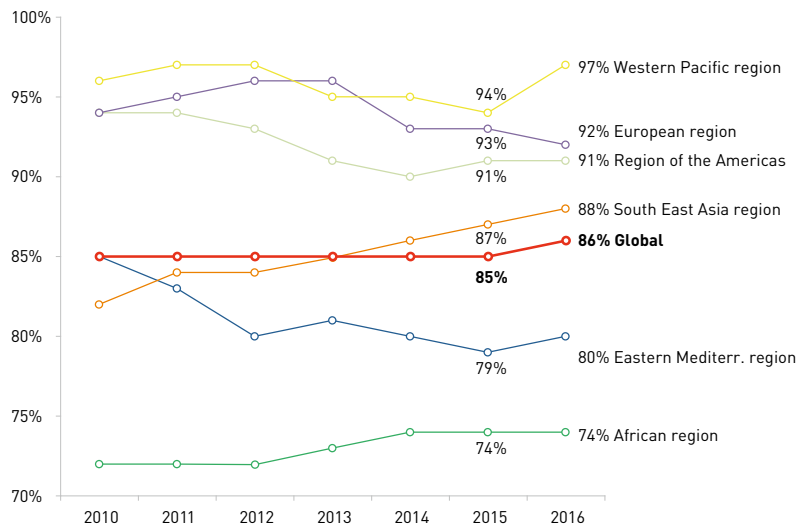
The Region of the Americas is also the only region to have achieved rubella elimination. Two WHO regions still do not have rubella elimination or control targets. Some 152 countries have introduced rubella vaccines, with national coverage ranging from 42% to 99%.

Seven additional countries were verified free of endemic measles in 2016

**1 in 10 infants** did not receive any vaccinations in 2016, putting them at serious risk of potentially fatal diseases

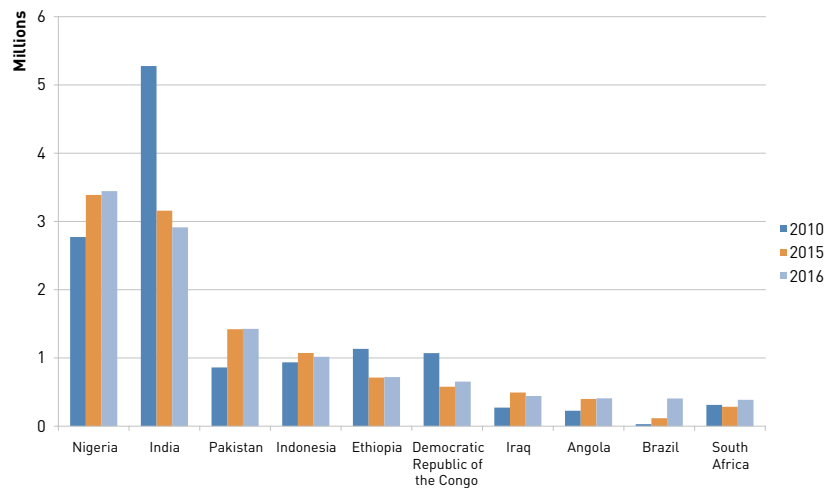
**Three countries** increased DTP3 coverage by 10% or more in 2016

GLOBAL DTP3 COVERAGE HAS SCARCELY CHANGED SINCE 2010



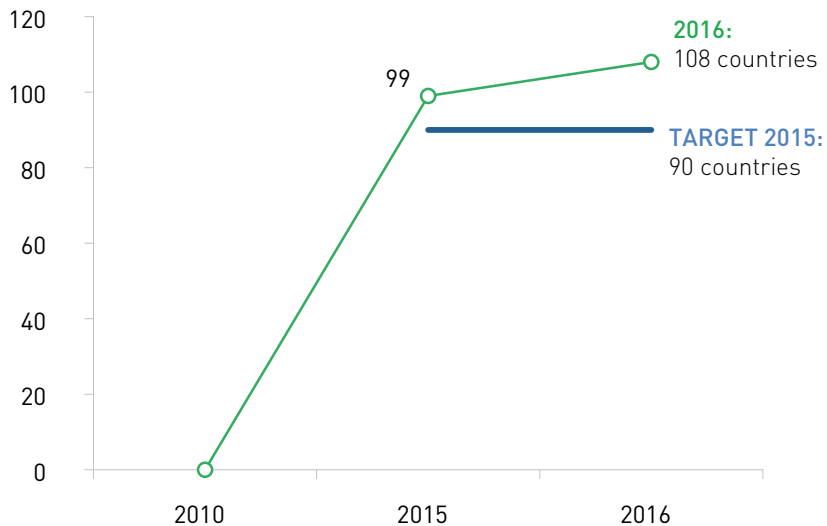
Coverage of three doses of the diphtheria-tetanus-pertussis vaccine (DTP3) is used as a proxy indicator of the performance of national immunization programmes. Globally, coverage was almost unchanged at 86%, masking variation between regions and within countries, with some seeing an increase in coverage and others a decline (or no change, while not reaching the target coverage of 90%).

THE NUMBERS OF UNVACCINATED CHILDREN ARE FALLING IN SOME BUT NOT ALL LARGE COUNTRIES  
Number of DTP3-unvaccinated children, top 10 countries



Because of their large populations, just six countries account for around half of the total number of unvaccinated children. While some countries – notably India, Ethiopia and the Democratic Republic of the Congo – have made significant gains in DTP3 coverage since 2010, in other countries the numbers of unvaccinated children have not fallen or have even increased.

**THE NEW VACCINE INTRODUCTION TARGET HAS BEEN MET**  
 Number of low- and middle-income countries to have introduced one or more new or under-utilized vaccines since 2010



Since 2010, 193 vaccine introductions have taken place in 108 out of 138 low- and middle-income countries

The GVAP new vaccine introduction target (new vaccine introductions in 90 low- and middle-income countries) was met in 2015. The number of such countries that have introduced new vaccines has continued to rise, reaching 108 in 2016; 78% of such countries have now introduced at least one new vaccine since 2010 and sustained use for at least a year.

A total of 65 countries introduced more than one vaccine, with the largest number of introductions occurring in the African region. The most commonly introduced new vaccine has been pneumococcal conjugate vaccine, followed by rotavirus vaccine.



**19.5 million**  
infants were under-  
or unvaccinated for  
DTP3 in 2016

## 4. CONCERNS

This year's indicator data confirm the trend observed in previous years and suggest that many of the GVAP goals will not be attained by 2020. Despite some progress, coverage levels are in general not increasing as rapidly as might have been hoped. It is disappointing that maternal and neonatal tetanus has yet to be eliminated and measles outbreaks continue to occur in several regions because of inadequate vaccine coverage. These are diseases that can, and should, be prevented.



WHO A Khan

Civil unrest has undoubtedly had an impact on coverage in a number of countries. However, signs of slippage in coverage over time in some previously well-performing countries, potentially hinting at dwindling political commitment to immunization, are a cause for concern, as are more rapid declines in countries facing acute health challenges, suggestive of a lack of resilience in immunization programmes. Although the investment made by national governments in immunization has been steadily increasing, a decline in the European region is worrying.

**Polio endgame:** The phasing out of funding to countries from the Global Polio Eradication Initiative has potential implications for both polio eradication and routine immunization, as well as global health security more generally. With poliovirus still circulating, albeit in only a few countries, polio is rightly still considered a Public Health Emergency of International Concern. It is essential that concerted efforts continue in affected and surrounding areas to interrupt transmission and achieve eradication, that these activities are adequately funded, and that the polio transition is sufficiently flexible to adapt to the changing situation in and around affected areas.

However, with polio eradication yet to be achieved, there is a risk of a mismatch in the timing of polio eradication and the polio programme transition. In some countries in regions where polio has been eliminated, surveillance is slipping; yet, in a globally connected world, poliovirus reintroduction remains a very real risk. Furthermore, in some countries polio eradication resourcing is being phased out before polio transition plans have been finalized, raising concerns about the long-term capacity for acute flaccid paralysis and poliovirus surveillance and the ability of countries to undertake the activities required for post-eradication certification.

Outbreaks of circulating vaccine-derived poliovirus (cVDPV) are a further reminder of the need to maintain a strong focus on polio control. In 2016, three countries were affected by cVDPV, and additional cVDPV cases were reported from two further countries in 2017. Maintaining effective surveillance and high vaccine coverage levels remain essential for preventing cVDPV outbreaks.

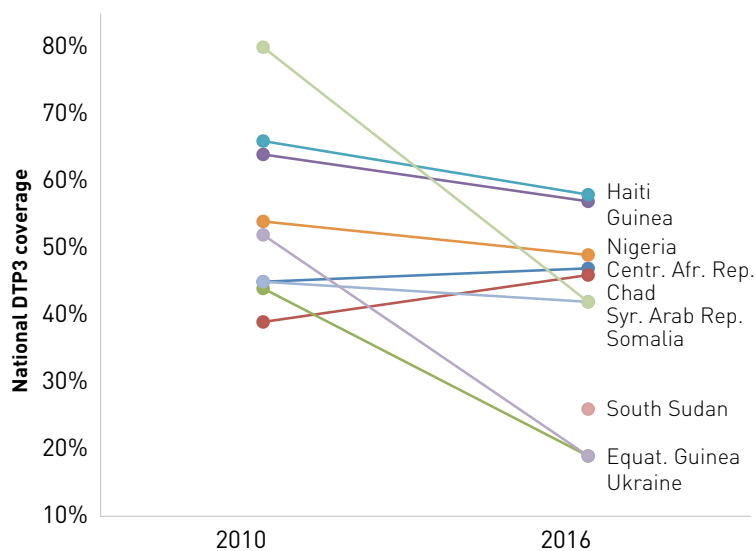
In some countries, resourcing and infrastructure for polio eradication have also been used to support other important surveillance activities and routine immunization programmes. As a result, where countries are unable to address the funding gap themselves, there is a significant risk that a phasing out of polio funding will undermine countries' infectious disease surveillance capacity and compromise national immunization programmes. As well as potentially affecting key GVAP indicators such as measles vaccine coverage, this could also have significant implications for disease control and global health security more generally. It is essential that polio transition plans identify mechanisms to maintain the support for essential activities and resources required both to ensure a polio-free world and to safeguard surveillance and routine immunization activities integral to the protection of communities and control of other infectious diseases.

A further point of concern is the possible simultaneous phasing out of support in countries affected by both the polio funding transition and a transition out of Gavi support. It is vital that these two processes are undertaken in a coordinated manner to minimize the potential impact of loss of resources and technical support on routine immunization programmes and associated functions such as surveillance.

**Outlier countries:** Globally, coverage in certain Member States is markedly below that achieved by other countries within the same region, and often has been for extended periods. In some cases, factors such as civil strife, natural disasters or acute economic disruption can be considered mitigating factors, but in other cases the causes of low coverage levels are less clear. Whatever the causes, low coverage levels leave large numbers of citizens at risk of preventable infectious disease, while also posing a challenge to regional and global health security.

In 2016, eight countries had DTP3 coverage of less than 50%

OUTLIER COUNTRIES SHOW PERSISTENTLY LOW NATIONAL DTP COVERAGE LEVELS



Change in DTP coverage between 2010 and 2016 in countries with coverage below 60% in 2016.

Since the reasons for low coverage levels are likely to vary from country to country, there is a need to adopt a tailored approach and to assess systematically the local factors that are affecting the performance of these immunization programmes. Recognizing that complex situations are not amenable to 'quick fixes', it will be important to undertake a thorough multidimensional, system-wide diagnostic assessment of the current situation within such countries (see Box).

This diagnostic assessment can be used to develop comprehensive system-wide remediation plans that outline the steps required to establish a high-performing and sustainable national immunization programme able to reach currently underserved populations within countries. These plans should integrate existing improvement plans and have a strong focus on the development of monitoring and evaluation frameworks to support effective implementation.

Given their understanding of local situations and context, this process should be led by WHO regional offices working in close collaboration with each country to develop culturally and context-specific plans, drawing on regional experience of effective approaches and good practice. CSOs may also have important insights to offer. Global partners should commit to supporting the implementation of national remediation plans.

#### **CORE ASPECTS OF A MULTIDIMENSIONAL FRAMEWORK FOR IMMUNIZATION SYSTEM ASSESSMENT**

- Political commitment
- Domestic funding
- Monitoring and evaluation
- Roles and responsibilities (national and devolved)
- Accountability (national and devolved)
- Planning/microplanning
- Human capacity within immunization programme
- Education, training and supervision
- Vaccine management and supply chain infrastructure
- NITAGs and independent technical advice
- Other national technical assets
- Regional collaboration/ RITAG engagement
- Surveillance
- Safety monitoring
- CSO engagement in immunization programme
- Social engagement
- Hesitancy assessment and planning

## I 5. EQUITY

A fundamental principle of GVAP is that all people should benefit from immunization, irrespective of where they are born, who they are, or where they live. This year's data continue to show that the benefits of immunization are shared unevenly, both between and within countries. Promoting more equitable access to immunization must remain a core ambition globally and nationally.



WHO E. Soteras Jalil

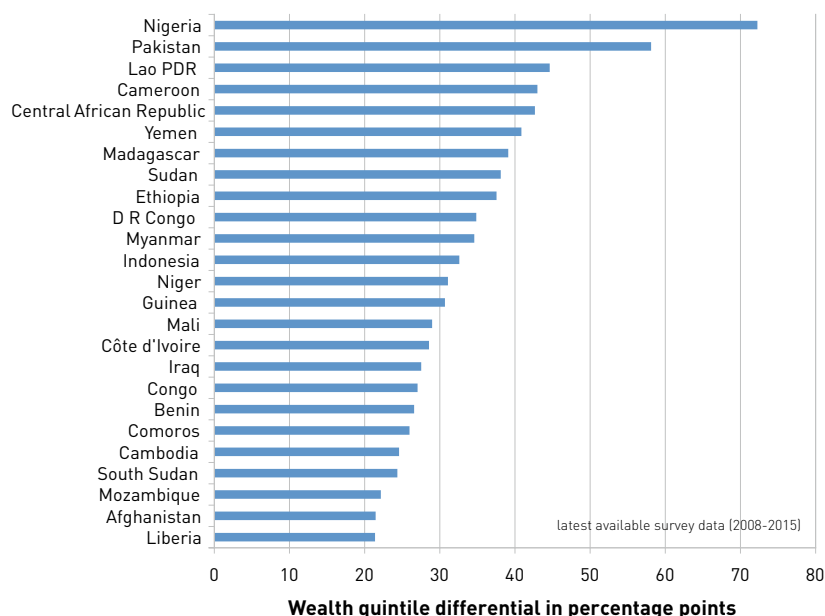
It is encouraging that new vaccine introduction targets are being met, but it is clear that the speed of introduction varies markedly across the world. While Gavi funding has clearly had a major impact on new vaccine introductions in many low- and middle-income countries, some Gavi-eligible countries have not taken advantage of this opportunity, and introductions in Gavi-ineligible middle-income countries has lagged significantly.

Within countries, socioeconomic status remains a significant factor affecting access to immunization, and equity gaps appear to be closing only slowly. With equity such a fundamental principle, it is essential that countries gather district-level and sociodemographic data that enable equity gaps to be assessed and addressed.

The largest equity gaps are typically seen in countries with low levels of vaccine coverage. General strengthening of national immunization programmes would therefore be likely to reduce equity gaps. Even so, achieving true equity is likely to require specific approaches to target populations that are hard to reach, for geographic or sociocultural reasons. There is a need to build the evidence base on how such hard-to-reach populations can be accessed effectively, ensuring that lessons learned are captured and shared, and good practice established and implemented.

In certain countries,  
a child from a rich  
family has  
**a nine times**  
greater chance of  
receiving three  
doses of DTP vaccine  
than a child from a  
poor family

MANY COUNTRIES SHOW HIGH LEVELS OF INEQUALITY  
IN DTP3 COVERAGE BETWEEN RICHEST AND POOREST POPULATIONS



Progress towards equality in coverage is difficult to judge due to the limited numbers of countries reporting DTP3 coverage by wealth quintile, although this increased from 64 to 84 Member States (43%) between 2015 and 2016. For those countries providing data, 59 (70%) met the target of a 20% or smaller difference in coverage between the wealthiest and poorest population quintiles; 25 had a quintile differential greater than 20%. Those with the greatest differences in coverage generally had relatively low national DTP3 coverage rates.

In 15 out of 28 countries with data for more than one year, the equity gap decreased, but in eight countries it increased and in five it was unchanged. Hence there is little evidence of significant progress in the closing of equity gaps.

**Maternal and neonatal tetanus:** Maternal and neonatal tetanus differentially affects the poorest, most neglected and underserved populations, making the disease an important indicator of health inequality. Indeed, achieving and maintaining maternal and neonatal tetanus elimination could be adopted as a key indicator of universal health coverage, given its strong association with social disadvantage.

Maternal and neonatal tetanus elimination also offers an important opportunity to address health service integration. Maternal immunization could be readily envisaged as a component of the WHO comprehensive programme of antenatal care.

Great progress has been made towards the elimination of maternal and neonatal tetanus, with the number of associated deaths falling from more than 780,000 in 1988 to 34,000 in 2015 and the number of countries affected dropping to just 16 by September 2017. In 2000, 18% of children born were at risk of neonatal tetanus (their mothers were not immunized against tetanus); this figure fell to 10% in 2010 and 5% in 2016. Nevertheless, the remaining cases were all preventable, and the ultimate target must be zero.

Maternal and neonatal tetanus elimination is a key GVAP goal, and one that is within reach. As the Decade of Vaccines draws to a close, SAGE again urges countries to re-energize their drive towards maternal and neonatal tetanus elimination by 2020. Although several countries are on track to achieve the milestones set out by SAGE in 2016 for elimination by 2020, Papua New Guinea and Sudan are falling behind.

Only 5% of newborns were at risk of neonatal tetanus in 2016, compared to 18% in 2000

Regional collaboration and the access to technical expertise and experience offered by RITAGs have a potentially critical role to play in identifying and overcoming implementation barriers. An investment case for maternal and neonatal tetanus elimination is currently being developed in collaboration with UNICEF, WHO and UNFPA.

Achieving the goal of elimination would be greatly facilitated by access to compact pre-filled auto-disable devices, which would expand the range of health workers able to contribute to maternal tetanus immunization programmes and enhance access to the most hard-to-reach populations. The funding case for deployment of such devices should be developed and assessed as rapidly as possible and, once the technology is available, countries should identify how best to exploit its potential at a local level to achieve the elimination goal.

**Mobile populations:** Among the groups least likely to benefit from immunization services are displaced people and other mobile populations. This grouping covers a wide range of situations, including individuals escaping conflict zones or natural disasters, economic migrants, seasonal migrants, those moving to urban centres, and traditional nomadic communities.

In 2015, an estimated 244 million people, or 3.3% of the world's population, lived outside their country of origin. Given current geopolitical realities, these numbers are unlikely to fall. The global immunization community will therefore need to consider the long-term implications of these trends for national immunization programmes facing considerable additional demands and the presence of vulnerable populations at risk of infectious disease outbreaks.

An important step forward has been the development by the WHO, UNICEF, Médecins Sans Frontières, and Save the Children of the Humanitarian Mechanism, launched in 2017. This mechanism has been designed to enable CSOs, governments and UN agencies to quickly procure affordable vaccine supplies on behalf of populations facing humanitarian emergencies and lacking access. By September 2017, the mechanism had been used five times, but so far only to provide access to pneumococcal conjugate vaccine.

Nevertheless, not all displaced and mobile populations are associated with humanitarian crises or are covered by the emergency humanitarian mechanism, and additional long-term solutions are required. Such vulnerable populations raise a number of challenges, including a potential lack of country 'ownership' of non-nationals, movement of migrants across multiple countries, the need to build trust with vulnerable communities, and the possibility that migrants become geographically disbursed and hard to track.

Maintaining immunization despite migration within countries or across borders, either voluntary or forced, will be a major future challenge for the global immunization community, but a vital step in the journey towards equitable access to immunization services. As a first step, there is a need to collate existing knowledge on best practices for reaching different categories of mobile populations, to identify knowledge gaps and provide a basis for the development of strategies to address the immunization needs of such vulnerable populations.

The UNHCR estimates that there are **65.6 million** forcibly displaced people worldwide

**1.5 million** people are added to the global urban population every week



Government investment in immunization has grown by 108% in the African region and by 78% in the Western Pacific region since 2010 but has fallen by 12% in the European region

Some 83% of countries reported on hesitancy in 2016; 33% of countries had carried out a hesitancy assessment

## 6. CONTEXT

While many core principles and key aspects of an immunization programme are shared, implementation and the success of national programmes are heavily dependent on local political, economic, geographic, demographic, social, environmental and other factors. Efforts to improve coverage and the performance of national immunization programmes will need to acknowledge and take account of these local contextual and cultural influences.

Country-level analyses clearly indicate how such wider contextual factors can affect national immunization programmes. Falling oil and commodity prices have had a major impact on many countries' economies, in some cases leading to cuts in health service and immunization programme budgets. Conflict inevitably has an impact on health service infrastructure, while major disease outbreaks may lead to the shifting of resources or lessening of attention on routine immunization. Vaccine hesitancy can rapidly undermine coverage of specific vaccines, often in highly localized settings.

Conversely, local political commitment can help to maintain and improve coverage levels, even under difficult circumstances. This emphasizes the crucial point, made in last year's recommendations and reiterated in the 2017 WHA Resolution, that countries must assume strong ownership of their immunization programmes, and take responsibility for developing their programmes to reach currently underserved populations.



WHO E. Soteras Jaiti

**Hesitancy:** Vaccine hesitancy is a prime example of a local context-specific factor that can have a dramatic impact on coverage. Vaccine hesitancy is of growing concern, and one that increasingly affects countries across the full range of income strata. Effects can be highly localized: certain high-income European countries have experienced significant hesitancy episodes related to specific vaccines yet, interestingly, there has been little evidence of a ripple effect, with concerns largely not spreading across country borders.

Globally, data on vaccine hesitancy have been collected only since 2014, but country response rates have already surpassed 80% (although survey data are available in only 33% of countries). A large majority of countries are reporting issues with hesitancy, but the nature of these issues varies by region and country income level. One risk is that immunization concerns are co-opted to serve political purposes.

Countries vary greatly in their preparedness for hesitancy 'outbreaks' or declining coverage, with middle-income countries in particular typically lacking the capacity to manage hesitancy challenges.

Given the potential for hesitancy to have a major impact on coverage, it is important that all countries take steps to understand both the extent and nature of hesitancy at a local level, on a continuing basis. There are a range of tools by which this can be achieved, including population surveys, media and social media monitoring, and through community dialogue. Allied to this work is the need to develop strategies for building and maintaining trust with communities – an area where health workers and CSOs can play valuable roles. The final key aspect is a plan for responding effectively to major hesitancy 'outbreaks'.

With only a minority of countries not reporting any experience of vaccine hesitancy, it is important that all countries develop comprehensive national hesitancy management strategies, encompassing regular assessment of local hesitancy, trust building, and emergency response planning. With the evidence base growing on how hesitancy can be forestalled and mitigated, there is also a need to extend efforts to capture lessons learned and share best practice.

**Civil society organizations:** CSOs can play a key role in advancing immunization, across a range of domains. It is important that countries consider both the range of CSOs with which they engage, and the breadth of activities to which CSOs might contribute.

CSOs have well-established roles in community mobilization and in helping immunization programmes access particular hard-to-reach populations. But they can also contribute directly to immunization services, play roles in education and dissemination of knowledge, and be an important source of technical expertise. On the national stage, CSOs can play a critical role in advocacy and in holding governments to account. They also have the potential to make significant contributions to national hesitancy management strategies.

Countries need to consider extending the range of organizations involved in immunization programme development, planning and operations. Bodies such as professional societies, academic institutions, religious and political organizations, philanthropic bodies, patient support groups, and community organizations may all have valuable contributions to make. In effect, countries should consider how they can best make the local environment 'CSO-friendly' for involvement in immunization programmes.

In addition, there is a need to understand better the contributions made by CSOs, to capture important lessons learned and to share best practice. It can be difficult to assess rigorously the impact of CSOs on immunization at the national level. The CSO Reporting Framework, developed for Gavi-supported countries, is an important step in this direction, and this new tool should be widely adopted, ideally also beyond Gavi-supported countries.

The advocacy function of CSOs can be aided by legislation laying down citizens' rights to immunization services, which provides a critical tool enabling CSOs to hold politicians to account. Indeed, at a national level, immunization can be strongly advanced through effective partnerships between the executive, the legislative system and civil society. More generally, there is a need to understand the variety of ways in which legislation and regulation have been used to advance the cause of immunization (including its use to address hesitancy), the impact of such measures, and the contextual factors that have influenced their effectiveness. A synthesis of the evidence on the use of legislative and regulatory instruments could guide national efforts to advance the immunization agenda.

**CSOs**  
can play multiple  
roles on the national  
stage, including  
advocating for  
immunization,  
mobilizing  
community support,  
and providing  
a source of  
technical expertise



## 7. SUSTAINABLE PROGRAMMES

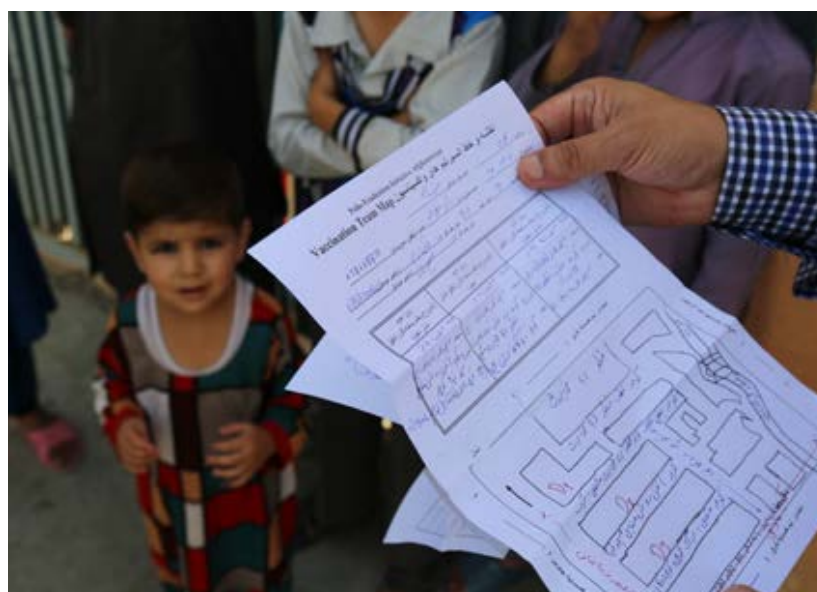
Effective, robust and sustainable immunization programmes are fundamental to achieving the GVAP goals. Increasing coverage is becoming an ever-greater challenge, as more hard-to-reach populations need to be accessed, the number of vaccines to be delivered rises, and the ages of vaccine recipients becomes more diverse. By establishing robust programmatic infrastructures, countries have a platform on which to expand their reach, extend their scope, and promote integration with other health, welfare and development services.

Adopting a multidimensional approach (see above) is an important step in assessing programme functions and identifying ways in which they can be strengthened. Evidence of its effectiveness comes from India, which has achieved impressive gains in coverage following a comprehensive national overhaul of its immunization programme, driven directly from the Prime Minister's office. This political commitment has been matched by increased investment in immunization services, a strong emphasis on technical capacity-building, detailed monitoring and evaluation with clear lines of accountability at national, state and district levels, and extensive community mobilization.

NITAGs, RITAGs and the Global NITAG Network all have potentially important roles to play in the strengthening of national immunization programmes, with NITAGs being specifically referenced in the 2017 World Health Assembly resolution. The number of countries with NITAGs complying with six basic process indicators has grown significantly since 2010, reaching 83 (42% of countries) in 2016. Recent progress has been particularly marked in the African and Western Pacific regions.

However, there remains a need to ensure that NITAGs function effectively. In particular, to perform their roles as independent advisory bodies, NITAGs need to maintain high levels of transparency and of disclosure and management of relevant interests. Some countries may also require innovative solutions for NITAG development, such as small island nations with small populations (but which collectively account for large numbers of people).

Regional collaboration will be important for increasing the numbers of NITAGs and strengthening their contributions to national immunization programmes. Specifically, RITAGs have the potential to support the establishment and development of NITAGs, particularly by enhancing their capacity for evidence-based review. The Global NITAG Network, which held its formal inaugural meeting in 2017, provides additional opportunities for boosting the role of NITAGs and for sharing good practice, particularly through the NITAG Resource Centre.



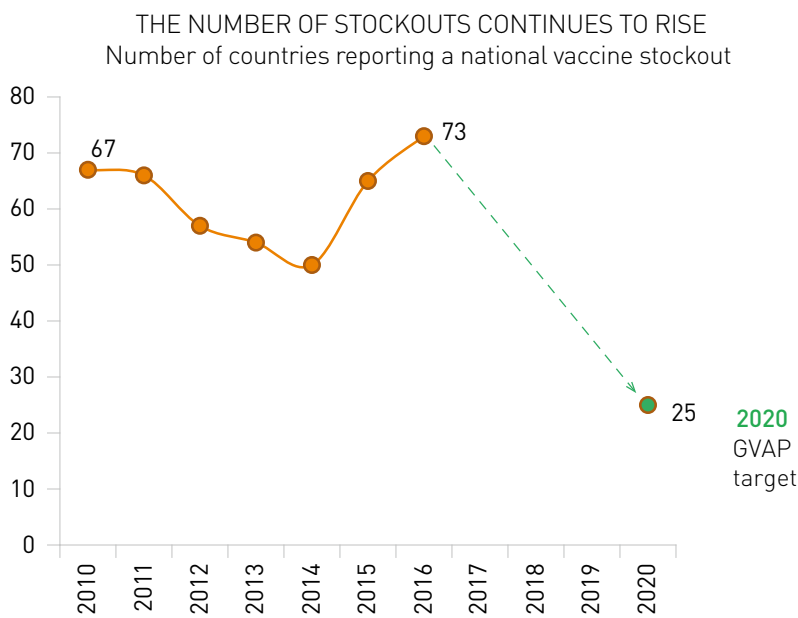
WHO J Swann

The number of countries with functional NITAGs doubled between 2010 (41) and 2016 (83)

**Technical capacity-building:** Many of the issues facing immunization programmes worldwide reflect shortfalls in technical capacity rather than just economic constraints. There is an ongoing need to enhance capacity, typically in situations where few additional resources can be mobilized.

It is therefore increasingly important to identify ways to make the best possible use of existing resources, leveraging local, regional and global opportunities to enhance technical capacity. The WHO, for example, has developed a range of resources and e-learning tools, and has established key norms and standards. There may also be opportunities to draw on technical expertise within local academic and training institutes (an approach adopted in India). Local CSOs, including the private immunization sector, may also represent a source of expertise or, with appropriate training, could be integrated into national programmes to expand capacity.

Given the likely importance of local and contextual issues, assessments of technical capacity-building needs should be carried out at a regional level. This would also provide opportunities for peer-to-peer learning. RITAGs could also make a major contribution to such assessments and to subsequent capacity-strengthening initiatives. A multidimensional approach should be adopted for the assessment of needs and in the development of capacity-building plans, to ensure a comprehensive system-wide analysis is carried out.

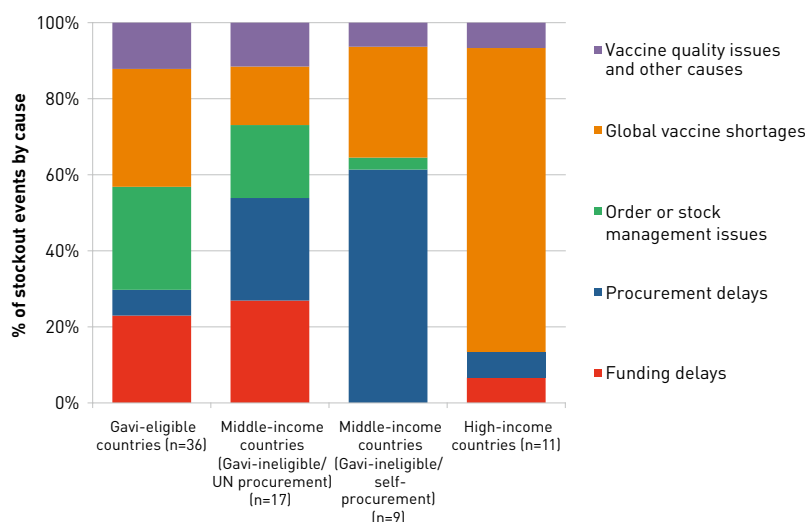


The number of countries reporting a national stockout rose again in 2016, continuing a recent trend of increasing disruptions in vaccine supply. Some 73 countries reported 131 national-level stockout events for at least one vaccine for an average duration of 51 days in 2016. These 73 countries account for 38% of WHO Member States and represent 34% of the world's birth cohort. The vaccine supplies most commonly affected were of DTP-containing vaccines and poliovirus vaccines.

**73 countries**  
reported at least  
one vaccine stockout  
in 2016

The annual value of pooled procurement through UNICEF now exceeds **US\$1.7bn**

### THE CAUSES OF NATIONAL VACCINE STOCKOUTS VARY



Countries of all income levels were affected by stockouts, although the causes tended to vary. Stockouts in high-income countries were generally caused by vaccine shortages but in other countries were often linked to factors such as inaccurate forecasting and delays in procurement.

**Vaccine access: Programme expertise:** The increasing incidence of stockouts and disrupted access to vaccines is of growing concern. The majority of these stockouts, especially outside high-income countries, are a result of internal (in-country) issues rather than vaccine production, such as inaccurate forecasts, stock management issues and procurement delays.

Ensuring reliable access to vaccines should be a core function of national immunization programmes. Well-established procedures exist to guide demand assessment and forecasting, procurement, and distribution, and principles of good practice outlined to ensure continuity of supply (for example, not relying on single manufacturers). The alarming rise in stockouts suggests there is a need to develop the capacity of programmes in effective procurement and stock management, again by adopting a multidimensional framework. Given the likely influence of local contextual issues, assessments of capacity development needs should be led at a regional level, enabling countries to share lessons learned and best practice and to provide peer-to-peer support.

One tool that could support such efforts is the Vaccine Product Price and Procurement (V3P) database. A total of 144 countries submitted 2016 vaccine price information to V3P, three times as many as in the preceding year. Just four years since its launch, V3P has therefore created high levels of price transparency covering 84% of all WHO Member States and 95% of the world's birth cohort.

V3P data confirm that pooled procurement mechanisms, such as those managed by PAHO and UNICEF, do manage to secure lower vaccine prices. This does not simply result from bulk purchasing but reflects the importance of other factors that can affect pricing (such as long-term commitments and payment guarantees). For self-procuring countries, V3P can also be used as a tool to support collaborative purchasing. In the European region, health authorities in three Baltic nations – Latvia, Estonia and Lithuania – have collaborated on procurement of three vaccines, and use of V3P enabled the countries to secure significant savings on vaccine costs.

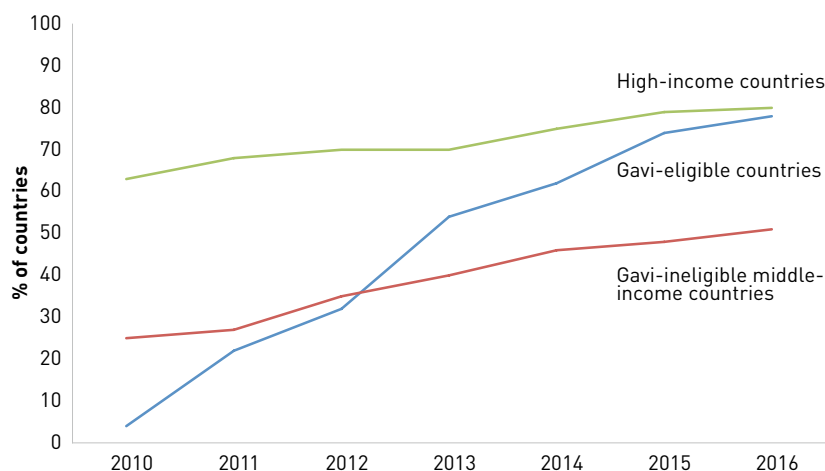
**Vaccine access: Production issues:** Supply-side factors and vaccine manufacturing capacity are also limiting access to vaccines used in routine immunization programmes, including inactivated polio vaccine.

Hence there is a need to assess whether global vaccine manufacturing capacity is sufficient to meet current and anticipated demand for the different vaccines and combination vaccines used in routine immunization programmes. A thorough assessment needs to be undertaken of current and projected manufacturing capacity, integrating and expanding relevant ongoing work such as the WHO's Vaccine Shortage Project and the Healthy Markets initiative jointly developed by Gavi, UNICEF, and the Bill and Melinda Gates Foundation.

**Middle-income countries:** Middle-income countries collectively account for a large proportion of the world's population, including 73% of the world's poorest people. Many are facing significant challenges in sustaining and developing their national immunization programmes. The economic development of many such countries has not progressed as anticipated, and those ineligible for Gavi funding have limited alternative sources of financial support for their immunization programmes. Furthermore, the number of countries in this situation will rise as countries transition out of Gavi support.

**15** middle-income countries had DTP3 coverage drops of 10 points or more

INTRODUCTION OF PNEUMOCOCCAL CONJUGATE VACCINE HAS BEEN SLOWER IN GAVI-INELIGIBLE MIDDLE-INCOME COUNTRIES



*The introduction of expensive vaccines such as pneumococcal conjugate vaccine is a significant challenge for Gavi-ineligible middle-income countries – in 2016, there was almost a 30 percentage point difference in the proportion of Gavi-eligible and Gavi-ineligible middle-income countries introducing this vaccine into their national immunization schedules. More generally, Gavi-eligible countries have been significantly more likely to introduce new vaccines (90%) than Gavi-ineligible middle-income countries (65%).*

There are concerning signs in some regions of declining coverage within middle-income countries, highlighting the risk that hard-won gains can be easily lost in the absence of continued commitment to immunization programmes. There is also some evidence that 'shocks' to national health systems – such as major disease outbreaks – can affect coverage, hinting at underlying fragility in immunization programmes.

Purchase of vaccines represents the biggest single contributor to the costs of immunization programmes in middle-income countries. Gavi-ineligible middle-income countries do not have access to the preferential pricing associated with Gavi support. Important efforts are being made to limit price increases for countries transitioning from Gavi support. Potentially, middle-income countries could seek to manage procurement costs through greater use of pooled procurement mechanisms (UNICEF, PAHO Revolving Fund) or collaborative procurement, facilitated by the V3P price transparency database.

On the other hand, progress in many middle-income countries is also being held back by a lack of technical capacity. At a regional level, the sharing of good practice and exchange of technical knowledge and experience should

be improved to enhance national technical capacities, including procurement capabilities. Global collaborations and technical resources could also be leveraged to support technical capacity-building.

As well as these important short-term measures, after the Decade of Vaccines concludes in 2020, it will be important to reassess the situation of middle-income countries and how they can best be supported to achieve immunization goals.

## I 8. CONCLUSIONS

Despite the enormous value of immunization to humankind, significant numbers of infants, children and adults still do not have access to immunization services and do not reap the benefits that many take for granted.

Ensuring that all people gain access to immunization, regardless of who they are and where they live, remains a fundamental global challenge. Looking forward, this challenge will need to be met in a changing world, characterized by large-scale conflict and civil strife, global warming and natural disasters, economic uncertainty, growing vaccine hesitancy, and multiple displaced and mobile populations.

One way in which the global immunization community can respond to these challenges, and spread further the benefits of immunization, is to **recognize and reinforce the alignment between immunization and emerging global health and development agendas**. The Sustainable Development Goals represent a holistic framework to health, wellbeing and development towards which immunization has much to offer. Global health security, universal health coverage and combating antimicrobial resistance are all global agendas to which immunization can and should be contributing.

A key principle to communicate will be **common interests and the mutual benefits of closer alignment**. Immunization platforms provide a way to reach a significant proportion of national populations, which could be leveraged to enhance other aspects of health, welfare and development. Immunization can help to combat global health threats such as antimicrobial resistance and infectious disease outbreaks. There are also key shared interests in areas such as surveillance, laboratory capacity-building and technical skills development.

A further important aspect of this shift in emphasis will be the **growing application of immunization beyond childhood**. A broader life-course perspective on immunization further emphasizes the importance of considering immunization within the context of integrated health delivery across the entire life course and health systems strengthening.

Opportunities also exist to **strengthen the dialogue with other sectors**, including business, economic and financial sectors, as well as with the diverse CSO sector. Again, such dialogue could stress mutual benefits – the health and economic benefits that immunization delivers and how the worlds of business and finance could support immunization financially or through technological or other innovations. Broadening the dialogue could help to re-energize immunization, addressing the risk not just of stalled progress but actual regression.

### ACHIEVING TARGETS

Achieving elimination and control targets – and sustaining them into the future – will require **an ongoing and unwavering commitment to immunization**. There are no short cuts or quick fixes. Progress will depend on maintaining a commitment to immunization and quest for constant improvement at global, regional and national levels. Extending coverage will not be easy, and building more effective immunization programmes will necessarily depend on **systematic and multidimensional analyses of current situations and future needs, recognizing the importance of local realities and contexts**. While there is undoubtedly a place for global support and resources, there are powerful arguments for regional responses tailored to local contexts and cultures.

There are growing opportunities for countries at a regional level, or at a similar stage of economic development, to collaborate and learn from one another, enabling them to make best use of inevitably limited resources. In addition, the international donor community has a vital role to play in providing the technical and financial support necessary to catalyse lasting change.

An estimated  
**2–3 million**  
deaths are  
averted each year  
through immunization



A further key theme is the **importance of research and the generation of evidence to support the most effective use of resources**. There is an increasing need to capture and share lessons learned, and to explore the impact of innovative new approaches. New technologies – from digital tools to drones – may provide novel ways to achieve step changes in coverage and close equity gaps.

As the Decade of Vaccines draws to a close, the global immunization community can reflect on the millions of lives that have been saved because more people have gained access to vaccines. Post-2020, **the challenge will be to ensure that these gains are protected and further extended** – to ensure more vaccines reach more people more rapidly.



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## I 9. RECOMMENDATIONS

### GENERAL

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

Main responsibility: Immunization community; other key stakeholders: countries

#### **Subsidiary recommendation:**

- 1b. **Joint External Evaluations:** An assessment should be made of immunization-related inputs into national Joint External Evaluations for Global Health Security, the immunization community's contribution to the development of national evaluation reports, and the reference made to immunization in these reports

Main responsibility: WHO regional offices, countries

### CONCERNS

2. **Funding transitions:** Until polio eradication is achieved, financial and technical support provided through the Global Polio Eradication Initiative, Gavi and WHO should be maintained in at least the 16 polio priority countries to ensure the success of eradication efforts and to mitigate the risks to infectious disease surveillance, routine immunization and global health security more generally

Main responsibility: Gavi, Global Polio Eradication Initiative; other key stakeholders: countries

3. **Polio and communicable disease surveillance:** Poliomyelitis laboratory and epidemiological surveillance capacities should be maintained in countries across all regions throughout and beyond the polio endgame and certification process, and built upon to strengthen surveillance for other communicable diseases, especially measles and rubella

Main responsibility: Countries; other key stakeholders: partners, immunization community

4. **Outlier countries:** Comprehensive multidimensional assessments should be undertaken in countries experiencing the greatest difficulties in achieving GVAP goals and used to develop bespoke and costed remediation plans addressing systemic weaknesses, integrating existing improvement plans and including a strong focus on monitoring and evaluation frameworks to support effective implementation

Main responsibility: WHO regional offices, countries; other key stakeholders: partners

### EQUITY

5. **Maternal and neonatal tetanus:** Concerted efforts should be made to achieve global elimination by 2020 and sustain thereafter, particularly by exploiting the opportunity to expand coverage to underserved populations through use of compact pre-filled auto-disable devices

Main responsibility: Immunization community, Gavi (pre-filled devices); other key stakeholders: countries, CSOs

6. **Displaced and mobile populations:** Existing knowledge on reaching displaced and mobile populations – including individuals escaping conflict zones or natural disasters, economic migrants, seasonal migrants, those moving to urban centres, and traditional nomadic communities – should be synthesized to identify good practice, innovative new approaches and gaps in knowledge

Main responsibility: WHO Secretariat, UNICEF Secretariat; other key stakeholders: WHO regional offices, national partners, academic community, CSOs



## CONTEXT

- 7. Hesitancy:** Each country should develop a vaccine hesitancy management strategy, to include ongoing national assessment of vaccine concerns, trust-building and active hesitancy prevention, and crisis response plans

Main responsibility: Countries; other key stakeholders: WHO regional offices, RITAGs, Global NITAG Network and associated technical experts, CSOs

- 8. Civil Society Organizations:** Countries should aim to broaden and deepen their engagement with CSOs, expanding the range of CSOs with which they interact and extending their input into areas such as programme planning

Main responsibility: Countries; other key stakeholders: WHO regional offices, CSOs

### **Subsidiary recommendation:**

- 8b. Legal frameworks:** A comprehensive global audit should be undertaken to document the ways in which legislation and regulation have been used to promote immunization at a national level, to identify how legal and regulatory instruments can best be applied in different contexts and for different purposes

Main responsibility: WHO Secretariat; other key stakeholders: countries, WHO regional offices, CSOs

## SUSTAINABLE PROGRAMMES

- 9. Technical capacity-building:** Through a multidimensional approach, the technical capacity of countries' immunization programmes should be systematically assessed and strengthened, by leveraging regional and national expertise and opportunities as well as global tools and resources

Main responsibility: WHO regional offices, countries; other key stakeholders: RITAGs, NITAGs, Global NITAG Network, CSOs, local higher education institutions, WHO Secretariat

- 10. Vaccine access: Programme expertise:** Multidimensional analyses should be undertaken to identify procurement and other programmatic issues affecting timely provision of vaccination, including to the most marginalized and remote populations, and used to develop more effective procurement, stock management and distribution plans

Main responsibility: WHO regional offices, countries; other key stakeholders: RITAGs

- 11. Vaccine supply:** Current and anticipated vaccine supply and demand for routinely used vaccines should continue to be mapped and constraints identified, integrating and expanding other relevant ongoing work and focusing on vaccines most at risk of supply shortages

Main responsibility: UNICEF Secretariat, WHO Secretariat and other partners; other key stakeholders: manufacturers, WHO technical advisers

- 12. Middle-income countries:** WHO regional offices should support middle-income countries in their regions by leveraging all opportunities to promote the exchange of information, the sharing of lessons learned and peer-to-peer support

Main responsibility: WHO regional offices, countries; other key stakeholders: WHO Secretariat

## ANNEX 1: SAGE DECADE OF VACCINES WORKING GROUP MEMBERSHIP

### SAGE MEMBERS

- Nora Noni MacDonald (Chair of the Working Group), Professor of Paediatrics, Dalhousie University, Canada
- Yagob Yousef Al-Mazrou, Secretary General, Health Services Council of the Kingdom of Saudi Arabia, Saudi Arabia

### EXPERTS

- Oleru Huda Abason, Member of Parliament, Parliament of Uganda
- Jon Kim Andrus, Adjunct Professor and Senior Investigator Division of Vaccines and Immunization Center for Global Health, University of Colorado, USA
- Narendra Arora, Executive director, International Clinical Epidemiology Network, India (SAGE Member from 2010 – 2016)
- Susan Elden, Health Adviser, The Department for International Development (DFID) London, UK
- Marie-Yvette Madrid, Independent Consultant, Geneva, Switzerland
- Amani Mahmoud Mustafa, Project Manager, Sudan Public Health Training Initiative, The Carter Center, Sudan (affiliation as of May 2014 and previously EPI Manager, Ministry of Health, Sudan)
- Rebecca Martin, Director of the Center for Global Health, US CDC, USA
- Helen Rees, Executive Director, Reproductive Health and HIV Research Institute, University of Witwatersrand, South Africa (former SAGE Chair 2010 - 2013)
- David Salisbury, Associate Fellow, Centre on Global Health Security, Chatham House, London, UK (previously Director of Immunization, Department of Health, UK and former SAGE Chair 2005 - 2010)
- Budihardja Singgih, Technical Director Australia Indonesia Partnership for Health Systems Strengthening, Jakarta, Indonesia
- Qinjian Zhao, Associate Dean, School of Public Health, Xiamen University, Xiamen, Fujian, China

### WORKING GROUP SECRETARIAT

- Bill & Melinda Gates Foundation
- Gavi, the Vaccine Alliance
- United Nations Children's Fund
- United States National Institute of Allergy and Infectious Diseases
- World Health Organization

## ■ ANNEX 2: SAGE MEMBERSHIP

- Alejandro Cravioto (Chair of SAGE), affiliated with the Faculty of Medicine of the Universidad Nacional Autónoma de México (UNAM), Mexico
- Rakesh Aggarwal, Professor of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India
- Yagob Yousef Al-Mazrou, Secretary General, Health Services Council of the Kingdom of Saudi Arabia, Saudi Arabia
- Ilesh Jani, Director General, Instituto Nacional de Saúde (National Institute for Health), Mozambique
- Jaleela Jawad, Head of Expanded Programme on Immunization, Public Health Directorate, Ministry of Health, Bahrain
- Youngmee Jee, Director General, Centre for Pathology and Immunology, National Institute of Health, Korean Centre for Disease Control and Prevention, Republic of Korea
- Kari Johansen, Expert Vaccine Preventable Diseases, European Centre for Disease Prevention and Control (ECDC), Sweden
- Nora Noni MacDonald, Professor of Paediatrics, Dalhousie University, Canada
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- Andrew J. Pollard, Professor of Paediatrics, Infection and Immunity, University of Oxford, United Kingdom
- Firdausi Qadri, Director, Infectious Diseases Division, Head and Senior Scientist, Mucosal Immunology & Vaccinology Laboratory, icddr,b, Dhaka, Bangladesh
- Nicola Turner, Director Immunisation Advisory Centre, University of Auckland, New Zealand
- Frederick Were, Executive Director and Professor, Department of Paediatrics and Child Health, University of Nairobi, Kenya
- Charles Wiysonge, Director, South African Cochrane Centre, South African Medical Research Council, South Africa

## **Tools for CSO engagement and reporting in support of national immunisation plans**

**Summary:** this is a brief report on how Civil Society Organizations (CSOs) are responding to the Strategic Advisory Group of Experts (SAGE) on Immunization's request, and developing a simple framework and comprehensive set of tools to support CSOs in engaging in immunisation and reporting on their work and its impact.

### **Background: Responding to SAGE's 2016 request**

SAGE in the 2016 Global Vaccine Action Plan (GVAP) report recommended that "CSOs should describe how their work maps against different national immunisation plans in their 2017 GVAP report, so that the geographic and programmatic scope of their work is more visible. Where possible, CSOs should also measure and share the impact of their work."

The Gavi CSO Constituency picked up the gauntlet to respond to SAGE's request. They sought to develop a CSO framework and tools to be used at the country level that would help CSOs focus their work on what has the greatest impact and would allow CSOs to capture and report on contributions to their country's national immunisation plan, as well as the impact of their work. This information would then be fed into annual GVAP report submissions.

To accomplish this, the Gavi CSO Constituency brought together a wide group of immunisation stakeholders in April 2017 to flesh out the elements of a framework. This group, and several additional interested stakeholders, became a global reference group for the work, which included several global and local iterations of the framework and its corresponding tools, as well as in-country pilots (Sierra Leone, Burkina Faso, and India) and virtual testing (Nigeria, Pakistan, and global stakeholders). The work was overseen by the Gavi CSO Steering Committee, specifically, the working group on Monitoring and Evaluation.

The Gavi CSO Constituency presented the framework and tools to the SAGE Decade of Vaccines (DoV) Working Group (WG) during its' three-day meeting August 29-31, 2017, in Geneva. The framework has now incorporated the SAGE DoV WG suggestions.

### **The CSO Framework and Tools in support of national immunisation plans**

It is a comprehensive set of simple tools for use by CSOs in any country (whether Gavi-supported or not), including middle-income and high-income countries. It includes a visual diagram on CSO engagement, and summary pages with key questions and metrics. It focuses on helping CSOs work together to report on their *collective* impact. It builds on what CSOs already do, and considers different types and levels of work across several areas:

- The Immunisation System – tools support CSOs in engaging in and reporting on immunisation planning, including identification of target populations and helping to improve the quality of the immunisation workforce, services and the experience of care. Although it focuses on improving routine immunisation, it also includes a "mini-module" on CSO engagement in immunisation campaigns.
- Advocacy & Accountability – these tools support CSOs in advocating for and holding accountable various stakeholders on key issues such as budget and spending for immunisation, and improving immunisation data quality and availability.

- Increasing Demand for Immunisation – these tools support CSOs in improving populations’ knowledge of and trust in immunisation, and helping to reduce social, cultural and access barriers.
- Fragile Contexts – a special module is included that is specifically tailored to fragile contexts, which can be national or sub-national and require a different approach than a normal environment. One key assumption is that when government systems are especially weak or not functioning, some CSOs step in to provide immunization services. Thus, this module has a service delivery component.
- Additional materials included in the framework:
  - A how-to guide on using the framework, including defining “the denominator” and other terms, and providing useful links.
  - Tally sheets
  - A Knowledge Translation plan

The complete set of materials will be available in October on <http://www.gavi-cso.org/Resources>

### **Next Steps**

The SAGE DoV WG and Gavi Secretariat requested that we implement the framework in two countries, and analyse and report back on the results. They also requested a plan on the way forward, including quantification of resources needed. Funding and support will be sought for the initial two-country pilot in the coming months.

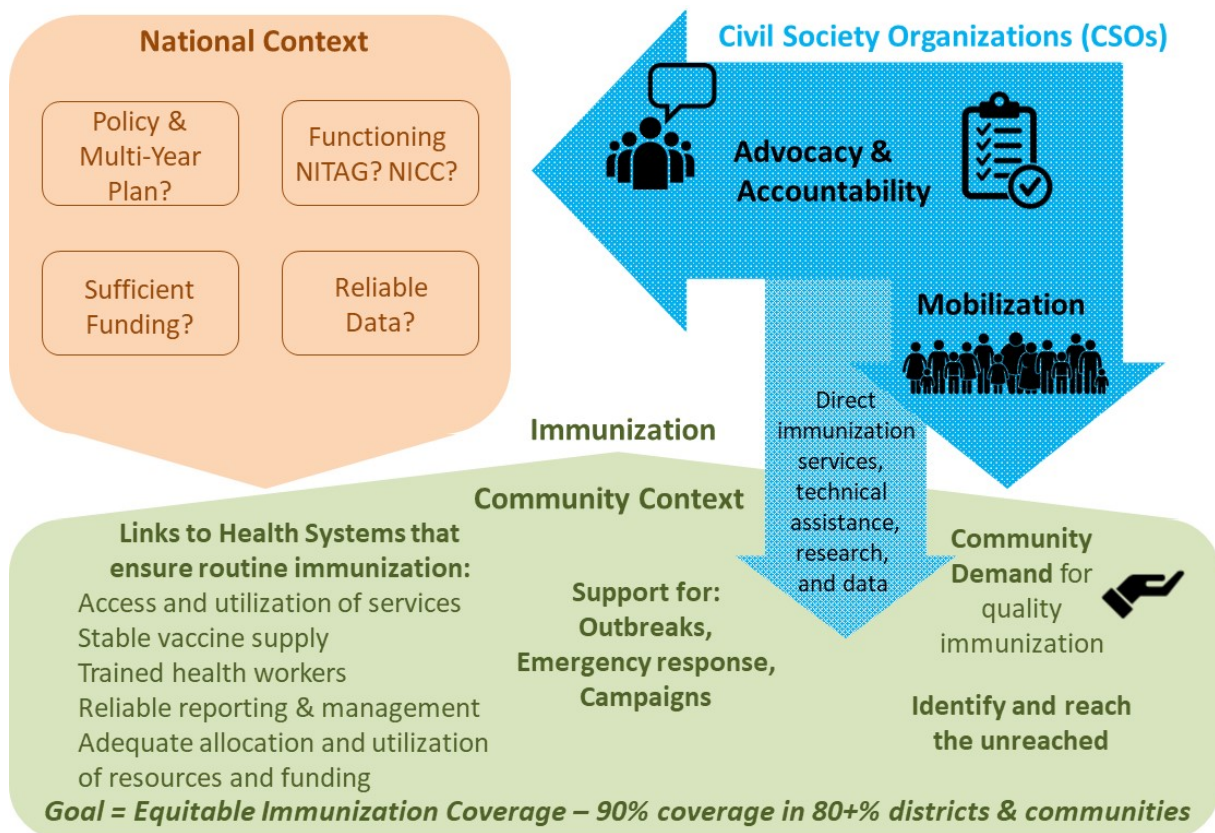
### **Role of Civil Society in immunisation and historic challenges**

Civil Society plays a key role in increasing immunisation coverage and equity in many countries. Civil Society Organisations (CSOs) often contribute to immunisation and health systems by creating demand for and uptake of routine childhood vaccines, directly supporting their country’s national immunisation goals and, at a broader level, GVAP goals.

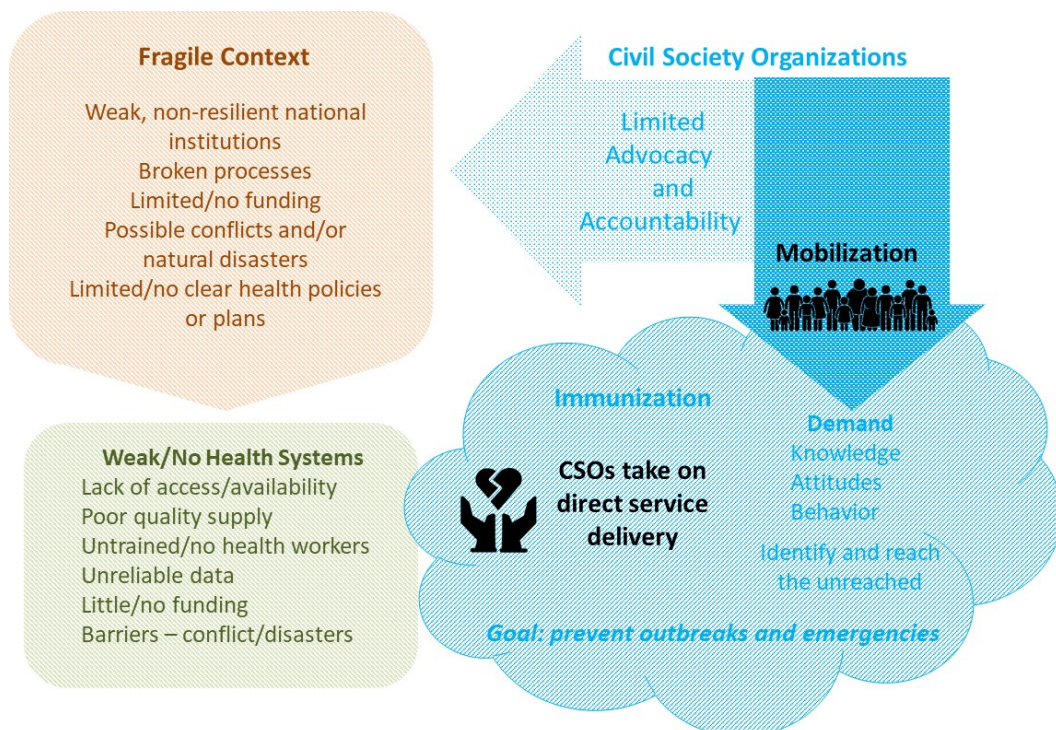
Despite the key role played by CSOs in supporting national immunisation programs, it has been challenging to document the impact of CSO contributions in a systematic way. The issue of measuring and reporting CSO contributions to national immunisation plans and systems is one that arises often in a variety of contexts, including throughout the DoV. The lack of clear information and data around the role and contributions of CSOs to countries’ immunisation plans and goals is often cited as preventing more robust support and funding for civil society. It also contributes to a continued “tokenistic approach” to including civil society in key discussions.



**Conceptual Framework:** CSOs represent communities and work in partnership with government and all immunization stakeholders

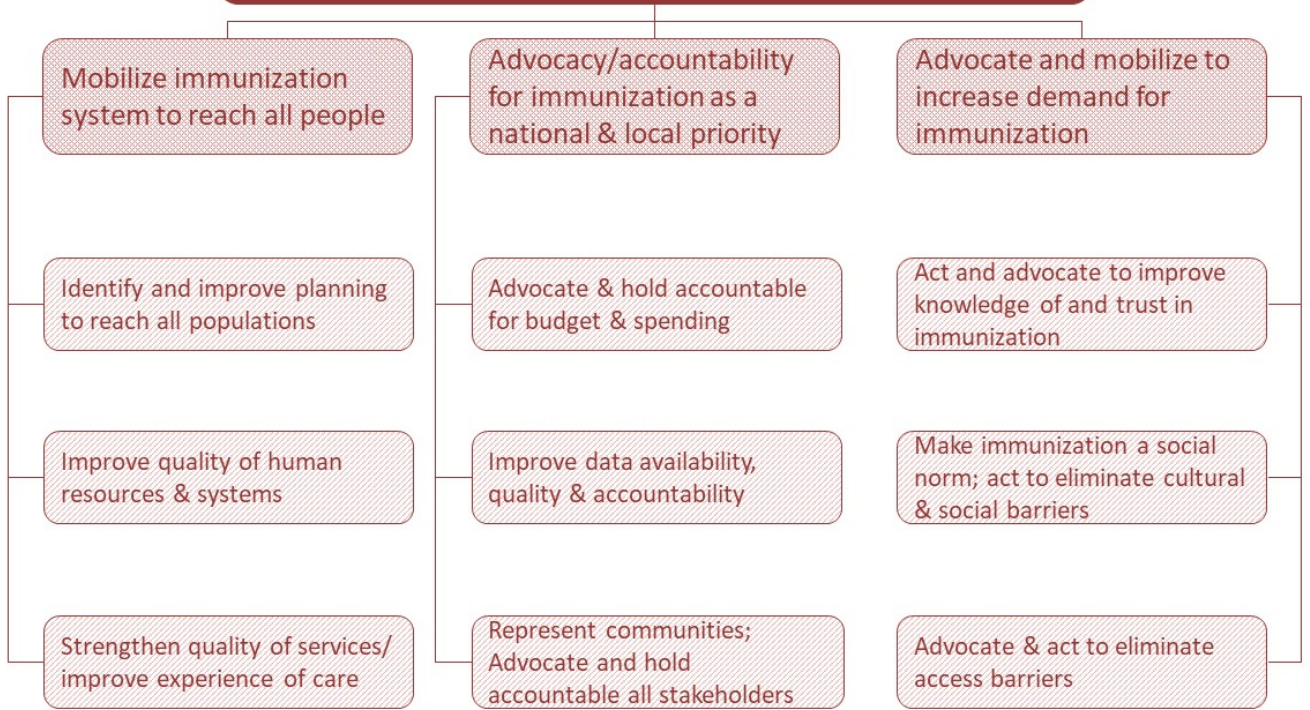


**Conceptual Framework: CSOs in Fragile Contexts**



**Increased Immunization Coverage: Results Framework for CSO actions\***

**CSO contributions toward increased coverage  
(90% coverage in 80% of districts and communities)**



\*Key assumption: CSOs work collaboratively w/EPI (Extended Program for Immunization) and all relevant stakeholders

**Background paper:**  
**PROPOSED REVISION OF THE POLICY ON RABIES  
VACCINES AND RABIES IMMUNOGLOBULINS**

*Prepared by the SAGE Working Group on Rabies vaccines and immunoglobulins  
and the World Health Organization (WHO) Secretariat  
September 22, 2017*



## EXECUTIVE SUMMARY

### Preamble

Rabies is a vaccine-preventable viral zoonotic disease responsible for an estimated 59,000 human deaths every year. The majority of cases occur in Africa and Asia, and more than 40% of cases occur in children less than 15 years of age. Dogs are responsible for over 95% of all rabies transmissions to humans.

Rabies prevention involves two main, non-exclusive strategies: (i) dog vaccination to interrupt virus transmission to humans; and (ii) human vaccination i.e. post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) using purified cell-culture and embryonated egg-based vaccines (CCEEVs).

PEP is administered promptly following exposure to rabies, and consists of timely, rigorous wound care, administration of rabies immunoglobulin (RIG) in severe exposures, and a series of intradermal (ID) or intramuscular (IM) rabies vaccines. Long, complicated PEP regimens and the high cost, low availability, uncertain quality and short shelf life of RIG are barriers to PEP implementation.

PrEP is indicated for individuals who face occupational and/or travel-related exposure to rabies virus in specific settings or over an extended period. PrEP consists of a series of rabies vaccines, followed by booster vaccinations in case of exposure.

Gaps exist between the current WHO recommendations and the present practice of PrEP and PEP administration in many rabies-endemic countries. This update addresses this mismatch using new evidence on rabies vaccine and RIG use, including: (i) shorter, more feasible PrEP and PEP protocols; (ii) cost-effectiveness of implementation; and (iii) the potential of new vaccines to improve access to care.

### Key Conclusions and Proposed Recommendations

#### Pre-exposure prophylaxis (PrEP)

PrEP as a population-level intervention is unlikely to be cost-effective, and should only be considered in extreme circumstances, where the incidence of rabies exposures is unusually high (>6%), and RIG use low. Recommendations for PrEP boosters and serological monitoring have been updated, taking into account: (i) timely access to rabies biologics; (ii) access to rabies serological testing; (iii) immunogenicity of booster vaccination; and (iv) cost-effectiveness.

The following accelerated PrEP regimens are considered as efficacious as current PrEP regimens:

- 2-site ID regimen on days 0 and 7
- 1-site IM regimen on days 0 and 7

Individuals who receive only a single dose of PrEP should be managed with full PEP in the case of potential rabies exposure prior to the second PrEP dose. Individuals who are immunocompromised should receive a 3-visit ID or IM PrEP regimen on days 0, 7 and between days 21 and 28, and should be managed with full PEP in the case of a potential rabies exposure with particular emphasis on rigorous wound washing.

#### Post-exposure prophylaxis (PEP)

Intradermal vaccination is cost and dose-sparing by up to 85% compared to intramuscular vaccination. Modelling estimates show that for every 1000 vials of rabies vaccine, almost 500 additional patients could be treated using an accelerated ID PEP regimen (described below) compared e.g. to the Essen IM PEP regimen.

The following accelerated ID PEP regimen is considered as efficacious as current PEP regimens:

- 2-site ID regimen on days 0, 3 and 7 (IPC regimen)

At present, there is no clinical data to support shortening IM regimens. The working group continues to recommend the Essen IM PEP regimen: 1-site IM regimen on days 0, 3, 7 and between days 14 and 28

Changing the route of administration during a PEP course (i.e. from ID to IM or vice versa) is acceptable in unavoidable circumstances. Restarting PEP is not necessary and the schedule for the new route should be adopted if this occurs.

PEP is safe and effective for use in pregnant women. PEP should not be withheld from pregnant women.

Individuals who are immunocompromised should receive meticulous wound cleaning, the most immunogenic PEP regimen available regardless of administration route, and high-quality RIG.

Individuals experiencing bat-mediated rabies exposure should receive any WHO PEP regimen. Bites from bats may go unrecognised; cautionary principles apply to bat exposures.

Persons exposed or re-exposed to rabies who have previously received PrEP, PEP, or who have discontinued PEP after receiving at least two doses of CCEEVs should receive either:

- 1-site ID PEP on days 0 and 3; or
- 4-site ID PEP on day 0

RIG is not indicated in previously immunized individuals.

#### **Rabies immunoglobulins (RIG)**

The recommendation to calculate maximum dosage of RIG based on body weight is maintained.

Local infiltration of as much RIG as possible into and around the wound is most effective in preventing rabies. Injection of remaining RIG distant to the wound site is unlikely to confer additional protection.

Equine (eRIG) and human (hRIG) rabies immunoglobulin are considered clinically equivalent. Skin testing prior to administration of eRIG should be abandoned.

RIG is not indicated for healthy persons who have previously received PEP or PrEP.

Where RIG is not available or affordable, its use should be prioritised for persons with multiple or deep wounds; bites to the head, neck, hands, genitals or other highly innervated areas; immunocompromised patients; patients bitten by a probable or confirmed rabid animal; and patients with bites, scratches, or other mucous membrane exposure to a bat.

Scrupulous wound cleaning and deep irrigation, with application of a potent antiseptic agent, and timely administration of the first CCEEV dose, are key to increasing survival where RIG is unavailable. This is supported by evidence from field data combined with modelling which show that, even in the absence of RIG, rigorous wound washing together administration of vaccines the same day as the bite and completion of the PEP course is highly protective against rabies (>95%).

Further development and assessment of monoclonal antibodies (mAbs) should be promoted as a potentially affordable and more accessible alternative to RIG. Post-marketing surveillance is needed for both RIG and mAbs.

#### **New vaccines and operational tools under development**

New vaccines under development have the potential to induce long-lasting immunity and improve programmatic delivery. Novel vaccine delivery tools such as micro-needle patches, ID injectors devices have the potential to increase uptake of ID vaccine administration.

Further programme-directed research on immunogenicity and clinical outcomes of rabies PrEP or PEP in immunocompromised individuals would allow better understanding of factors important for seroconversion.

Further innovation, research and development in collaboration with manufacturers is required to improve community delivery of rabies biologics, and to optimize cost-effectiveness, safety and efficacy of vaccines.

#### **Conclusion**

Updated, more programmatically feasible recommendations are critical to improve public health impact from a neglected disease like rabies. The practical guidance relevant to rabies-endemic settings particularly aims to improve community delivery of rabies PEP. The recommendations will facilitate meeting the need, especially in underserved populations that should have a better opportunity to access affordable, life-saving rabies biologics more equitably, as the world strives to reach the goal of zero dog-transmitted human rabies deaths by 2030.

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## 1. ABBREVIATIONS

<b>BHKV</b>	Baby Hamster Kidney (cells) Vaccine
<b>BMI</b>	Body mass index
<b>CCV</b>	Purified cell-culture vaccine
<b>CCEEV</b>	Purified cell-culture and embryonated egg-based vaccines
<b>CTC</b>	Controlled temperature chain
<b>DHIS2</b>	District Health Information Software 2
<b>DPT</b>	Diphtheria, pertussis and tetanus
<b>DRIT</b>	Direct rapid immunohistochemistry test
<b>EEV</b>	Embryonated egg-based vaccine
<b>ELISA</b>	Enzyme linked immunosorbent assay
<b>eRIG</b>	Equine rabies immunoglobulin
<b>F(ab')<sub>2</sub></b>	Antigen-binding immunoglobulin fragments
<b>FAO</b>	Food and Agriculture Organization of the United Nations
<b>FAT</b>	Fluorescent antibody testing
<b>FAVN</b>	Fluorescent antibody virus neutralisation test
<b>GAVI</b>	Global Alliance for Vaccines and Immunization
<b>GARC</b>	Global Alliance for Rabies Control
<b>GMT</b>	Geometric mean titre
<b>GRADE</b>	Grading of Recommendations, Assessment, Development and Evaluation
<b>HDCV</b>	Human diploid cell vaccine
<b>HIV</b>	Human immunodeficiency virus
<b>hRIG</b>	Human rabies immunoglobulin
<b>ID</b>	Intradermal
<b>IM</b>	Intramuscular
<b>IPC</b>	Pasteur Institute of Cambodia
<b>IU</b>	International units
<b>JE</b>	Japanese encephalitis
<b>mAB</b>	Monoclonal antibody
<b>NTV</b>	Nerve tissue vaccine
<b>OIE</b>	World Organisation for Animal Health
<b>PARACON</b>	Pan-African Rabies Control Network
<b>PCECV</b>	Purified chick embryo cell vaccine
<b>PDEV</b>	Purified duck embryo cell vaccine
<b>PEP</b>	Post-exposure prophylaxis
<b>PIKA</b>	Polyinosinic-polycytidylic acid based adjuvant
<b>PPHKCV</b>	Purified primary hamster kidney cell vaccine
<b>PrEP</b>	Pre-exposure prophylaxis
<b>PVRV</b>	Purified vero cell vaccine
<b>RABV</b>	Rabies virus
<b>RFFIT</b>	Rapid fluorescent focus inhibition test
<b>RIG</b>	Rabies immunoglobulin
<b>RNA</b>	Ribonucleic acid
<b>RT-PCR</b>	Reverse transcriptase PCR
<b>RVNA</b>	Rabies virus neutralizing antibodies
<b>SAGE</b>	Strategic Advisory Group of Experts on Immunization
<b>SDG</b>	Sustainable Development Goal
<b>SIRVERA</b>	Sistema de Información Regional para la Vigilancia Epidemiológica de la Rabia
<b>TRC</b>	Thai Red Cross

## 2. INTRODUCTION AND BACKGROUND

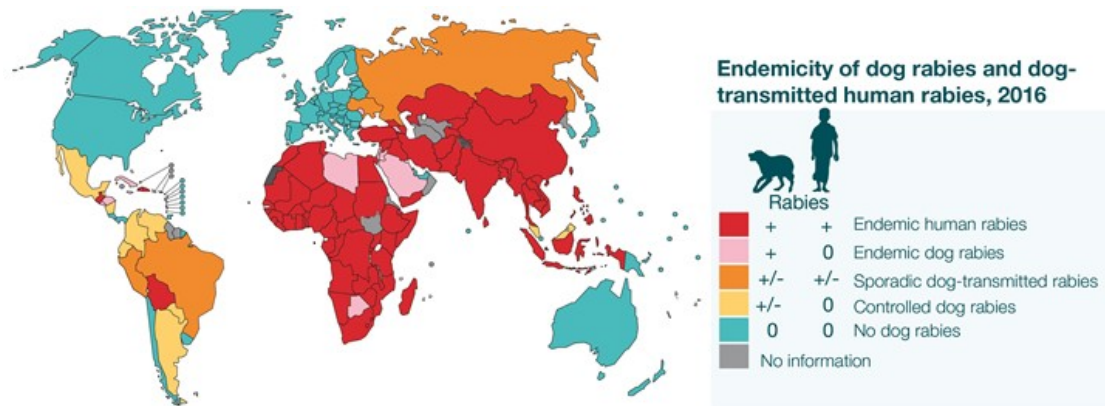
### 2.1. Key Points

- A global target of zero human rabies deaths by 2030 was set in line with the Sustainable Development Goals (SDG) 3.3 to end Neglected Tropical Diseases by 2030 and SDG 3.8 to achieve Universal Health Coverage
- Rabies is a vaccine-preventable viral disease with the highest documented case-fatality rate, close to 100%
- Rabies occurs in more than 100 countries and territories
- Infection causes an estimated 59000 human deaths every year
- Dogs are the main source of human rabies deaths worldwide, causing up to 95% of all rabies transmissions to humans.
- Rabies is an underreported, under- or misdiagnosed disease of underserved populations; data is scarce.
- There are still numerous countries where rabies vaccine and/or RIG is not part of the essential medicines list.
- Around 40% of people bitten by suspect rabid animals are children under 15 years of age.
- Prevention of rabies has two main, non-exclusive strategies: 1) dog vaccination to interrupt virus transmission; 2) human vaccination as post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP).
- Awareness on rabies and education on bite prevention are powerful tools to avoid rabies exposures
- PEP consists of immediate, rigorous wound care, administration of rabies vaccine and simultaneous administration of rabies immunoglobulin (RIG) in severe exposures. Completion of the vaccination schedule is essential.
- Rabies vaccines (CCEEVs) are safe and highly immunogenic, PEP is effective in preventing rabies
- The high cost, low availability and supply, batch to batch variation affecting efficacy, uncertain quality (no WHO prequalification) and short shelf life of RIG are barriers to implementing PEP

### 2.2. Introduction to Rabies:

Rabies is a zoonotic disease caused by the rabies virus (RABV). RABV belongs to the genus *Lyssavirus* in the family *Rhabdoviridae*; *Lyssaviruses* all elicit an acute progressive encephalitis in humans. The genome of RABV is single-stranded negative-sense RNA that codes for five proteins; the most important of these from an immunizations perspective is the G glycoprotein, which includes the antigenic sites targeted by rabies vaccines and passive immunization (WHO, 2013).

Rabies is of public health concern to over three billion people worldwide, and causes an estimated 59 000 human deaths annually (Hampson et al., 2015). While bats and several wildlife species can transmit rabies, dogs are the source of over 95% of human cases. Marginalized and rural populations are disproportionately affected, experiencing the greatest burden with the least access to affordable preventative treatment. The majority of cases occur in Africa and Asia (Figure 1), and more than 40% occur in children under the age of 15 (Knobel et al., 2005).



**Figure 1:** Endemicity of dog and dog-transmitted human rabies based on data of 2016 (WHO, 2017)

Rabies is transmitted through direct contact between the virus (e.g. in contaminated saliva), and mucous membranes or wounds. Human infection most frequently occurs following a transdermal bite or scratch from an infected animal (WHO, 2013). All age groups are susceptible, although children are at increased risk of sustaining bites to the head or neck, and may be less likely to report bites or scratches sustained in play. With the exception of organ transplants from rabid patients, human-human transmission has never been confirmed, including after close contact during health case. Very rarely, rabies has been contracted by inhalation of virus-containing aerosol. The risk of sexual transmission remains theoretical. In most cases the incubation period is two to three months. This can vary from less than one week (e.g. in the case of direct nerve inoculation) to more than one year, depending on the amount of virus inoculated, and its proximity to the central nervous system (WHO, 2013).

Inoculated virus travels via the peripheral nerves to the central nervous system. Upon reaching the brain, it replicates and disseminates rapidly to the salivary glands, throat muscles and other tissues. The rabies virus is concealed from immune surveillance and neutralization by immunoglobulin by its location inside the neurons. Therefore, antibody responses in serum and cerebrospinal fluid (CSF) are rarely detected before the second week of illness (WHO, 2013). The virus does not enter the bloodstream, and human immunoglobulin prophylaxis is considered to be effective only when the rabies virus is present in the bite wound.

Clinical diagnosis of rabies is informed by patient presentation, history of exposure to a suspect rabid animal, and whether preventative measures such as PEP have been administered. Once clinical signs appear, the disease is almost always fatal. Laboratory confirmation of human rabies can be performed ante-mortem or post-mortem on saliva, spinal fluid or tissue biopsies to detect intact virions, viral genomic RNA, antibody or antigen (WHO, 2013). With the exception of hydrophobia, clinical signs of rabies can be unreliable, and contribute to under- or misdiagnosis of rabies in humans. Additionally, rabies patients often die at home, or leave hospital when no treatment can be offered, and are therefore not included in clinical databases and mortality statistics (WHO, 2017).

The initial symptoms of rabies are fever, pain or paresthesia at the wound site. As the virus spreads through the central nervous system, a progressive fatal encephalomyelitis develops, characterized by hyperactivity and fluctuating consciousness. Other clinical symptoms include hyperactivity, hallucinations, and hydrophobia (furious rabies), or paralysis and coma (paralytic rabies), followed by death (WHO, 2013). In both furious and paralytic forms, death usually occurs by cardiorespiratory arrest within 7-10 days of the first clinical sign. While rabies is considered nearly 100% fatal, it is also 100% preventable. It differs from many other infections in that the development of clinical disease can be prevented through timely immunization, even after exposure to the infectious agent. Rabies can be prevented both before and after exposure via pre-exposure prophylaxis or post-exposure prophylaxis. Education and awareness are key to prevent bites from and thus exposure to rabid animals.

## 2.3. Rationale for an update and previous recommendations from the Position Paper

### 2.3.1. Rationale for an update

Despite highly efficacious biologics preventing rabies when exposed, there has been a continued observation of discrepancy between the current practice of rabies PrEP and PEP in (rabies-endemic) countries and the feasibility to implement the current standard according to the WHO recommendations in many settings. This has led to major health equity gaps, particularly between urban and rural areas as well as between socioeconomic classes of populations. There was an urgent need to review accumulated new evidence for vaccine and RIG use, particularly shorter and more feasible PrEP and PEP protocols, cost-effectiveness of implementation and the potential of new vaccines with the view to improve access to care and increased public health impact, worldwide. The global conference on rabies, which was held on December 2015 in Geneva (WHO, 2016), proposed a framework that set an ambitious global goal for elimination of human dog-mediated rabies by 2030, coinciding with the Sustainable Development Goals target date. This global strategy is in line with the priorities of SDG 3.3 to end Neglected Tropical Diseases by 2030 and SDG 3.8 to achieve Universal Health Coverage.

In the effort to improve affordability and access, particularly for vulnerable populations in rabies-affected countries, rabies vaccines are a candidate for inclusion in the vaccine support programme through Gavi, the Vaccine Alliance. Every five years, Gavi reviews its vaccine investment strategy (VIS) to determine which vaccines are made available through their programme. Rabies vaccines were considered in the past two cycles, 2008 and 2013, but weak data and knowledge gaps have postponed its decision on the inclusion until the next VIS in 2018. While a solution on rabies vaccines roll out to countries in demand is in sight, channels for scaling up access to RIG as part of PEP in severely exposed patients still needs to be identified.

### 2.3.2. Recommendations from the 2010 position paper

The 2010 WHO position paper on rabies vaccines summarizes standards on concentrated and purified cell-culture (CCV) and embryonated egg-based (EEV) rabies vaccines (jointly referred to as CCEEVs) and re-iterates their safety, efficacy and high immunogenicity (WHO, 2010). Since the late 1980s, WHO has advocated for replacement of nerve tissue vaccines (NTVs) by CCEEVs. The production and use of NTVs is not recommended by WHO. The recommendations specify indications for and administration mode of CCEEVs, duration of immunity, including recommended PrEP and PEP regimens for healthy people of all age groups and immunocompromised people. Recommendations on PEP include further procedures for wound care, indications for and correct administration of rabies immunoglobulins for passive immunization in severe rabies exposures.

Evidence for the following conclusions was assessed and graded during the elaboration of the 2010 WHO position paper:

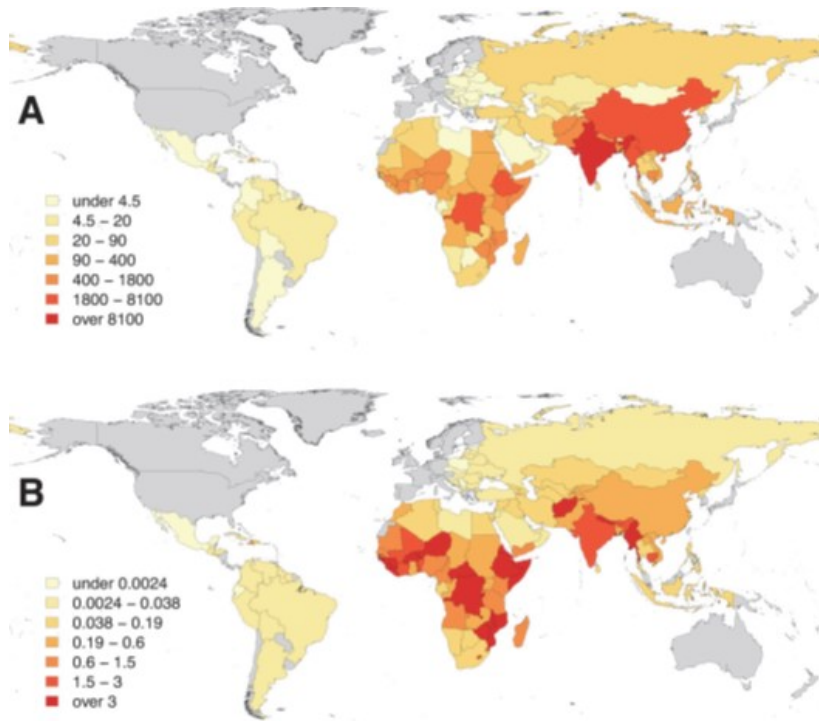
- Duration of immunity following pre- or post-exposure immunization with cell-culture-based rabies vaccines: Moderate scientific evidence that using cell-culture-derived rabies vaccines induces  $\geq 10$  years of immunity against rabies.
- Efficacy of cell-culture-based rabies vaccines: High scientific evidence that cell culture-derived rabies vaccines when used according to WHO's recommendations are efficacious against rabies and/or induce antibodies against rabies virus following intramuscular (IM) or intradermal (ID) administration.
- Safety of cell-culture-based rabies vaccines: Moderate level of scientific evidence that cell-culture-based rabies vaccines are safe. (However, transient local reactions may occur, in particular following ID administration)

## 2.4. Magnitude of the Problem of Rabies

Rabies occurs in over 100 countries and territories, where it causes an estimated 59 000 human deaths every year (Hampson et al., 2015). Underreporting and frequent misdiagnosis of rabies means this figure is likely higher. Africa and Asia bear the heaviest rabies burden (Figure 2), due to the epidemiological, cultural and

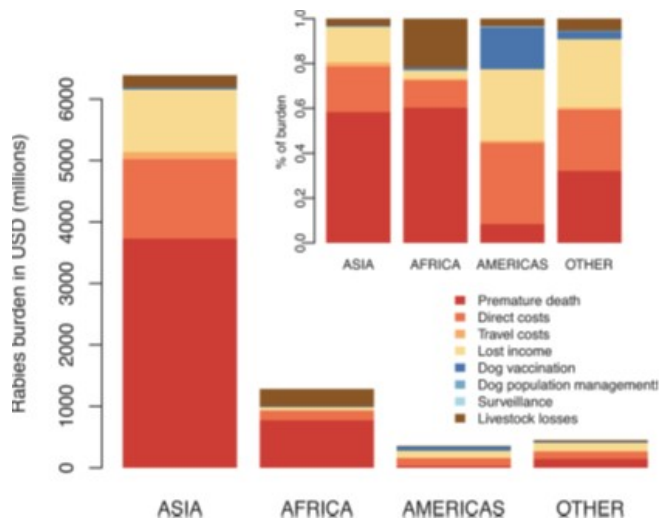


socioeconomic factors (e.g. lack of rabies awareness, lack of access to affordable healthcare) that allow many neglected tropical diseases to persist in those areas) (Knobel et al., 2005). As PEP failures are very rare, rabies deaths primarily occur in those who cannot afford or access timely and effective post-exposure treatment. In the absence of PEP, an estimated 3 million people would die from rabies worldwide each year (Hampson et al 2015).



**Figure 2:** Hampson et al 2015, the distribution of the global burden of rabies: A) human rabies deaths, B) per capita death rates (per 100,000 persons), countries shaded in grey are free from canine rabies.

Globally, rabies carries an estimated economic burden of 8.6 billion USD per year (Hampson et al, 2015). This is comprised of economic burden due to premature death, direct cost of PEP, lost income while seeking PEP, livestock losses, dog vaccination, dog population management, and surveillance (Figure 3).





**Figure 3:** Division of costs associated with rabies, prevention and control across sectors by region. Inset shows proportional expenditure in different regions. (Hampson et al., 2015)

## 2.5. Rabies Epidemiology, Surveillance and Laboratory methods:

Rabies is present on all continents, except for Antarctica. Dogs are responsible for more than 95% of human rabies cases, however bats are thought to be the original animal reservoir. Rabies transmission to humans via wildlife other than bats is considered rare. Dog-transmitted rabies has been eliminated in Western Europe, North America, Japan, South Korea and parts of Latin America. It remains endemic in much of Asia, Africa and the Middle East, and is re-emerging in parts of China and emerging in certain previously non-affected territories (Figure 2) (WHO, 2013).

Integrated global reporting systems exist for notification of animal rabies cases to the World Organisation for Animal Health (OIE) (through the World Animal Health Information System - WAHIS) and of human cases to WHO (through the District Health Information Software or DHIS2 feeding into the global health observatory data base). Regional databases exist in Europe (Rabies Bulletin Europe), Latin America (SIRVERA) and Africa (PARACON). Widespread underreporting of human and animal rabies cases contributes to underestimation of rabies disease burden and surveillance systems require strengthening worldwide (WHO, 2017).

A clinical suspected case of rabies is defined as *“A subject presenting with an acute neurological syndrome (i.e. encephalitis) dominated by forms of hyperactivity (i.e. furious rabies) or paralytic syndromes (i.e. paralytic rabies) progressing towards coma and death, usually by cardiac or respiratory failure, typically within 7–10 days after the first sign, if no intensive care is instituted. This may include any of the following signs: aerophobia, hydrophobia, paresthesia or localized pain, dysphagia, localized weakness, nausea or vomiting.”*<sup>1</sup>

Laboratory confirmation in humans can be obtained ante-mortem or post-mortem using saliva, spinal fluid or tissue biopsies. Fluorescent antibody testing (FAT) is gold standard, however enzyme linked immunosorbent assays (ELISA), direct rapid immunohistochemistry tests (DRIT), lateral flow tests and reverse transcriptase polymerase chain reaction (RT-PCR) are also used. Test sensitivity depends on stage of disease, immune status, viral shedding and technical expertise. While a positive laboratory result indicates rabies, a negative result does not rule out infection (WHO, 2013). Access to rabies confirmatory testing in endemic countries is extremely limited.

The measurement of rabies virus neutralizing antibody (RVNAs) is the most convenient method of confirming an immunological response after rabies PrEP or PEP. The Rapid fluorescent focus inhibition test (RFFIT) has been the serological assay of choice for quantitatively measuring the presence of neutralizing antibodies after rabies vaccination. An ELISA to monitor antibody titres in vaccinated humans against rabies virus glycoprotein has been used as an alternative. Initially, measurement of RVNA was performed in vivo using the mouse neutralization test. Subsequently, the virus neutralizing assays, rapid fluorescent focus inhibition test (RFFIT) and the fluorescent antibody virus neutralization test (FAVN), have been recommended for post-vaccination monitoring and determination of need for booster vaccination. The level of neutralizing antibody in serum samples is determined by comparing results with a standardized reference serum. The RFFIT is considered to be a complex assay due to the fact that the sensitivity and specificity are dependent upon many factors. It is therefore important that laboratories conducting the RFFIT to adhere to strict quality control procedures and also to participate in quality assurance programs. The value of 0.5 IU/ mL (IU/mL) has been recommended by WHO as indicative that a vaccinated person has responded to rabies vaccine. It is important to understand that a serological titre of 0.5 IU/ml reported from a RFFIT on one day may be reported as 0.4 or 0.6 on another day due to the nature of the test, and that this measures antibodies as a proxy for protection, which may nevertheless be warranted by lower antibody titres (Moore & Hanlon 2010).

<sup>1</sup> Cases are classified as (WHO 2013):

- Suspected: compatible with the case definition.
- Probable: a suspected case with reliable history of contact with a probable or confirmed rabid animal.
- Confirmed: a suspected or probable case that is laboratory-confirmed.

## 2.6. Rabies pre- and post-exposure treatment

### 2.6.1. Principles PrEP / PEP

Risk of exposure to rabies can be reduced by bite prevention education, dog population management and responsible pet ownership, including vaccinating dogs against rabies. Rabies in humans can be prevented, both before and after exposure via PrEP or PEP, respectively. PrEP consists of a series of rabies vaccine injections to prime the immune system. This enables a fast recall of an immune response in case of re-exposure to the virus, and following administration of a post exposure vaccine booster. PEP, after a potential exposure, consists of proper wound management followed by administration of immunoglobulin, if indicated, and a series of injections of rabies vaccines (Figure 4).

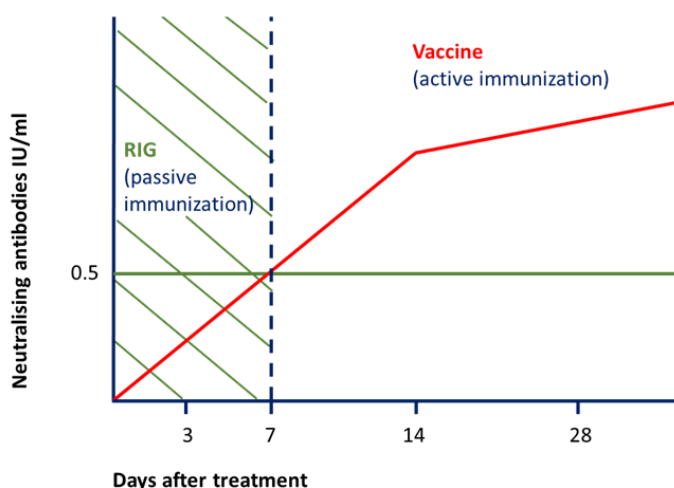
Prompt post-exposure use of CCEEVs combined with proper wound management and simultaneous administration of RIG in severe exposures is close to 100% effective in preventing rabies. However, delay in seeking treatment, improper wound care, unnoticed wounds, direct nerve inoculation, and lack of patient compliance to vaccination schedules, among other factors (e.g. vaccine and cold chain quality), may contribute to treatment failure and subsequent death (Wilde, 2007). Thus, mitigation of these circumstances has been emphasized in educational programmes, particularly for those in rabies endemic areas.

The indication for PEP depends on the type of contact with the suspected rabid animal:

Category I	touching or feeding animals, licks on intact skin (that is, no exposure);
Category II	nibbling of uncovered skin, minor scratches or abrasions without bleeding;
Category III	single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, licks on broken skin, exposures due to direct contact with bats.

PEP is indicated for those with category II or III rabies exposures, and should be sought as urgently as possible following exposure (WHO, 2010). Because rabies is fatal, no contraindications exist to PEP following category II or III exposure, even months later (e.g. PEP is indicated in persons co-exposed to the bite of an animal which caused a human rabies case). PEP requires three steps: (a) wound washing and care, (b) vaccination, and (c) administration of rabies immunoglobulin. RIG should be administered in all people with category III exposure and to those with category II exposure who are immunodeficient or had a direct contact exposure to a bat. RIG, derived from the blood of humans or horses, is currently used as a component of PEP as a method of passive immunization. RIG neutralizes the rabies virus in situ, before the subject's immune system responds to the vaccination by producing rabies virus neutralizing antibodies. RIG has to be administered only once, as soon as possible and before day 7 after the first dose of vaccine. All wounds, however small, should be located and infiltrated with RIG.

The recommended first aid procedures include immediate, thorough flushing and washing of the wound with soap and water, detergent, povidone iodine or other substances with viricidal activity. Thorough wound washing is considered to reduce the risk of rabies infection. Depending on the characteristic of the wound, antibiotics, analgesics and tetanus vaccine booster might be indicated. Residents of rabies-endemic areas should be taught how to prevent dog bites, learn about simple local wound treatment, in particular to look for small or missed wounds, and to not use procedures that may further contaminate or enlarge the wound. Detailed descriptions of the currently available rabies biologics see below.



**Figure 4:** Principles of rabies post-exposure prophylaxis. A neutralising antibody titre of 0.5IU/ml is considered protective in all cases.

### 2.6.2. Types of Vaccines:

For decades, CCEEVs have been supported as safe and effective in preventing rabies. These vaccines are intended for both PrEP and PEP. Currently there are 3 human rabies vaccines that are WHO pre-qualified including: Rabavert® and Rabipur® (EVV) produced by GSK and Verorab® (CCV) produced by Sanofi Pasteur. Two additional rabies vaccines are subject to an assessment for WHO prequalification. CCEEVs are available in 0.5 ml or 1 ml vials, mostly in lyophilized form (see Table 1), the size of the vial does not impact the immunization practice. After reconstitution with sterile diluent, the vaccines should be used immediately or within 6-8 h if kept between +2°C to +8°C (WHO, 2015), as partially used vials of rabies vaccine may rapidly become contaminated.

China produces the largest number of brands of human rabies vaccines followed by India. An overview of human rabies vaccines currently in use is available in Table 1.

In a few remaining countries, populations at high risk of rabies may still depend on rabies vaccines derived from animal nerve tissues for PEP. Nerve tissue vaccines may induce very severe adverse reactions and are less immunogenic than CCEEVs; therefore, WHO has strongly recommended against their production and use (WHO, 2013).

The table below was compiled through enquiries with various networks, including the International Federation of Pharmaceutical Manufacturers, Developing Countries Vaccine Manufacturers Network and systematic online searches for manufacturers to reflect the most inclusive evidence available to date, without claiming completeness.

**Table 1:** Human rabies vaccines and producers worldwide, as per August 2017:

Vaccine <sup>a</sup>	Brand	Producer	Country	Cell line	WHO Pre-qualified	Type
PVRV	NA	Butantan Institute	Brazil	Vero cells	NO	Liquid
HDCV	Chengdu Kanghua	Changdu Kanghua	China	Human diploid cells	NO	Lyoph
PVRV	SPEEDA	Liaoning Chengda co., LTD	China	Vero cells	NO	Lyoph

PVRV	NA	Changchun Changsheng Life Sciences Ltd.	China	Vero cells	NO	Lyoph
PVRV	NA	Guangzhou Nuocheng biological products co., LTD	China	Vero cells	NO	Lyoph
PVRV	NA	Ningbo RongAn biological pharmaceutical co., LTD	China	Vero cells	NO	Lyoph
PVRV	NA	Jilin Maifeng biological pharmaceutical co., LTD	China	Vero cells	NO	Liquid
PPHKCV	NA	Zhongke biological pharmaceutical co., LTD	China	Hamster Kidney Cells	NO	Liquid
PPHKCV	NA	Henan Yuanda biological pharmaceutical co., LTD	China	Hamster Kidney Cells	NO	Liquid
PIKA rabies vaccine, inactivated, with a TLR3-based adjuvant		Yisheng Biopharma Inc	China	Vero cell	NO	?
PVRV	Verorab	Sanofi Pasteur	France	Vero cells	YES	Lyoph
HDCV	Imovax	Sanofi Pasteur	France	Human diploid cells	NO	Lyoph
PCECV	Rabavert	GSK	Germany	Chick embryo cells	YES	Lyoph
PCECV	Rabipur	GSK	India	Chick embryo cells	YES	Lyoph
HDCV	Rabivax	Serum Institute of India	India	Human diploid cells	NO	Liquid
PDEV	Lyssavac-N /Vaxirab	Zydu-Cadila	India	Duck embryo cells	Production stopped	Lyoph
PCECV	Vaxirab-N	Zydu-Cadila	India	Chick embryo cells	NO, successor of Vaxirab	Lyoph
PVRV	Indirab	Bharat Biotech	India	Vero cells	NO	Lyoph
PVRV	Abhayrab	Indian Immunologicals	India	Vero cells	NO	Lyoph
BHKV	'Вакцинация КОКАВ	Tarasevich Institute	USSR	BHK	NO	??
NTV	?	?	Bolivia	Mouse brain	NO	Liquid?
NTV	?	Pasteur Institute Algiers	Algeria	Mouse brain	NO	Liquid?
NTV	?	Ethiopian Public Health Institute	Ethiopia	Sheep brain?	NO	Liquid?
NTV	?	?	Argentina	Sheep brain?	NO	Liquid?

<sup>a</sup> Purified chick embryo cell vaccine (PCECV), Purified vero cell vaccine (PVRV), Human diploid cell vaccine (HDCV), Purified duck embryo cell vaccine (PDEV), baby hamster kidney cells (BHKV), Purified Vaccine of Primary Hamster Kidney Cells (PPHKCV)

Because rabies is a fatal disease, randomized controlled trials in rabies-exposed humans involving untreated comparison groups are unethical and not performed. Direct assessment of vaccine-induced protection is based on the efficacy of PEP following category II or III exposures from laboratory-confirmed rabid animals.

Furthermore, animal models serving as human surrogates have been used to demonstrate the protective efficacy of CCEEVs after experimental infection. An indirect assessment of vaccine efficacy can be made through immunogenicity studies. All CCEEVs induce high rabies virus neutralizing antibody response to the viral G protein within ~7 days. The WHO specified minimum titre of 0.5 IU/mL of serum, measured by RFFIT or the fluorescent antibody virus neutralization test (FAVN) is a widely-used reference (WHO, 2010). In healthy individuals, this level should be achieved by day 14 of a post-exposure regimen, with or without simultaneous administration of rabies immunoglobulin and irrespective of age. When new rabies vaccines are introduced, their immunogenicity is usually evaluated by comparing the rabies-virus neutralizing antibody titres induced by the vaccine being tested with those induced by a vaccine of demonstrated efficacy.

The cost of CCEEVs limits their widespread use in many rabies-endemic areas. Intramuscular administration of rabies vaccine is safe and immunogenic. Intradermal administration of reduced dose rabies vaccine offers a preferable, cost-effective alternative. ID administration requires lower doses of rabies vaccine, and can, under optimal conditions, reduce the volume and direct cost of vaccine by up to 60-80%, compared to IM administration (Hampson et al., 2011).

Although this plays no role in preventing rabies after a given exposure, the development of immunological memory after vaccination with CCEEVs is critical for the establishment of long-lasting immunity against rabies in humans. Individuals who had received their primary series 5–21 years previously showed good anamnestic responses after booster vaccination (Kessels et al., 2017). Long-term immunity is also achieved with ID immunization and may persist even when antibody titres are below 0.5I U/ml or are no longer detectable. The ability to develop an anamnestic response to a booster vaccination is not related to the route of administration of the initial series (IM or ID), or to whether the patient received pre-exposure prophylaxis, as long as the post-exposure series was completed (Saraya et al 2010, Venkataswamy et al 2015).

In general, CCEEVs have been shown to be safe and well tolerated. However, in 35–45% of vaccinated individuals, minor and transient erythema, pain and/or swelling may occur at the site of injection, particularly following ID administration of a booster. Mild systemic adverse events following immunization, such as transient fever, headache, dizziness and gastrointestinal symptoms, have been observed in 5–15% of vaccinated individuals. Serious adverse events, mainly of allergic or neurological nature, are extremely rare (WHO, 2010).

Rabies vaccines can safely be administered alone or alongside diphtheria, pertussis and tetanus, Japanese encephalitis (JE), or polio vaccines (Kessels et al. 2017)

Previous severe reaction to any components of the vaccine is a contraindication to further use of the same vaccine. As with all other immunizations, vaccinated individuals should if possible be kept under medical supervision for at least fifteen to twenty minutes following vaccination.

### **2.6.3. Types of RIG:**

Three classes of biological product are available for passive immunization: human rabies immunoglobulin (hRIG), equine rabies immunoglobulin (eRIG), including eRIG-derived highly purified antigen-binding immunoglobulin fragments (F(ab')<sub>2</sub>) and monoclonal antibodies (mAbs) (Table 3). If hRIG, eRIG and F(ab')<sub>2</sub> products are correctly administered they eliminate the virus at the wound site within a few hours. The dosage of hRIG and eRIG is weight-based, 20 IU/kg and 40 IU/kg respectively.

A single mAb product, as an alternative to RIG was licensed in 2016 for use in India.

The high cost, low availability and supply, batch to batch variation affecting efficacy, uncertain quality (no WHO prequalification), short shelf-life even with correct cold chain, and correct administration of RIG are barriers to implementing the standard previously set by WHO for PEP in individuals severely exposed to rabies. The table below was compiled through enquiries with various networks, including the International Federation of Pharmaceutical Manufacturers, Developing Countries Vaccine Manufacturers Network and systematic

online searches for manufacturers to reflect the most inclusive evidence available to date, without claiming completeness.

**Table 3:** Overview on rabies immunoglobulin products and producers worldwide as per August 2017

Category	RIG product name or brand name <sup>a</sup>	formulation per ml / per vial	Vial size	Company name	Country
eRIG	Anti-rabies serum	N/A	N/A	Butantan Institute	Brazil
eRIG	CARIG (enzyme refine)	300 IU/ml	4 ml	Cadila Pharma	India
eRIG	Rabix-IG	200 IU/ml	5 ml	Incepta Pharmaceuticals	India
eRIG	Abhay-RIG	300 IU/ml	5 ml	Indian Immunological	India
eRIG	Anti-rabies serum	300 IU/ml	5 ml	Haffkine	India
eRIG	EquiRab	300 IU/ml	5 ml	Bharat Serums and Vaccines	India
eRIG	Pars	200 IU/ml	5 ml	Newgen (Cadila Pharmaceuticals Ltd.)	India
eRIG	Anti-rabies serum	300 IU/ml	5 ml	Serum Institute of India	India
eRIG	Anti-rabies serum	300 IU/ml	5 ml	Central research Institute Kasauli HP	India
eRIG	Plasmarab	300 IU/ml	5 ml	Premium Serums	India
eRIG	TRCS eRIG	200 IU/ml	5 ml	Queen Saovabha Memorial Institute	Thailand
hRIG	Human Rabies immunoglobulin	100 IU/ml	2 ml or 5 ml	HualanBiologicalBacterin Co. Ltd.	China
hRIG	Human Rabies immunoglobulin	100 IU/ml	1 ml, 2 ml or 5 ml	Sichuan Yuanda Shuyang Pharmaceutical Co. Ltd	China
hRIG	Human Rabies immunoglobulin	100 IU, 200 IU or 500 IU/vial	N/A	China National Biotec Group (Sinopharm subsidiary)	China
hRIG	Human Rabies immunoglobulin	200 IU/Vial	2 ml	China Biologic Product. Inc	China
hRIG	Imogram Rabies-HT	150 IU/ml	2 ml or 10 ml	Sanofi Pasteur	France
hRIG	Pars	150 IU/ml	2 ml	Newgen (Cadila Pharmaceuticals Ltd.)	India
hRIG	Berirab-P	150 IU/ml	2ml or 5 ml	Bharat Serums and Vaccines	India
hRIG	Rabglob	150 IU/ml	2ml or 5 ml	Bharat Biotech International Ltd.	India
hRIG	Kendrab	150 IU/ml	2 ml or 10 ml	Kamada Ltd.	Israel
hRIG	Human Rabies immunoglobulin	150 IU/ml	vials with 500 IU	Bio Products Laboratory Limited	UK
hRIG	HyperRAB S/D	150 IU/ml	2 ml or 10 ml	GRIFOLS USA , LLC	USA
hRIG	Rabigam	150 IU/ml	2 ml	National Bioproducts	South Africa
RmAb	Rabishield	40 IU or 100 IU/ml	2.5 ml	Serum Institute of India	India

#### 2.6.4. Rabies vaccine potency:

The 2010 WHO rabies vaccine position paper recommends a potency  $\geq 2.5$  IU per IM dose. No WHO potency recommendation exists for doses injected intradermally, which are a fraction of the IM dose. However, an additional WHO recommendation sets the volume of ID injection to 0.1 mL, thereby constraining the potency per ID dose. The need to define a minimum potency per ID dose, in addition to the recommended volume, has been a topic for discussion among experts in the past years. Such discussion was in part prompted by the

observation that the 0.5 mL Purified Vero Cell Vaccine (PVRV) vaccine vials provide maximally 5 ID doses with potency per dose  $\geq 0.50$  IU, whereas other vaccines supplied in 1.0 mL vials provide around 10 ID doses with potency  $\geq 0.25$  IU. Concerns were raised that ID vaccination may sometimes involve an insufficient amount of antigen. The national regulations of some countries (e.g. in South and South East Asia) specify rabies vaccine potency above 5 IU/ml.

To address this question, a systematic literature review was conducted by an external expert (see Annex II evidence profile on vaccine potency). The first search focused on the immunogenicity of rabies vaccines given by ID route. It identified 299 publications in the period 1997-2017, of which 38 studies were included in the analyses. A second search investigating the effectiveness of ID vaccination resulted in 227 hits for the period 2007-2017, of which 11 suitable publications were retained.

The immunogenicity of current rabies vaccines was analysed in 3 different ways: proportion of subjects reaching the antibody threshold of 0.5 IU/ml after ID vaccination, relationship between potency and immunogenicity of the vaccine given intra-dermally, and comparison of antibody responses after IM or ID vaccination. Overall, vaccines administered by ID route were found to be highly immunogenic, irrespective of their IU content per IM dose. PEP by ID route appeared as least as immunogenic as that administered by IM regimens. By contrast, ID PrEP trended towards lower antibody titres than IM vaccination, but the observation was not associated with any clinical relevance.

Vaccine effectiveness was assessed by investigating survival after exposure. Data from an approximate total of 36 000 patients who received PEP indicates that vaccines administered ID are as efficacious as vaccines administered IM. The current recommendations, including both  $\geq 2.5$  IU/mL per IM dose and a volume of 0.1 mL per ID dose correspond to a recommendation of  $\geq 0.25$  IU per ID dose. Available data do not indicate that vaccines meeting this requirement lack efficacy.

## 2.7. Rabies Prevention and Control Strategies:

Strategies to prevent and eliminate human rabies include mass dog vaccination campaigns to halt disease transmission at its source, and the provision of accessible, affordable, timely and effective prophylaxis to people exposed to rabies. Vaccinating 70% of at-risk dog populations is considered sufficient to reliably and sustainably interrupt rabies transmission in dogs, and has ensured the elimination of canine rabies from developed countries (Coleman & Dye, 1996; Hampson et al., 2009). Global initiatives to build rabies awareness include World Rabies day (September 28) and the End Rabies Now campaign. These engage and educate communities on rabies, bite prevention, and the importance of vaccinating dogs to prevent human disease. In 2015, stakeholders set a goal of zero human rabies deaths by 2030, worldwide (“Zero by 30”). This was followed by the launch of the Global Framework to Eliminate Dog-Mediated Human Rabies by 2030 (WHO, 2016). A Global Business Plan will be launched this year. This takes a country-centric approach, with international partners (WHO, OIE, Food and Agriculture Organization of the United Nations (FAO) and the Global Alliance for Rabies Control (GARC)) united to empower and catalyse nations to eliminate rabies (WHO, 2017). WHO is currently building the evidence base for consideration of human rabies vaccine in the 2018 GAVI Vaccine Investment Strategy. If successful, this would ensure free access to human rabies vaccine for those who need it in lower income, GAVI-eligible countries.

## 3. PRE-EXPOSURE PROPHYLAXIS:

### 3.1. Key Points

- There is no medical contraindication for rabies PrEP
- PrEP can be considered for certain exposed sub-populations in remote areas, but cost-effectiveness of this public health intervention should be assessed individually by countries within their specific context
- Modelling estimates indicate that PrEP, as a large scale public health intervention, is not cost-effective and would become only cost-neutral in situations where RIG is rarely administered and at the same time the dog-bite incidence exceeds 6%



- Options for PrEP and serological testing for sub-groups of professionals and travellers have been updated
- The WG concluded on accelerated regimes as follows:
  - a 2-site ID regimen on day 0 and 7 would be efficacious as a PrEP regimen
  - a 1-site IM regimen on day 0 and 7, would be efficacious as a PrEP regimen
  - Individuals who receive only a single dose of PrEP should complete the second dose of PrEP as soon as possible and be managed with full PEP (including RIG as indicated) in the case of potential rabies exposure prior to the second PrEP dose
  - Individuals who are immunocompromised should receive a 3-visit, 2-site ID or 1-site IM PrEP regimen (day 0, 7 and between day 21 and 28) and should be managed with full PEP in the case of potential rabies exposure

### 3.2. Review of Scientific Evidence

PrEP has been successfully used over decades to prevent rabies infection in people of all ages. PrEP should not distract from essential canine vaccination efforts, PEP provision, and rabies educational and advocacy programmes. A systematic review on PrEP was conducted and summarizes relevant new evidence (Kessels et al., 2017). Three studies found PrEP safe and immunogenic for children up to 5 years in combination with other childhood vaccines such as Japanese encephalitis (JE), diphtheria, pertussis, tetanus (DPT) and oral and inactivated poliomyelitis vaccines (Vien et al., 2008; Laang et al., 2009; Pengsaa et al., 2009).

#### 3.2.1. Boosters for occupationally exposed:

PrEP is indicated for individuals who face occupational and/or travel-related exposures to rabies (virus) in specific settings or over an extended period of time.

The available evidence suggest that complete PrEP triggers a long-lasting (> 20 years) immunological memory with rapid recall of the immune response when boosted. The new evidence on occupational categories and risks of rabies exposures is limited. Therefore, the update of options for pre-exposure rabies immunization of individuals occupationally or otherwise exposed (Table 4, adapted from Müller et al. 2015) mostly relied on expert knowledge. Aspects of timely access to biologics, animal rabies epidemiology and simplification on serologic testing were taken into consideration.

**Table 4: Indications for pre-exposure rabies immunization** (adapted from Müller et al. 2015)

Examples of typical individuals and populations	Likelihood and nature of exposure to rabies virus	Timely access to rabies biologics	Recommendations on pre-exposure immunization <sup>a</sup> and serologic testing
<b>Occupational exposure</b>			
Individuals involved rabies research, rabies biologics production <sup>b</sup> .	Virus may be present continuously, usually in high concentrations. Specific exposures may not be recognized.  Bite, non-bite, or aerosol exposures.	Yes	PrEP recommended. Suggested timeframes for serologic testing: After primary immunization and the every ~6 months up to every 1-2 years. Routine booster vaccination <sup>c</sup> , if antibody titre falls below 0.5 IU/ml <sup>d</sup> .
Individuals working in rabies diagnostic laboratories <sup>b</sup> , in hospitals with clinical rabies cases <sup>e</sup> , animal disease control, wildlife management, bat handling or with professional activities in caves likely to lead to direct contact with bats.	Settings or areas where rabies is enzootic and where exposure may not be recognized.  Presence of bats, particularly non-haematophagous bats. Bite, non-bite, or aerosol exposures.	Variable, mostly yes  Variable	PrEP recommended. Serologic testing every ~2 years. Routine booster vaccination if antibody titre is below 0.5 IU/ml.  PrEP recommended. No serologic testing or routine booster vaccination.
Individuals working or residing in remote areas for extended periods and involved in e.g. dog vaccination campaigns, animal disease control programmes, peace keeping, military or religious missions.	Remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures.  Partly remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures.	Variable, mostly not  Variable	PrEP recommended. Serologic testing unnecessary unless risk of exposure remains. Otherwise, test and boost if antibody titre falls below 0.5 IU/ml, or alternatively give a routine booster vaccination before departure.
Individuals involved in e.g. animal disease control with direct contact with terrestrial animals.	Settings where rabies is uncommon to rare. Exposure typically episodic with source recognized. Bite or non-bite exposures.	Variable, mostly yes	PrEP recommended. No serologic testing or routine booster vaccination.
<b>Travellers</b>			

Individuals with mainly leisure related exposures by potential direct contact, particularly with carnivores or bats, during activities over an extended period e.g. backpackers, bicycle or motorbike riders, people visiting friends and relatives. Consider cumulative exposure in frequent travelers.	Remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures.  Partly remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures.	Variable, mostly not  Variable	PrEP recommended. Serologic testing unnecessary unless risk of exposure remains. Otherwise, test and boost if antibody titre falls below 0.5 IU/ml, or alternatively give a routine booster vaccination before departure.
Individuals with leisure activities in caves leading to likely direct contact with bats.	Settings or areas where rabies is enzootic and where exposure may not be recognized.  Presence of bats, particularly non-haematophagous bats.  Bite, non-bite, or aerosol exposures.	Variable, mostly yes  Variable	PrEP recommended. Serologic testing every ~2 years. Routine booster vaccination if antibody titre is below 0.5 IU/ml  PrEP recommended. No serologic testing or routine booster vaccination.
<b>Sub-populations</b>			
Residents of remote areas where animal rabies control is impaired by difficult access, epidemiological and other factors	Settings or areas where rabies is enzootic, particularly in wildlife and where episodic exposure may not be recognized.  Bite or non-bite exposures.	Variable, mostly not	PrEP recommended. No serologic testing or routine booster vaccination.
General population	Areas where rabies is enzootic or epizootic. Exposure always episodic with source recognized.  Mostly bite, also non-bite exposures.	Yes	No PrEP recommended. PrEP for general populations is unlikely to be a cost-effective intervention and is usually more expensive than other measures to prevent human rabies deaths, such as post-exposure prophylaxis and dog vaccination campaigns.
In case of a WHO category II or III exposure to a rabid animal (or lyssavirus), post-exposure prophylaxis including thorough wound care is always required.  People who have received PrEP should be instructed accordingly.			

<sup>a</sup>A primary course of pre-exposure immunization consists of either a two-site intradermal administration of 0.1 ml of vaccine on days 0 and 7 or one vaccine dose for intramuscular administration on days 0 and 7. Administration of booster doses of vaccine depends on nature and duration of the rabies exposure risk as above.

<sup>b</sup>Assessment of relative risk and any extra monitoring of immunization status of laboratory workers is the responsibility of the laboratory supervisor (as an example, see guidelines in the current edition of the United States Department of Health and Human Services' Biosafety in Microbiological and Biomedical Laboratories).

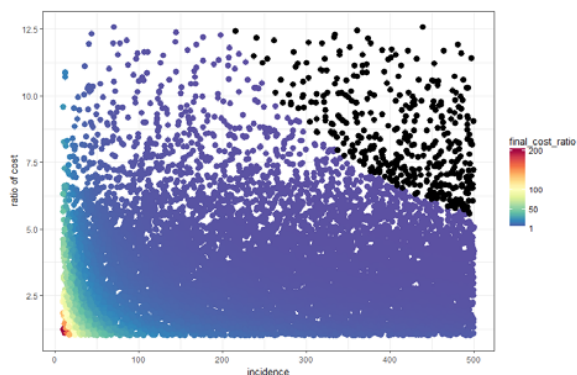
<sup>c</sup> A routine pre-exposure booster vaccination consists of one dose of modern cell culture vaccine, ID or IM (i.e., deltoid area).

<sup>d</sup>An acceptable antibody level is 0.5 IU/ml or 1:5 virus neutralizing antibody titre (complete inhibition in the RFFIT at a 1:5 dilution, approximately equivalent to 0.1 IU/ml). Boost if the titre falls below this level, as long as the person remains at risk of viral exposure.

<sup>e</sup>Human-to-human transmission of rabies has never been confirmed outside of the transplant setting. However, rabies virus can be found in saliva, tears, and nervous tissues of human rabies cases and represents a theoretical route of transmission. Therefore, pre-exposure immunization might be indicated and can alleviate the psychological burden of fear from infection of health care staff who are regularly attending to patients with clinical rabies.

### 3.2.2. PrEP for subpopulations

Although PrEP will not eliminate rabies at its source, it can play a valuable role in protecting high risk populations in remote areas, especially where the risk of bat rabies is not easily controlled. The systematic review includes experiences and results from national programmes implementing PrEP for high-risk populations in remote settings of the Philippines (focusing on children, mainly canine-mediated rabies), Peru and Brazil (all age groups, canine- and bat-mediated rabies) (Kessels et al., 2017). This review also addresses available evidence on cost-effectiveness of such interventions in these specific sub-populations. To overcome the scarcity of cost-effectiveness data a model was developed to quantify the potential benefits and relative costs of inclusion of rabies PrEP within a routine Expanded Programme on Immunization (EPI) schedule in settings where rabies is endemic. The results highlight that PrEP as a large scale public health intervention, e.g. PrEP delivery as part of the EPI programme, is likely to be substantially more expensive than other measures to prevent human rabies deaths, such as PEP and dog mass vaccination campaigns (see evidence profile Question 1). PrEP for entire populations is unlikely to be an efficient use of resources (Figure 5) and should only be considered in extreme circumstances, where the incidence of rabies exposures is unusually high (incidence >6%) and RIG use is low. For details refer to evidence profile on Question 8. Modelling could be used to support decision-making in specific high-exposure incidence contexts of local settings.

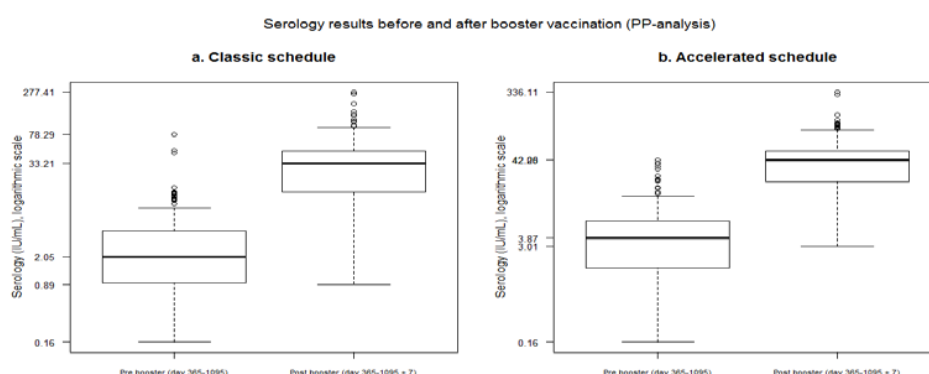


**Figure 5:** Ratio of the costs of PrEP + PEP versus PEP alone, by varying dog bite incidence and relative cost of PEP in naïve individuals compared to cost of PrEP + PEP in primed individuals. Note that simulations with a final cost ratio  $\leq 1$  are indicated in black.

### 3.2.3. Accelerated or modified PreP regimens:

Ten published studies exploring accelerated or modified PrEP regimens were considered and have shown evidence that 1-week or even single day regimens are non-inferior to the currently recommended 3-4-week regimens (see evidence profile).

- a. The **2-visit regimen** with 2-site ID or 1 IM doses on days 0, 7: Evidence available is consisting of one randomized clinical trial (Soentjens et al. A 2017) conducted in Belgian soldiers, see [Figure 6](#)) and two observational studies (Mills et al. 2011; Wieten et al. 2013). There is substantial confidence that a day 0 and 7 ID regimen would be efficacious for rabies PrEP. From the curves of the antibody response post booster, by day 3 those who have received PrEP have already mounted an antibody response, and by day 7 all were seroconverted, indicating that the 3<sup>rd</sup> dose on day 21 is not needed. The studies (Mills et al. 2011; Wieten et al. 2013) presented data using only 2 ID injections on day 0 and 7, showing that this regimen produces similar consistent antibody responses as the current WHO-recommended PrEP regimen after priming. The randomized clinical trial conducted in the Belgian soldiers showed that 100% of the subjects ( $n=238$ ) seroconverted  $> 0.5$  IU/ml and 100% had titres  $> 0.5$  IU/ml if boosted up to 3 years after primary vaccination. It is likely but not certain underweight children or overweight adults would respond similarly to healthy soldiers (male and female).



**Figure 6:** Median serological titres RCT, (Soentjens et al. A 2017), a) WHO recommended PreP regimen, b) investigational 2-site ID regimen days 0, 7.

- b. The **single visit regimen**: Two ID or one IM injection(s) will result in an adequate antibody titre for at least one year. This has been documented using WHO pre-qualified rabies vaccines with either IM or two ID injections and subsequent booster around 1 year later (see overview trials Table 1 in the evidence profile)

Questions 3&4). However, the age range of the study participants, as well as the timeframes considered for booster response, show limitations. Data from a head-to-head study in Thailand observing a single IM dose and a single day 2-site ID dose, show that ID and IM are clinically equivalent and interchangeable (Khawplod et al. 2012; Jonker & Visser 2017; Suandork et al. 2007; Kamoltham et al. 2007; Soentjens et al. B, 2017). The two groups demonstrated equivalent geometric mean titres (GMTs) one year after primary immunization. When boosted, both groups had an adequate recall of immune response. However, additional evidence is needed on PEP after an incomplete course of or single visit PrEP including a larger range of age groups. Per the precautionary principle, in the case of an exposure, individuals who had a single visit PrEP should either get a second dose as soon as possible or be managed as if they are immunologically naïve and given full PEP including RIG.

#### **PrEP in immunocompromised patients**

Data on accelerated or modified PrEP regimens in immunocompromised individuals are scarce and the recommendations were based on expert opinion. Immunocompromised patients may have a lower immune response to vaccine, and thus 2 sessions of vaccine administration may not be enough to confer protection. Seroconversion is likely to vary depending on the individual patient, their medical history, and the clinical management of their condition. For example, if the patient's condition is well-managed, a clinician could elect to treat the person as immunocompetent. Conversely, if the patient's condition is poorly managed or if no clinical history is available, the clinician may decide to treat the person as immunocompromised. All immunocompromised patients should receive the most immunogenic vaccine schedule (i.e. a 3-visit regimen, either 2-site ID or 1-site IM). Currently, there is no evidence to support a 2-visit PrEP regimen in immunocompromised individuals. Where serologic testing is available, clinical experience suggests that health care providers could administer a 2-visit PrEP (day 0 and 7) regimen, followed by serology, and administer a third dose of vaccine if the patient has not seroconverted.

#### **Concurrent chloroquine drug use**

There is no novel evidence on the potentially affected immune response to ID rabies vaccination of people by antimalarial drugs, particularly chloroquine, which is also used for treatment of certain auto-immune diseases. Almost all sources can be traced back to an older randomized clinical trial on PrEP and ID administration route by Pappaioanou et al. (1986). This trial did investigate the potential effect of chloroquine (and derivatives thereof) on efficacy of ID PrEP with HCDRV compared to a control group. Despite statistically significant lower GMTs for the antimalarial drugs groups, titres were adequate in all study participants and above the threshold up to day 105. However, the magnitude of this difference is relatively small and is unlikely to be clinically significant. This effect was only observed if the drug was used for more than one month. Based on pharmacovigilance, there have been no reports of individuals with rabies who received appropriate PEP, with or without PrEP (according to WHO protocols), who were reported as being concurrently on chloroquine drugs. Based on the long years' clinical experience, any PrEP regimens can be recommended for people who are on chloroquine or other related drugs. Nevertheless, it should preferably be given in advance of starting antimalarial prophylaxis or treatment whenever possible. In addition, pharmacovigilance and reporting of any failures would be essential.

## **4. POST-EXPOSURE PROPHYLAXIS**

### **4.1. Key Points**

- There is no medical contraindication for life-saving PEP
- PEP consists of vigorous wound washing, a series rabies vaccine injections and [rabies immunoglobulins](#), if indicated

- Timely access to affordable and effective PEP is primarily hindered by high cost to the national governments and out of pocket expenses for the patients, the long and complicated PEP regimens, low availability in remote areas and the knowledge and skills of health care staff
- Many countries face difficulties or are unable to forecast rabies biologics needs
- Based on both immunogenicity and clinical protection data, a 3-visit regimen consisting of two ID doses on day 0, 3, and 7 ('IPC regimen') is recommended. An overview table summarizes the criteria for alternate ID and IM PEP regimens.
- Although there is some evidence that there are immunogenically comparable GMTs following the 3rd session for IM, there is no clinical data to support shortening IM regimens. Therefore, out of an abundance for caution, the WG will continue to recommend a four dose Essen IM regimen, given at day 0, 3, 7 and the last dose between day 14 to 28.
- Modelling results indicate that the investigational PEP regimens were all more cost-effective than the currently approved IM or ID PEP regimens, both, in clinics with small or large patient throughput
- Modifications for PEP regimens for specific risk groups such as those who are immunocompromised and those with bat exposures have been proposed.
- Changes in the route of administration during a PEP course is acceptable in unavoidable circumstances and restarting PEP is not necessary. The schedule for the new route should be adopted.

#### 4.2. Review of evidence:

The 2010 WHO position paper states that: *"New PEP regimens, particularly those using ID administration, even if shown to be safe and efficacious, must have clear practical or economical advantages, or both, over existing regimens if they are to be endorsed."*

Evaluation criteria for investigational rabies regimens differ from those applied to other vaccines. In the past, criteria used to recommend a new rabies PEP regimen required at least (a) ~100 patients exposed to known rabid animals with 100% survival rates after receiving a complete regimen of PEP including RIG, (b) proven non-inferiority if used with commonly known vaccines, (c) immunogenicity data, among other potential considerations, and (d) efficacy data. Adequate antibody titres alone were not considered sufficient when trying to reduce the number of visits or doses in a regimen. The 100-person benchmark was based on experience, and not on statistical calculations. The WG concluded that new rabies regimens in order to prove non-inferiority, need to show that:

1. Immunogenicity data maintains non-inferiority in comparison to current regimens
  2. Data on clinical outcomes (desirable follow up of patients = min.6 month)
  3. Improved feasibility compared to current regimens
- OR
4. Cost and supply improved without compromising effectiveness

Evidence on investigational or formerly assessed PEP regimens was retrieved from 5 publications from the systematic literature review and 7 related publications (from reference lists) prior to 2007. The latter were excluded from this background paper as no longer relevant to the regimens under discussion. Additionally, recent and yet unpublished studies (epidemiological and immunological) from Institute Pasteur Cambodia were taken into consideration. An overview on the findings for the different regimens by assessment criteria is available in [Table 5](#).

##### 4.2.1. Assessment of investigational PEP regimens:

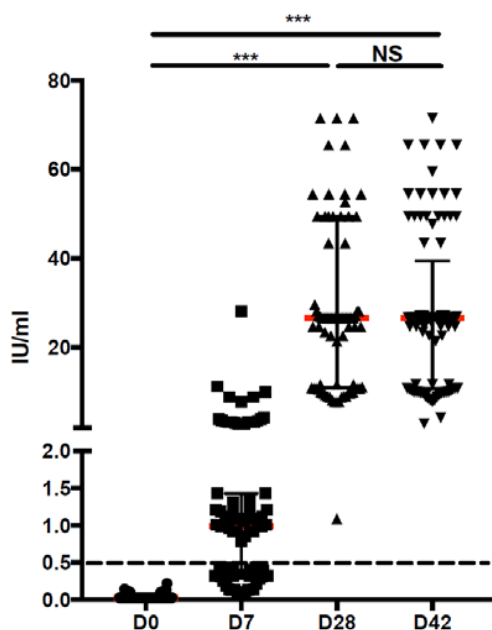
###### 1-week 2-site ID 'IPC' regimen (2-2-2-0-0)

The evidence for the newly recommended 3-visit 1-week ID schedule (2-2-2-0-0) was based on a broad range of patients exposed to sick looking or confirmed rabid dogs from the rabies clinic of the 'Institut Pasteur du Cambodge' (IPC). The suggested new name for this regimen is thus "IPC regimen".

This clinical effectiveness, active follow-up study after at least 6 months found two probable rabies deaths (99.87% rabies survival) among 1,593 persons bitten by confirmed rabid dogs who received 4 or more sessions of two intradermal doses of PVRV with or without eRIG and one death among 127 persons (99.21% survival)

who only returned to receive three sessions with or without eRIG. All three deaths were discussed with international experts and attributed to direct nerve inoculation and/or protocol deviations. Another arm of the study, in persons similarly managed after exposure to rabid-suspect, but untested dogs, found no deaths among 155 patients who received only three sessions versus 904 patients who received four sessions at least (100% survival in both groups). There were no other passively reported suspect rabies deaths among over 250,000 patients referred or self-referred to that centre during the period studied (2003-2014). Further a prospective study was conducted in Cambodian patients received at the rabies treatment centre at IPC between 20 May 2016 to 14 June 2017. The eligible 105 study participants of all ages were all patients with a category III exposure to laboratory confirmed rabid dogs and received the updated TRC regimen (PVRV) and RIG. Serology was conducted for all patients, results are currently available for 88 patients, for the remaining 15 patients, analysis is pending. Blood samples were collected on days 0, 7, 28 and 42. The possible impact of body mass index (BMI), viral load and inoculum, escape mechanisms of RABV, impact of RIG, and concurrent other infections on immune response to rabies immunization were also investigated. The mean titre of day 7 was 1.9 IU/ml (min 0.11, max 28 IU/ml), mean titre of day 28 was 38.5 IU/ml (min. 1.1, max. 148.5), see [Figure 7](#). All participants were protected after 3 sessions of 2 ID doses, including underweight patients (around 30%) or individuals with other diseases (e.g. parasitoses, other infections, etc). The GMT of day 28 was higher than the GMT of day 42. Twenty-two of these patients were also explored for B-cell phenotyping and no statistical difference was found between the two groups. The patients were followed up for at least 6 months, no rabies-related death was observed.

The set of studies support the PEP effectiveness on short- and medium-term protection, including clinical outcome data and in consequence support the removal of the fourth session of the updated TRC regimen on day 28. The countries implementing ID PEP administration are currently using the updated TRC regimen, so the new regimen would be easy to adopt, in that it follows the same schedule but without the fourth dose.



**Figure 7:** Dot plot of neutralizing antibody titres as measured by RFITT (considered adequate if  $\geq 0.5$  IU/ml, RESIST-2 study, Cambodia 2016-2017 (n=88)

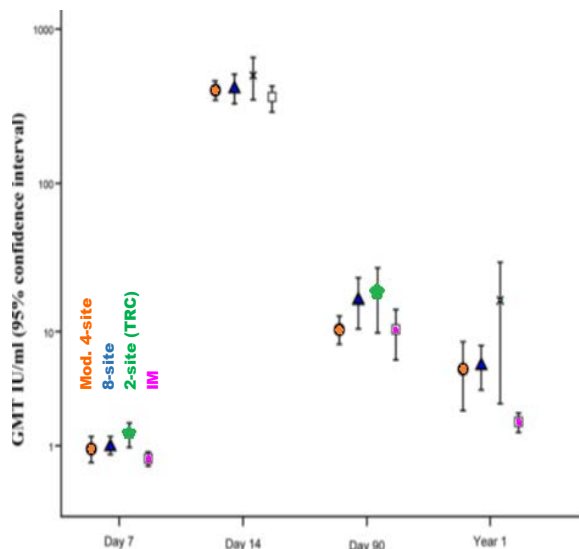
**Modified 4-site ID regimen (4-0-2-0-1)**

Warrell et al. 2008 evaluated a randomized controlled trial of a simplified 4-site ID regimen ([Figure 8](#)). This regimen is an adaptation of the 8-site Oxford regimen and proposes vaccination on day 0 (4sites), day 7 (2

sites), day 28 (1 site). Although this trial proposed a 90-day schedule, the final dose is no longer used with any PEP regimen including the 8-site regimen (WHO 2010 position paper). The trial compared the 4-site ID regimen to three established regimens: 1) 2-site ID 2) 8-site ID 3) Essen 5-dose IM. Participants in all study arms had RVNA concentrations  $\geq 0.5$  IU/ml. Compared to the 2-site TRC ID regimen, this modified 4-site ID regimen requires fewer clinic visits, is likely to be more practical in smaller clinics and to provide a wider margin of safety in case of incomplete PEP course.

Quiambao et al. 2008 investigated on 400 healthy volunteers and people with category I or II exposures to healthy dogs or cats in the Philippines. This 4-arm study using PVRV investigated A) 96 patients for 8-site ID regimen; B) 96 patients modified 4-site ID regimen; C) 97 patients a 5-dose Essen IM; D) 99 patients a 5-dose TRC ID regimen (with eRIG or exceptionally hRIG IM). By day 14, all subjects had seroconverted. The GMT of all groups on day 14 was above 0.5 IU/ml, with the GMT of the 8-site ID group significantly higher than all other groups on day 7 (arms B-D equal). Unfortunately selected low level sera were retested and one group was given RIG, so the valid comparisons on immunogenicity of the regimens is impaired. The GMT of all groups on day 14 was above 0.5 IU/ml. There was a follow up of patients until day 90.

Ambrozaitis et al. 2006 conducted a 2-arm study in Lithuania using a modified 4-site ID regimen A) with PCECV in 91 people and B) with PVRV in 89 people. By day 7, 3% in arm A) and 6% in arm B) had titres  $>0.5$  IU/ml while GMTs of day 7 were higher in PCVC than in PVRV. By day 14 all had adequate titres until day 105 (99-100%). This regimen was considered immunogenic with both vaccines used.



**Figure 8:** Rabies neutralising antibody results by RFFIT (modified from Warrell et al 2008)

### 1-week 4-site ID regimen (4-4-4-0-0)

Three randomized clinical trial investigated this newly proposed regimen:

Sudarshan et al. (2012) evaluated the safety and immunogenicity of a one-week ID regimen in healthy volunteers. All participants (100%) had adequate protective rabies virus neutralizing antibody concentrations until day 180. However, after one-year post immunization, only 62.5% in the PVRV group and 78.9% in the PCECV group demonstrated antibody titres above the threshold considered protective. The regimen also induced strong immunological memory, demonstrated by the quick anamnestic response observed after boosting (in participants with titres that dropped below 0.5 IU/mL after one year). The regimen was also well-tolerated and adverse event rates relatively low. They concluded that further studies are needed in individuals possibly exposed to rabies.

Shantavasinkul et al. (2010) evaluated the safety and immunogenicity of this one-week ID regimen in healthy volunteers. This study included 3 arms 1) 4-site 1-week ID schedule in healthy volunteers 2) 4-site 1-week ID schedule plus eRIG in healthy volunteers and 3) original TRC-ID regimen in patients that presented with



category III rabies exposures. The 1-week ID regimen was found to be safe and immunogenic. All participants had protective rabies virus neutralizing antibody concentrations  $\geq 0.5$  IU/ml on days 14 and 28. The proportion of subjects that had antibody concentrations  $\geq 0.5$  IU/ml on day 360 were similar across the three study arms. Narayana et al. (2015) evaluated the immunogenicity and safety of this schedule in animal bite cases (bitten by rabies suspect animals, without laboratory confirmation).

The studies support the regimen which elicited adequate and protective rabies virus neutralizing antibody concentrations  $\geq 0.5$  IU/ml from day 14 onwards until day 365 as per WHO criteria considered protective against rabies. The incidence of local and systemic reactions in these 3 study was comparable to that of rates reported for WHO approved regimens. While this investigational regimen proves highly immunogenic and reduces the number of visits, the number of ID doses required is above the updated TRC regimen.

#### **4-dose Essen IM regimen and other IM regimens**

The truncation of the 4-dose Essen IM regimen to 3-doses (days 0, 3 and 7) was considered. However, despite the likely valid inference that IM regimens are clinically equivalent to ID regimens (CDC 1982, Saraya et al 2010, Venkataswamy et al. 2015, Recuenco et al 2017), there are limited clinical outcome data for a 1-week, 3-dose IM regimen. The study by M. Warrell et al 2008 included comparative immunogenicity data of the 5-dose Essen IM regimen for days 0, 3, 7 and found similar GMTs for both, IM and ID administration. However, IM GMTs were slightly lower (not statistically significant). While there is no direct evidence for the immunogenicity of a 3-dose IM regimen, numerous studies assessing 4- and 5-doses (comparing investigational schedules to the standard IM Essen regimen) showed adequate antibody titres after the second dose (for example Phanuphak et al 1987, Jaiaroensup et al 1998). No comparative study has been made of the immunosuppressive effects of RIG. Therefore, out of caution, the WG concluded that it will continue to recommend a 4-dose Essen IM regimen (day 0, 3, 7, and 14). The fourth dose can be given at any time between day 14 and 28.

The established 3-visit Zagreb IM regimen (two doses on day 0, 1 dose each on day 7 and 21) will be maintained.

The quality of another recent study (Huang et al 2014) that assessed a 1-week, 3-dose IM schedule had limitations and further investigation of this regimen would be necessary before a new policy recommendation could be made.

#### **4.2.2. Programmatic challenges of procurement, distribution and delivery of PEP**

An ongoing multi-country survey initiated by WHO evaluates the logistic and regulatory pathways how countries procure, distribute and deliver biologics for PEP. Preliminary results from over 20 countries (mainly Africa and Asia) show that the quality and format of the data or information available highly vary between countries. All countries have distribution systems for EPI vaccines, but only 2 countries use it also for rabies vaccines. However, 40% use the same cold chain as for EPI vaccines. All countries have rabies vaccine available to some extent, yet it was frequently cost-prohibitive and of limited availability in the public sector, particularly in rural areas. In countries where it is unavailable in the public sector, it is often still available in the private sector, but at a higher cost. In contrast to the relative availability of rabies vaccine, RIG was very scarce in the majority of countries and often prioritized to those with very severe or high-risk exposures. At least 6 countries reported to have no RIG available in their country. Cold chain, distribution channels and frequency, monitoring and reporting methods varied both between countries and within countries. Countries with robust rabies PEP systems have identified rabies as a national priority and/or established a national rabies control programme. There is limited information on vaccine demand and utilization due to the lack of standardized monitoring tools. Until rabies programmes get stronger and generate more data, modelling may assist in closing these knowledge gaps and levels of uncertainty (e.g. for vaccine need forecasting).

Based on first results there is a need to (a) develop standardized global guidelines for reporting and monitoring rabies PEP use, (b) inclusion of rabies PEP in joint reporting forms, (c) leveraging systems that are already

established for distribution of rabies or other vaccines and (d) employing alternative delivery strategies. Specific case studies and an overview on global findings will be highlighted in forthcoming publications.

Regarding vaccine forecasting WHO encourages countries requesting biologicals for PEP treatment of bite exposures will be requested to (i) provide future vaccine forecasts demonstrating a clear strategic plan for sustained vaccine deployment together with long term financing plan (ii) provide records on the use and impact of the biologicals supplied by the bank. This data will be used to generate quality disease data, assessing not only the impact of the stockpiles, but also other parameters necessary to track impact and disease elimination goals.

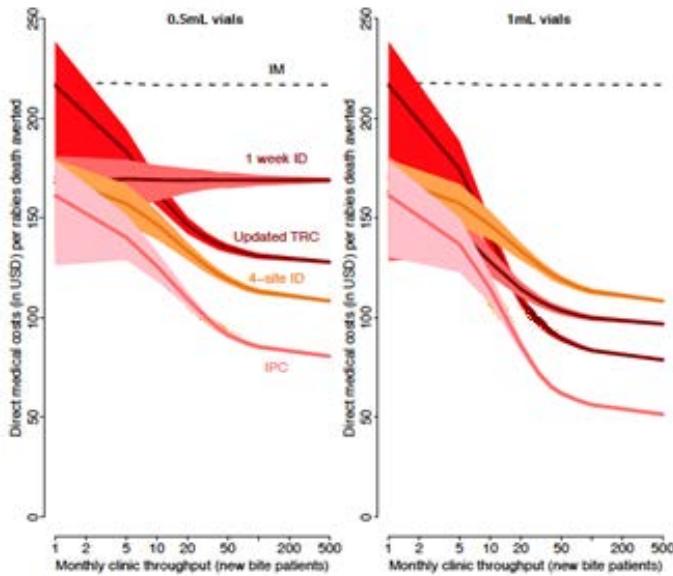
Researchers from prominent institutions worldwide are currently adapting existing models for vaccine forecasting and investment for elimination to identify and predict resource needs.

#### **4.2.3. Cost-effectiveness and public health impact of different PEP regimens, modelling results:**

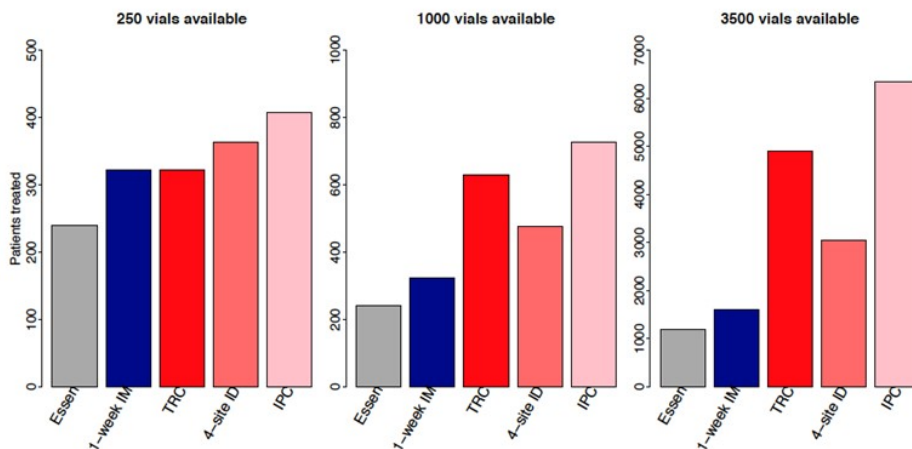
There is limited information on PEP demand and utilization due to the lack of standardized monitoring tools. Until programmes get stronger and generate more data, modelling may assist in closing these knowledge gaps and levels of uncertainty. Detailed methods and results are available in the evidence profile of Question 5. Based on a simulation framework previously developed for evaluating vaccine use (Hampson et al., 2011) the potential benefits and relative costs of delivering post-exposure vaccination according to currently recommended and proposed rabies PEP regimens was quantified (Figure 9). For methodological details see evidence profile of question 6&7. Results suggest that the cost-effectiveness of IM regimens does not change with clinic throughput whereas the cost-effectiveness of ID regimens improves with patient throughput as vials (not injection material) can be shared between patients.

Clinic throughput affects the capacity for vial sharing, and therefore the cost-effectiveness of ID administration relative to IM. As throughput increases, ID regimens become increasingly cost-effective, using up to 85% less vaccine. Yet, even clinics with relatively low throughput (~10 new patients/month) would considerably reduce vial use by switching from IM to ID administration of PEP and even at lowest throughput ID administration is equivalent in cost to IM. Increased use of ID regimens could therefore prevent vaccine shortages and enable wider vaccine distribution, both increasing the number of patients that can be treated and the overall accessibility of PEP.

ID administration of PEP is generally more cost-effective than IM administration and reduces the amount of vaccine used up to 85%. This is an important programmatic consideration given the frequency with which PEP vaccine shortages occur at clinics in many rabies-endemic countries. The use of insulin syringes should provide clinicians with further confidence in vaccinating patients and reduce vaccine wastage per vial as more accurate volumes of vaccine can be injected. These savings become more apparent in clinics that receive more than 10 new bite patients presenting each month.



**Figure 9:** Direct medical costs per rabies death averted for ID regimens in relation to clinic throughput. The Essen 5-dose IM regimen is also illustrated for comparison and updated TRC regimen serves as a reference. 4-site = modified 4-site ID regimen (4-0-2-0-1)



**Figure 10:** Patients treated under different PEP regimens given limited vaccine availability. It was assumed that clinics had only 250, 1000 or 3500 vials available over a 1-year period. Note the different y-axis limits.

In conclusion, modelling results confirm the cost-effectiveness of ID regimens, already in clinics with a limited monthly throughput. Wider adoption of ID regimens has the potential to serve more patients in settings where vaccine shortages occur.

#### 4.2.4. Update on modified PEP protocols for specific risk groups affected by additional health conditions:

Specific risk groups affected by diverse health conditions that might affect their response to rabies vaccine were identified. These include pregnant women, immunocompromised patients and people exposed to bat-mediated rabies or other lyssaviruses.

#### 4.2.4.1. Immunocompromised individuals

Many circumstances induce immunosuppression and different immunoregulatory pathways lead to a compromised immune response. In most settings, it is not possible to determine the source or severity of immune-suppression when patients consult for PEP.

##### a) Individuals with human immunodeficiency virus (HIV) infection

HIV patients under treatment and monitoring would most likely react like not severely immunocompromised patients or HIV uninfected individuals as observed in studies conducted for routine vaccines (Simani et al. 2014).

Sirikwin et al. (2009) evaluated the immunogenicity of a modified 8-site ID regimen in 27 HIV-infected patients, a risk group that is known to have reduced immune responses to vaccination. Individuals whose CD4+ cell counts both below and above 200 cells per microliter were studied. All patients had adequate antibody concentrations  $\geq 0.5$  IU/ml on day 14 after immunization. There was no statistically significant difference between individuals with CD4+ cell count  $< 200$  and CD4+ cell count  $\geq 200$  up to day 360. Sirikwin et al. (2009) concluded that PCECV is immunogenic in HIV-infected patients with CD4+ cell counts below 200 when administered in a modified 8-site ID regimen.

Older studies (Pancharoen et al 2001, Thisyakorn et al, 2000) did not confirm that a higher antigen dose results in a more adequate immune response in seriously immunocompromised individuals.

##### b) Other potentially immunocompromised patients:

Sampath et al. 2005 investigated 45 malnourished children aged 8 months to 16 years who received PEP (5-dose Essen IM regimen, WHO pre-qualified vaccine) for their immune response. All children had developed RVNA levels  $\geq 0.5$  IU/ml by Day 14. There was no significant difference in antibody concentrations between the malnutrition categories.

Tanisaro et al. (2010) evaluated the use of an ID regimen in haemodialysis patients with end-stage renal failure, receiving adequate dialysis, using a 5-dose TRC-ID regimen (2-2-2-0-1-1). All subjects (n=14) had adequate antibody responses against rabies 14 days post vaccination. At day 90, 13 of the 14 patients had protective antibody levels, resulting in a 92.8% response rate. These results suggest that ID rabies vaccine administration is immunogenic in haemodialysis patients and may be suitable for use in immunocompromised individuals. However, due to the small sample size of the study, more evidence may be needed before a recommendation be made.

Rahimi et al. (2015) evaluated the immune responses of the 5-dose Essen regimen in healthy volunteers compared to patients with specific medical conditions and a category II or III rabies exposure, such as pregnancy, diabetes I or II, chronic infection with the hepatitis B virus, different types of cancer such as lymphoma, and those who were immunocompromised due to receiving corticosteroids such as rheumatoid arthritis patients and lupus erythematosus patients. On day 14 post-immunization, all subjects had neutralizing antibody concentrations  $\geq 0.5$  IU/ml. GMTs were 16.2 IU/ml and 8.73 IU/ml in immunocompetent and immunocompromised participants, respectively. On day 35, all subjects in both groups were also protected. The GMTs were 30.3 IU/ml (8.3-45.5 IU/ml) and 20.7 IU/ml (8-30.2 IU/ml) in immunocompetent and immunocompromised participants, respectively. Although the average antibody titres were greater for the immunocompetent participants, the GMT ranges overlap and are above the threshold in both groups, which suggests that the immune responses are comparable. Therefore, if immunocompromised patients mount comparable immune responses to the 5-dose Essen regimen, it suggests that other regimens may be suitable for specific risk groups. This is especially pertinent considering that ID regimens have been shown in other studies to elicit a stronger immune response compared to IM regimens.

In conclusion, clinical studies on PEP in immunocompromised patients are mainly available from HIV-infected individuals. Clinical experience suggests that whenever possible to allocate the best PEP options available (the most immunogenic regimen available, high-quality RIG), regardless of the route of vaccine administration. Further, meticulous and very thorough wound cleaning as first aid to bite patients is of utmost importance in

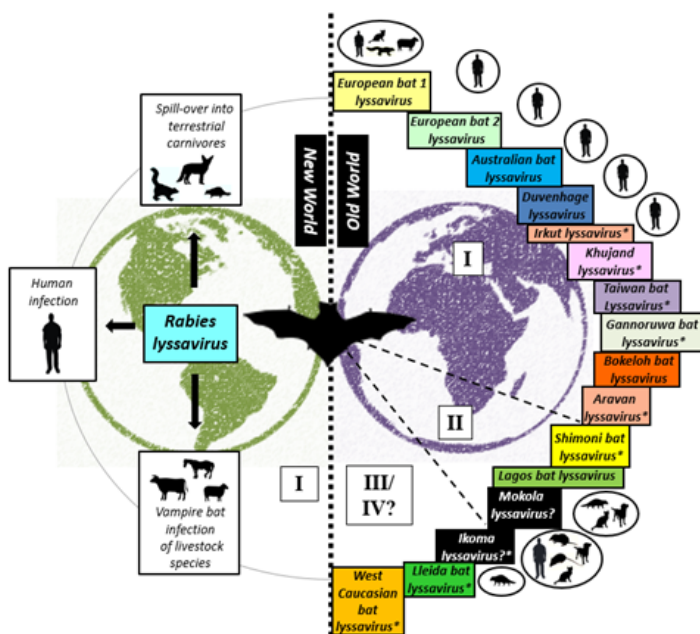
immunocompromised patients. The high variability of causes compromising the immune system in patients and the limited number of studies call for targeted studies.

#### 4.2.4.2. Pregnant women

Recent literature reviews on vaccines and pregnancy including reference to rabies are available from de Martino et al. (2016) and Crowcroft et al. (2015) and confirm safety and efficacy of PEP in pregnant women. Huang et al. (2013) evaluated the safety of PEP using the Essen 5-dose regimen among pregnant women with potential rabies exposures. All of the infants exhibited normal development and both PVRV and PCECV were supported as safe for use in pregnant women. No rabies cases were reported for any of the subjects or babies. All three authors highlight that educational gaps exist about the safety of PEP during pregnancy. Life-saving PEP in pregnant women is safe and efficacious. PEP should never be withheld from this risk group and any of the WHO recommended PEP regimens can be used.

#### 4.2.4.3. Bat-mediated exposures

In the Americas, rabies virus is the only lyssavirus isolated from bats. In other parts of the world, lyssaviruses other than rabies virus are present in bats. Reported exposures and bat-associated lyssavirus infections in humans are extremely rare in the 'old world'. The number of bat lyssaviruses identified has increased over the years. At present, three phylogroups of lyssavirus species are recognised in bats. Rabies virus, and also Australian, European some other bat lyssaviruses, are in phylogroup I. Experimental evidence indicates that currently available rabies vaccine strains are ineffective against lyssaviruses in phylogroup II and phylogroup III (Figure 11) (WHO, 2017). In absence of novel, pertinent evidence on improvements of PEP in individual who experienced a bat-mediated rabies or lyssavirus exposure, the recommendations on PEP regimens remain unchanged.



**Figure 11:** diversity of lyssaviruses. © Crown Copyright, 2017. Used with permission of Prof A. Fooks & Dr A. Banyard, Animal and Plant Health Agency.

#### 4.2.4.4. PEP considerations for atypical rabies exposures:

Consuming raw milk from a rabid animal is not advised, however there is no evidence that this practice constitutes an exposure to the rabies virus, so PEP is not indicated. Pasteurized milk presents no risk.

Human cases resulting from consumption of meat from a rabid animal are extremely rare. Consuming the meat from a rabid animal is not advised, particularly when consumed raw. PEP should be considered in persons who experience a category II or III exposure during the processing of meat from a rabid animal, or persons who have consumed raw meat from a rabid animal.

Human-to-human transmission of rabies through corneal or other organ transplantation is rare but documented. Caution should be exercised before transplanting organs from people who have died with neurological symptoms or signs. It may sometimes be necessary to provide PEP to the partners of patients, as close contact and sexual intercourse in the early stages of the disease carry a hypothetical risk for transmission. Infectious rabies virus is present in the saliva, but no reports have clearly established human-to-human transmission (WHO, 2017).

#### **4.2.5. Changes in the route of administration during a PEP course**

Ravish et al. (2014) provided supporting evidence that changes in the type of CCEEV (n=43) or the route of administration (n=47) of rabies vaccines (n=24 from IM to ID and n=23 from ID to IM) are safe and immunogenic. This observational study suggests that changes in the CCEEV and/or the route of administration should be allowed in unavoidable circumstances to promote completion of the lifesaving PEP regimen. Detailed immunogenicity data are available in the evidence profile.

In a slightly different context Sudarshan et al. (2006) conducted a study on n=20 volunteers who previously received a complete course of PEP. The recall of the immune response was assessed by mimicking PEP for previously immunized people and forcing a change in route of administration. This practice has been shown safe and immunologically efficacious, even after cross-over from the ID to the IM route and vice versa. The scarce evidence combined with expert knowledge led the group to conclude that changes in the route of administration during a PEP course is acceptable in unavoidable circumstances and restarting PEP is not necessary. The regimen of the new administration route should be adopted.

#### **4.2.6. PEP in previously immunized individuals:**

People exposed or re-exposed to rabies, who have previously received PrEP, PEP, or who have discontinued a PEP series after receiving at least two doses of CCEEVs, should receive booster vaccination with either: one site, two visit IM or ID PEP (days 0 and 3); or four site, single visit ID PEP (day 0, with four injections of 0.1ml vaccine equally distributed over the left and right deltoids, thigh or suprascapular areas). RIG is not indicated for previously rabies immunized individuals (WHO, 2017). A single study by Sudarshan et al. (2011) indicates that healthy people may not require booster vaccination, if exposed to rabies for up to three months after receiving either PrEP or PEP. Vigorous wound washing and proper wound management is also stressed in these situations.

## **5. RABIES IMMUNOGLOBULINS:**

### **5.1. Key Points**

- Vigorous wound washing together with immediate administration of the first dose of vaccine and subsequent completion of the PEP regimen can save up to 99% of bite victims from fatal rabies
- The maximum dose for RIG, calculated by body weight, is maintained
- Local infiltration of RIG as much as possible into and around the wound is most effective
- Injection of the remaining dose of RIG distant to the wound site is unlikely to confer additional protection
- eRIG and hRIG are considered clinically equivalent
- The skin testing prior to administration of eRIG should be abandoned. This practice has been discouraged for several years, but remains stated on the package labels of the product
- An algorithm for prioritization of the allocation of RIG in case of shortage or other constraints has been proposed



- The newly licensed mAb product (SII RMAb) was assessed, provides an opportunity to improve availability of RIG
- Promoting mAbs as an affordable and accessible alternative or supplement to scarce RIG is of high priority
- Future improvements should be considered for a 'cocktail product' with more than 1 mAb
- The optimal pricing of this product (SII RMAb) will be crucial to assure uptake and acceptability (ideally below the market price of eRIG)
- Post-marketing surveillance is needed for both RIG and mAb

## 5.2. Review of Scientific Evidence

RIG, derived from the blood of humans or horses, is used as a component of PEP as a method of passive immunization. RIG neutralizes the rabies virus at the inoculation site in the time before the immune system responds to the vaccine by production of rabies virus neutralizing antibodies. Both active and passive immunization prevent the rabies virus from infiltrating the central nervous system, but become ineffective once the virus has crossed into the central nervous system. RIG is administered only once, preferably at or as soon as possible after initiation of PEP. It is not indicated beyond the seventh day after the first dose of rabies vaccine, regardless of whether the day 3 and day 7 doses were received, because an active antibody response to the CCEEV has already started, and there may be interference between active and passive immunization. RIG should ideally be administered in all people with category III exposure and to individual with category II exposure who are immunodeficient or who had an exposure with direct contact to a bat.

The high cost, low availability and supply, batch to batch variation affecting efficacy, uncertain quality (no WHO prequalification), short shelf-life, cold chain challenges and correct administration of RIG are barriers to implementing the standard previously set by WHO for PEP in category III bites. RIG is often a barrier for attaining public health impact because of a hesitation to use vaccine without RIG and therefore manufacturers and countries often do not want to make vaccines available without RIG, which means no PEP at all. In most rabies-endemic countries, RIG is in short supply and is cost-prohibitive for patients with limited financial resources. Public health authorities' budget for procurement of RIG is in most cases very limited or even absent. Conversely, in other settings there may be a tendency of overuse. It is estimated that only around 1-10% of patients who need it receive RIG as part of PEP following exposures to potentially rabid animals (Khawplod et al., 2002; Wilde et al., 2002; Warrell, 2012).

There are only a few studies with observational data on the efficacy of RIG. As rabies is a fatal disease, and RIG considered a mainstay of rabies PEP, conducting randomized controlled trials with placebos presents ethical and logistical challenges.

### 5.2.1. Safety and efficacy of eRIG

Currently, eRIG is an underutilized biological in part because of the misperception that scarce and costly hRIG is superior and safer. In the past, impurified eRIG conferred high rates of serum sickness, anaphylaxis and other severe adverse reactions (Madhusudana et al, 2013). But nowadays, eRIG is highly purified and enzyme-refined and contains over 85% F(ab')<sub>2</sub> (Madhusudana et al., 2013; Shantavasinkul & Wilde, 2011; Quiambao et al., 2008, Kittipongwarakarn et al. 2011, Reveneau et al. 2017). Through purification techniques such as heat treatment, pepsin digestion and enzyme refinement, the crystallisable/constant (Fc) fragment is removed and the nonspecific protein content of the purified sera is decreased to less than 3% (Behera et al., 2011; Chawan et al., 2007). As the Fc fragment in impurified eRIG is responsible for direct complement activation and anaphylactic reactions, the high F(ab')<sub>2</sub> content and low Fc protein content allow for increased safety and specific activity (Chawan et al., 2007; Madhusudana et al., 2013; Quiambao et al., 2008). Indeed, data show that adverse reaction rates for eRIG are similar to that of penicillin (Wilde, 2012). eRIG treatment has even been shown to be safe for pregnant women, as F(ab')<sub>2</sub> is not shown to cross the placenta (Dixit et al., 2016). F(ab')<sub>2</sub> fragments have a shorter half-life in vivo than intact immunoglobulins. There have been concerns that effective neutralization with F(ab')<sub>2</sub> products therefore might wane in the critical period before active immunity and RVNAs appear. Quiambao et al. (2009) discuss that, while the clearance of F(ab')<sub>2</sub> eRIG is faster



than that for impurified eRIG and hRIG, the F(ab')<sub>2</sub> fragments have a higher specificity and instance of antigen-binding reactions, and therefore its efficacy is preserved. Both et al. (2012) state that purified eRIG “is generally highly effective, [although] the reduced half-life of these experimentally induced antigen-binding fragment products might have contributed to a few anecdotal PEP failures, and related data derived from animal studies have shown that intact immune globulin products are more effective for rabies PEP than derived F(ab')<sub>2</sub> fragments”. The differences in half-life of hRIG and eRIG was not considered clinically relevant, as RIG should be administered immediately after exposure and the half-life of RIG is days, not hours (half-life eRIG ~3 days, hRIG 21 days). Both eRIG and hRIG are highly efficacious in eliminating the virus at the wound site within a few hours.

In a similar manner to the discussion of its safety and following WHO standards for PEP in category III bites, the efficacy of eRIG is supported, considering the price and scarcity of hRIG and the 100% mortality of clinical rabies.

There are no more scientific grounds for performing a skin test prior to administering eRIG because testing does not predict possible reactions, and life-saving RIG should be given whatever the result of the test. The treating physician should be prepared to manage anaphylaxis which, although rare, could occur during any stage of administration. Unfortunately there has been a persisting gap between regulatory agencies' statements on skin tests and RIG product labels still insisting on skin testing, e.g. for liability reasons. A revised classification of adverse effects after RIG administration is proposed (Table 6). It should be used to encourage more countries participating in post-market surveillance on RIG and reporting back to international organizations and to the RIG producers. Examples for reporting forms from other vaccines are available from the “Global Manual on Surveillance of Adverse Events Following Immunization “

[http://www.who.int/vaccine\\_safety/publications/aefi\\_surveillance/en/](http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/)

**Table 6:** Types of reactions which may occur after rabies immunoglobulin administration (Adapted from Baldo, 2013; Buelow et al., 2017; Krishnamurthy & Hoang, 2017; Schryver et al., 2015)

	Signs	Frequency / Severity	Delay	Mechanism
<b>Local</b>	Local redness, tenderness and swelling	High / Benign	Immediate or within hours	Local trauma or inflammation due to injected volume
<b>Serum sickness-like reaction</b>	Fever, myalgia, epigastric pressure, rash, thrombocytopenia, anorexia, arthralgia	Medium / Medium	Usually within days, sometimes within hours	Type III hypersensitivity reaction, mediated by IgA/IgM
<b>Hypersensitivity reaction (urticaria)</b>	Rash, urticarial, wheezing, dyspnoea, hypotension, swelling, tachycardia, dizziness, chest pain, nausea	Medium / Medium	Immediate in previously sensitized patients, minutes in others	Type I hypersensitivity reaction mediated by IgE
<b>Anaphylaxis</b>	Skin itching, sweating, faintness, dizziness; nausea and vomiting, diarrhoea, are inconstant; Cardio-respiratory collapse then shock is possible.	Rare / Severe	Within minutes	Type I hypersensitivity reaction mediated by IgE

### 5.2.2. Simplification of Administration of RIG

Evidence regarding new data and improved quality of RIG suggest that the recommendations for the administration of RIG may be simplified. Clinical considerations for RIG administration use include the risk of

compartment syndrome, e.g. if large volumes of RIG are injected into a small body area with limited tissue, such as a wound located on a fingertip or the pinna. Administering RIG into subcutaneous fat reduces or delays effectiveness. Injection of RIG into the central gluteal area should be avoided due to the risk of damage to the sciatic nerve (WHO, 2013).

#### **Dose calculated by body weight**

The recommendation on body weight dosage was originally derived from studies in which impurified eRIG was administered systemically. Therefore, the body weight recommendation gave consideration for biological half-life of heterologous proteins and extent of distribution and dilution in the body (Bharti et al., 2016; Madhusudana et al., 2013). These recommendations lack empirical support and appear outdated in light of the newer, more efficacious highly purified and enzyme refined immunoglobulins containing only antigen binding components. However, to avoid any interference between RIG and vaccine induced RVNA the maximum dose calculated by body weight should be maintained.

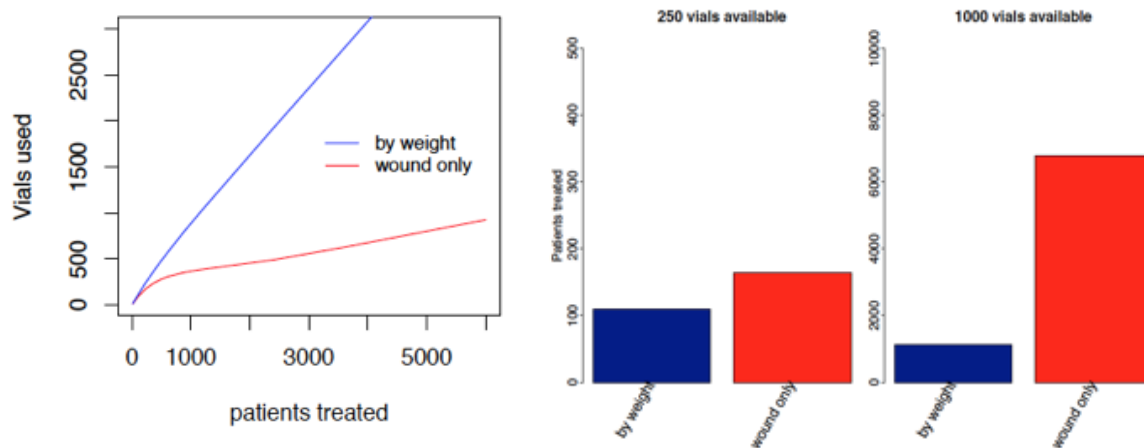
#### **RIG infiltration method**

Following the calculation of a RIG dose by body weight, often there is too small a volume of RIG to be distributed to the wound(s), or too large a volume of RIG to be infiltrated into the wound space (Bharti et al., 2016 and 2017). When too small a volume of RIG is allotted, it is often diluted with saline so that the volume may be spread between all wounds; this action decreases the concentration of RIG (Bharti et al., 2016; Madhusudana et al., 2013). If these spaces are areas that contain many peripheral nerve endings, increases the risk of the virus entering nerves (Behera et al., 2012). When the amount of RIG allotted is too large a volume to be infiltrated into the wound this can lead to a compartment syndrome. Therefore, the remainder is currently administered intramuscularly (Bharti et al., 2016; Madhusudana et al., 2013). This practice is considered wasteful and inefficient (Madhusudana et al., 2013; Wilde, 2016). As experimental data show that neutralization by RIG occurs at the site of infection, its injection into and around the wound(s) is likely to be the most efficacious and efficient method (Bharti et al., 2016; Wilde, 2016).

Bharti et al. (2016) investigated cost-effective alternatives to the current RIG standards. The study group included 269 patients with category III suspected rabies exposure (140 from dogs, in a rabies-endemic area), to which all were administered RIG volumes just sufficient to infiltrate wounds irrespective of body weight'' (Bharti et al., 2016). The doses of RIG ranged from 0.25 mL to 8 mL, with an average volume of 1.26 mL (Bharti et al., 2016). In total, 42 vials were used to treat all patients, compared to 363 vials had the doses been calculated according to body weight, a 60% to 80% reduction in RIG dose volume compared to those of the body weight standards' group (Bharti et al., 2016). Additionally, no administered dose exceeded the dose calculated by body weight as currently recommended, therefore avoiding concerns of interference of RIG with vaccine-induced rabies-neutralizing antibodies. This aspect was supported by serological tests done on 20 of the patients around day 14 after RIG administration. The circulating RVNA of all patients were equivalent to an active immune response to the vaccine, thus no interference was observed between RIG and vaccine induced RVNA (Bharti et al., 2016). Within the 82% follow-up rate for a time period of over 9 months, there was a 100% survival rate (Bharti et al., 2016). The most recent study of Bharti et al. 2017 using the same methodology, investigated 26 WHO category III rabies exposed patients who had been bitten by laboratory confirmed rabid dogs. The patients were followed for over one year and all survived. Despite the limitations in quantity and quality of studies, the data support abandonment of IM administration of remaining RIG distant to the wound. In conclusion, the primary benefit of RIG arises from thorough and complete local injection of the product directly into the wound. In settings facing shortage of RIG or where patients face difficulties to obtain or afford RIG, the most important injection site is into the wound site. The value of RIG injected at a distance from the wound is unknown, and might be unnecessary. In settings where RIG is available in sufficient quantity, the remainder can still be administered IM. In settings where RIG is of limited availability, IM administration should be avoided to allow for the possibility to divide vials between patients in need. Open RIG vials need to be

stored aseptically and best be drawn up in separate syringes, to provide the maximum benefit for multiple patients.

Modelling results exemplify the public health impact of a change in RIG administration policy. Details on modelling methods and assumptions are available in the evidence profile of Question 10.



**Figure 12:** Patients treated with RIG when administered according to current WHO recommendations (blue) and at the site of the wound only (red). We compared vials used under different levels of patient throughput (left), and also how many patients could be treated given limited vial availability (right) with examples shown for 250 vials and 1000 vials per year.

### 5.2.3. Subcategories of patients to be given highest priority for RIG administration

As RIG is of low availability, clinics in canine rabies-endemic areas wait months for orders to be filled, and some remain unfilled (Wilde et al., 2002), particularly on the African continent (Dodet et al.2009). Even when RIG is available, many patients cannot afford it (Hossain et al, 2010, Mallewa et al., 2007; Hampson et al., 2008; Ly et al., 2009; Sambo et al., 2013) or it is allocated to patients who can afford it, but who do not necessarily bear the highest risk for rabies infection. In rabies-endemic, low-income countries RIG is estimated to be available for less than 1% of category III exposed patients (Warrell, 2012).

Limited published evidence identifies risk factors that increase the risk for fatal rabies infection. These include (but are not limited to) the use of a nerve tissue vaccine (instead of a recommended CCEEV), injuries to the head, neck, face, hands, or other places with a high density of peripheral nerve endings (See Table 5), immunocompromised patients and a laboratory confirmed rapid biting animal (Dimaano et al., 2011; Hossain et al., 2011; Tarantola et al., 2015; Shim et al., 2009; Wilde et al., 2013). Proper wound care with scrupulous cleaning and deep irrigation, followed by application of a potent antiseptic agent and timely administration of the first CCEEV dose are a key factor for increasing survival in cases which RIG is unavailable (Shantavasinkul and Wilde, 2011; Wilde et al., 2002).

It has long been known that anatomical sites, their degree of innervation and proximity to the brain are major determinants of incubation and transmission risks (WHO 2013). Although many authors cite nerve density as a factor positively associated with transmission, the exact role of nerve ending density and its attrition with age and sex is unclear (Gøransson et al. 2004). Post-exposure prophylaxis failures and short incubation times may be due to direct inoculation of RABV into nerve endings (Hemachudha et al 1999). Estimated probabilities of transmission after a bite are summarized by Cleaveland et al. (2002) are described in Table 5.

**Table 5:** Estimated probability of rabies transmission following the bite of a rabid dog, by anatomical site (Cleaveland et al. 2002)

Area of bite	Transmission risk
Head/Neck	30-60%
Arm	15-40%
Hand	15-40%
Finger	15-40%
Genitalia	15-40%
Trunk	0-10%
Leg	0-10%
Foot	0-10%

Observational data on patients with incomplete PEP courses with or without RIG and clinical outcome:

- 1) Cambodia (2003 – 2014): After being bitten by a confirmed rabid dogs, seven patients did not complete the TRC regimen (only 3 sessions of ID vaccines TRC), while the second group of 45 patients received 4 or 5 sessions of the TRC regimen. RIG was unavailable for both groups(shortage). All survived, as did 69 patients who received 3 sessions and 120 who received 4 or 5 sessions and also no RIG after a bite from a suspect rabid, but untested dog.
- 2) Tanzania: From 2,196 persons bitten by animals which were subsequently traced and classified as clinically suspect rabid animals 88 human rabies deaths were identified. The vast majority of these patients did not receive any PEP and none of these bite victims received RIG. Amongst the bite victims that started PEP promptly, only one death occurred and that was the result of the patient, who was bitten on the head, receiving only the first dose of vaccine. Among the patients that had delayed PEP, 4 deaths occurred out of 261 patients who presented 1 day late, 5 deaths occurred out of 319 patients that presented 3 or more days late, and 1 death occurred out of 130 patients that started PEP >7 days late. These data also highlight that most patients do not seek or obtain PEP promptly – 19% of rabid bite victims fail to obtain PEP, 36% of bite victims obtain PEP at least one day late and 9% obtain PEP 1 week late.
- 3) Observational contact tracing data supported by modelling: Data from persons bitten by suspected rabid dogs were grouped into four categories according to the part of the body where bitten: head and neck, trunk, arm and hand, and leg and foot. For individuals with multiple bites only the highest risk bite was used for this categorization, established via the hierarchy of risk reported by Shim et al. (2009) that proposed (from highest to lowest risk) head, arms, legs, trunk. Based on the health outcomes of bite victims that did not receive PEP the probability of developing rabies following a bite to a specified part of the body was calculated. The risk hierarchy was checked, the data re-categorized with the new hierarchy: head, trunk, arms, legs and the probability of death according to bite site recalculated. The overall probability of rabies transmission from a suspect rabid animal bite ( $p=0.1656$ , based on simulation from a mixture model) was then estimated based on the proportion of bite victims bitten on different parts of the body and the risk of developing rabies given the bite site. The protective effect of imperfect PEP for individuals bitten by suspect rabid animals ( $P_{\text{effective}}$ ) was based on a subset of these data with individuals that received RIG ( $n=1$ ) or whose deaths were caused by tetanus or injury ( $n=1$  and  $n=5$  respectively) removed. Nine suspect rabies deaths were identified from 891 patients bitten by suspect rabid animals but given imperfect PEP, i.e. the probability of death under imperfect PEP is 0.010 therefore  $P_{\text{effective}}$  is 0.990. Eight of these deaths were attributable to delays in PEP administration and the other was associated with timely PEP delivery of the first 2 PEP doses only (similar observations from Haiti).

In practice, prioritization is happening due to shortage of RIG (and vaccines), cost, age, severity of exposure, etc. Based on published data, clinical experience and expert knowledge an algorithm for more prudent and equitable use of RIG is proposed to support clinical management of bite patients potentially exposed to rabies.

This decision support for clinicians for most appropriate use of biologicals and patient care, would also ease ethical and logistical challenges.

#### **5.2.4. Monoclonal Antibodies:**

A prospective alternative to RIG is an anti-rabies monoclonal antibody cocktail. While mAbs were initially used for diagnostic and experimental purposes, they are now often employed as treatment and therapeutic agents in a variety of clinical settings. Efficacious and safe anti-rabies mAbs would increase access and affordability of PEP and subsequently decrease rabies deaths.

The first mAb against rabies (a single monoclonal antibody) was recently licensed by the Serum Institute of India (SII) (Gogtay et al., 2017) and is expected to be launched in Indian clinics for use in PEP in late 2017 (personal communication from SII, 19 August 2016). SII shared pre-clinical and clinical data with WHO and this evidence was reviewed by independent experts. The data shows that this mAb neutralizes a broad panel of globally prevalent rabies virus isolates, has shown equivalent response to HRIG in a hamster challenge model and the PEP regimen consisting of this mAb mounts rabies neutralizing activity to a level that is similar or higher than that with PEP containing hRIG in patients with Category III exposure. Additional evidence from the scientific literature was considered (see evidence profile Question 13).

As the first product has only been licensed recently, in consequence there is limited clinical and published evidence available. However, due to circumstances of low affordability and access to RIG, finding alternatives or supplements for RIG would have a big public health impact. Therefore and for the first time, WHO will propose a recommendation to include the use of mAbs for passive immunization against rabies.

mAbs can be produced in standardized quality and large quantities, eliminate the use of animals in the production process, reduce the risk of adverse events and reduce cost. Though it is hypothesized that mAbs should include two or more mAbs with non-overlapping epitopes, till date, only SII mAb has demonstrated safety and efficacy in clinical trials when used in PEP, and offer a potential solution to the lack of availability of RIG.

Considering the above factors this mAb should be used as part of PEP. The currently available single mAb and its use in selected geographic and epidemiological settings will serve as an important learning process for future mAb products. Post-marketing surveillance and close monitoring of adverse events, including in depth investigations on suspected PEP failures associated should be conducted. The uptake of mAb will also depend on pricing

Passive prophylaxis in the PEP in the form of RIGs is a critical component of rabies prevention. Though RIG have been available for last several decades, their use has been rather limited because of various reasons like limited availability, cost, concerns of allergic reactions, practice of unnecessary skin sensitivity tests, potential transmission of blood borne pathogens, etc. For the first time, a monoclonal antibody as a potential replacement to RIGs (SII RMAB) has been developed and licensed for use in rabies PEP as a passive antibody component. The data so far shows equivalence of its performance to hRIG. The availability of this mAb has the potential to address critical public health gaps. Since this mAb is made by recombinant technology, it will be less prone to problems such as availability, safety and purity. This mAb should be recommended for use in the public health programmes, based on epidemiological and geographic settings, along with monitoring of its safety and efficacy (clinical outcomes) during the post marketing use.

## **6. OVERVIEW OF NEW RABIES VACCINES AND OPERATIONAL TOOLS UNDER DEVELOPMENT**

### **6.1. Key points**

- New vaccines in the pipeline have the potential to lead to long-lasting immunogenicity and improve programmatic delivery
- Further innovation, research and development in close collaboration with manufacturers is needed to optimize cost-effectiveness, easier storage, longer shelf-life and still retain vaccine safety and efficacy

- Novel vaccine delivery tools have the potential to facilitate ID vaccine administration in a wider range of settings

## 6.2. Review of Evidence of the potential of new vaccines

Novel vaccines have the potential to simplify delivery and increase affordability of PEP and PrEP (Table 7). New vaccines are in different phases of development, and some are being reviewed by national and international regulatory bodies.

**Table 7:** Overview on novel vaccine candidates and a preliminary assessment of their potential

Vaccine type/group	Suitable for PEP	Suitable for PrEP	Administration mode (ID, IM, SC, other)	Safety	Efficacy, immunogenicity	Cost-effectiveness	Potential for improvements in delivery
Attenuated rabies vaccines	yes	yes	IM/ID/oral	depends	High	yes	Variable, 1 dose
Deactivated, genetically modified rabies virus	yes	yes	IM/ID	high	High	maybe	Lyophilized 2 doses
Protein vaccines	yes	yes	IM/ID	high	to be determined	No	Yes 3 doses
Peptide vaccines	no	no			Low		
DNA/RNA vaccines	no	yes	IM/ID	high	Low	maybe	Yes 3-5 doses
Adenoviral vectors	no	yes	IM/potentially oral	high	High	yes	Yes 1 dose
Other viral vectors	no	yes	IM/potentially oral	variable	Variable	maybe	Variable 1 dose
Bacterial vectors	no	yes	IM/potentially oral	depends	Low	no	No, 1 dose

### Stages of adjuvant development for rabies

#### *In clinical trials*

PIKA vaccine: Rabipur and Polyinosinic-Polycytidylic Acid Based Adjuvant - allows for reduction in vaccine dose (2 IU instead of ~6) and accelerated vaccination (2 doses on day 0, 2 on day 3, 1 on day 7).

### Vaccine in clinical testing

#### *In clinical trials:*

RNA-active rabies vaccine: Based on 3 doses of an mRNA encoding the rabies virus glycoprotein.

Phase II, Rabies G protein nanoparticle vaccine: Based on 3 doses of a baculovirus-derived glycoprotein that spontaneously form micelles (nanoparticles).

#### *Scheduled for clinical testing:*

E1-deleted adenovirus vector of chimpanzee-origin expressing rabies virus glycoprotein (Oxford/Wistar):

Planned trial will test a one dose regimen followed by a late boost with 2 doses of a conventional vaccine to assess recall responses. Clinical results are expected to become available by late 2020. The trial includes an arm that tests a new method to enhance thermostability at ambient temperatures. Discussions are underway with partners for larger scale clinical trials. It is expected depending on the efficacious dose that the vaccine

may eventually be made available for <\$1. Thermostabilization, a long-term goal, may increase the overall cost.

In conclusion, there are a number of novel, promising vaccines that may prove useful in the future to overcome challenges of delivery of the vaccine to the patient. Programme-directed research, innovation and development in close collaboration with manufacturers is needed to optimize cost-effectiveness, delivery at community level, easier storage, thermostability, longer shelf-life and still retain vaccine safety and efficacy. Research and development have to take into consideration the requirements for vaccines that are mainly needed in resource-limited settings where considerable logistic and operational challenges might be associated. Mutual exchanges between manufacturers, academia and WHO would allow to better adapt objectives and progress of development of new vaccines or adjuvants to programmatic needs in countries.

### 6.3. Operational tools under development to improve programmatic delivery

Novel intradermal immunization devices are currently being developed to simplify and improve delivery of ID vaccination. These include needle-based devices such as intradermal adaptors, mini-needles and microneedles; disposable-syringe jet injectors; and microneedle patches. The prices of such devices are still a barrier and appropriate training of health care providers will be needed. WHO prequalification protocols are already established for jet injectors, and under development for needle and syringe based ID devices. Innovation in controlled temperature chain (CTC) would allow for the storage and transport of compatible vaccines outside of conventional 2° to 8° Celsius cold chain, increasing cost-effectiveness, efficiency, and reach of immunisation programmes. A number of CTC compatible vaccines have been developed and prequalified, or are undergoing prequalification, and at present six countries have implemented CTC strategies. Studies suggest CTC could reduce vaccine delivery costs by up to 50% (Kahn et al., 2017).

The majority of individuals affected by rabies live in low resource and marginalized communities, therefore innovative delivery of medical drugs and vaccine are under consideration, such as delivery through drones. Enhanced efforts to train health care staff in ID administration of rabies vaccines, research on (easier) subcutaneous administration of rabies vaccines, coordinated use of existing cold chains and decentralisation of animal bite treatment clinics will further support the goal of improved health equity.

## 7. QUALITY OF EVIDENCE ASSESSMENT

### 7.1. Introduction and objectives:

The SAGE working group (WG) on rabies was established in mid-2016 (Appendix 1). In accordance with the guidance document for the development of evidence-based vaccine related recommendations <sup>2</sup>, the WG held a series of conference calls and face-to-face meetings to identify priority questions, for which recommendations need to be developed, for consideration by SAGE. The WG prioritized a list of issues for good practice recommendations, landscape analysis and for formal Grading of Recommendations, Assessment, Development and Evaluation (GRADE) review. A total of 14 key questions, and two additional questions relating to rabies vaccine potency and rabies vaccines under development, were identified. The key questions and outcomes **in bold** were agreed upon for a formal GRADE review. Evidence for the remaining questions was either entirely or partly based on modelling estimates (Questions 1, 5, 6, 7) or we conducted a landscape analysis on best practice or expert opinion available (Questions 2, 10, 14 and information on new vaccines). Evidence to Recommendation Tables are available for questions 3, 4, 6, 7, 10, 11, 12, 13, 14.

<sup>2</sup> [http://www.who.int/immunization/sage/Guidelines\\_development\\_recommendations.pdf](http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf)

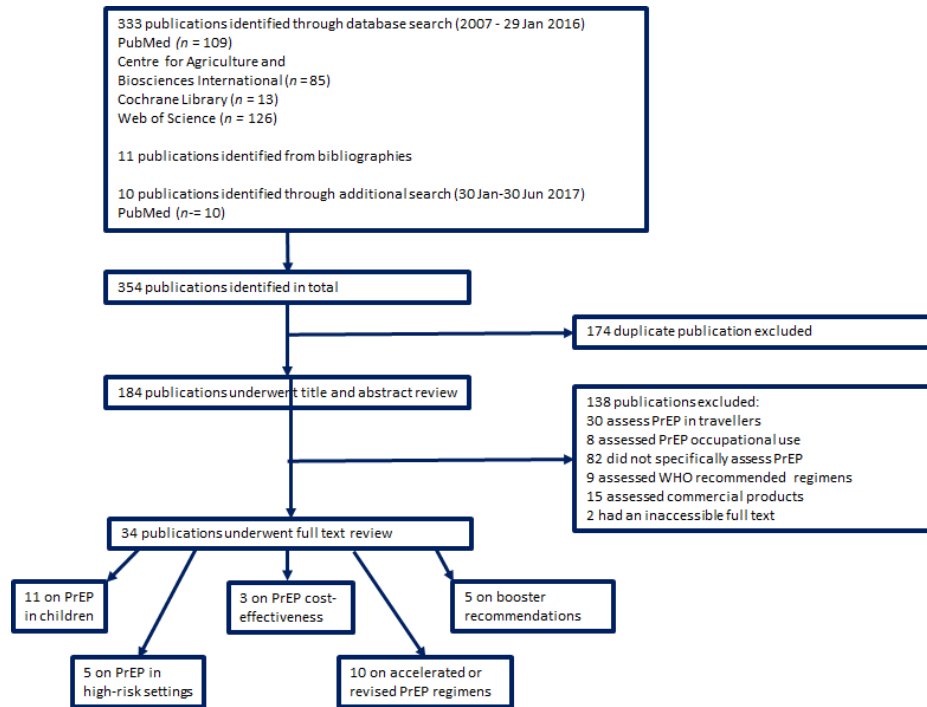


- Question 1: Does novel evidence support the use of PREP in particular sub-populations, apart from persons bearing an occupational rabies exposure risk?**
- Question 2: Does novel evidence support the need for rabies booster doses in persons at continual or frequent risk of occupational rabies exposure?
- Question 3: Can the duration of the entire course of current PREP regimens be reduced while maintaining immunogenicity and clinical protection?**
- Question 4: Can the number of doses administered in current PREP regimens be reduced while maintaining immunogenicity and clinical protection?**
- Question 5: Which (operational) parameters affect cost-effectiveness of intradermal (ID) compared to intramuscular (IM) administration route of PEP? a. in urban settings; b. in rural settings.
- Question 6: Can the duration of the entire course of current PEP regimens be reduced while maintaining immunogenicity and clinical protection?**
- Question 7: Can the number of doses administered in current PEP regimens be reduced while maintaining immunogenicity and clinical protection?**
- Question 8: Does novel evidence support recommendations on modified PEP protocols vs current PEP protocols for specific risk groups of rabies exposed patients, such as: Immuno-compromised patients (e.g. HIV-infected); patients concurrently using antimalarial drugs; pregnant women; bat exposures (i.e. for bat lyssavirus)?**
- Question 9: Does a change in route of administration (IM or ID) during a single course of a PEP regimen affect immunogenicity of PEP?
- Question 10: Are there novel approaches to RIG (-sparing) injection vs current practice as part of PEP for category III exposed patients?**
- Question 11: Is there clinical equivalence in the safe use of eRIG compared to hRIG in category III exposed patients?**
- Question 12: Is there clinical equivalence in the efficacious use of eRIG compared to hRIG in category III exposed patients?**
- Question 13: Can monoclonal antibodies be safely and efficaciously administered in category III exposed patients compared to standard RIG?
- Question 14: In cases of RIG shortage and constraints, can subcategories of patients be identified who should be given highest priority for RIG administration?**

## 7.2. Methodology:

Systematic literature reviews were performed for questions addressing PEP and RIG. For questions related to PrEP a systematic literature review was already available (Kessels et al.). Searches were primarily conducted in the English language, using the literature databases PubMed, Cochrane reviews, Science Direct and the WHO GIFT database. Given the relatively small number of randomized clinical trials (RCTs) available in the field of rabies, the WG included observational and unpublished data, and did not restrict the GRADE review to randomized controlled trials only. The WG focussed on data available since 2007, as the 2010 position paper considered most of the relevant literature before 2007. However, the WG considered key publications before 2008 for any question, and particularly where limited new evidence was available. References prior to 2007 were included from citations of relevant publications where applicable. Articles were not considered to be mutually exclusive, and could provide evidence for more than one question of interest.

The publication on **PrEP** by Kessels et al systematically reviews relevant published literature from 01 January 2007 to 29 January 2016, and case studies of rabies elimination programmes where PrEP has been used from Peru and the Philippines. The systematic literature review was updated to June 2017 to account for three published studies, and two manuscripts in preparation, on accelerated PrEP schedules (Questions 3 & 4), two additional publications for questions on PrEP boosters (Question 2) and one publication on PrEP as a public health intervention in sub-populations (Question 1). The results of the systematic literature review are available in [Figure 13](#). Question 1 was further supported by modelling results (see evidence profile).



PrEP: pre-exposure prophylaxis; WHO: World Health Organization

**Figure 13:** Results systematic literature review on PrEP

The **systematic literature review on PEP** (Figure 14): The search was conducted without language restrictions for articles published between January 2007 and June 2017. Search terms used in PubMed: ("Rabies Vaccines"[nm] AND "Humans"[MeSH terms]) AND ("post-exposure"[title/abstract] OR "postexposure"[title/abstract]). The 17 included articles comprised 5 randomized controlled trials, 7 observations studies and 5 review articles. These were considered relevant to address the WG Questions 6, 7, 8 and 9. The evidence base was extended by data from an ongoing clinical study in Cambodia, expert opinion and unpublished data from clinical practice in countries. Evidence for Question 5 was mainly retrieved from modelling results and programmatic experiences of countries (see evidence profile). For Question 9 evidence for decision was mainly derived from expert opinion, as the thorough literature search revealed only 2 relevant publications.

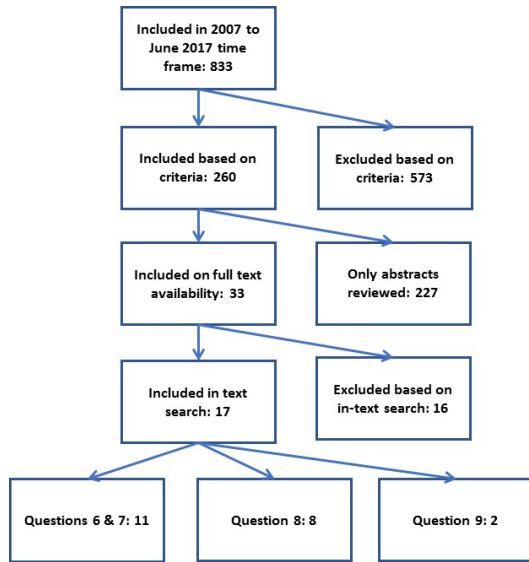


Figure 14: Search results for PEP

The **systematic literature review on RIG** encompasses all relevant literature from January 2007 to June 2017. General search terms for RIG were applied first, followed by distinguishing searches for each of the questions (Figure 15). A total of 9 relevant publications were considered for each of Questions 10, and the combined questions 11 & 12 (Figure 16). 21 publications were added to the evidence base for Question 14, which consists mainly of unpublished observational data and expert opinion.

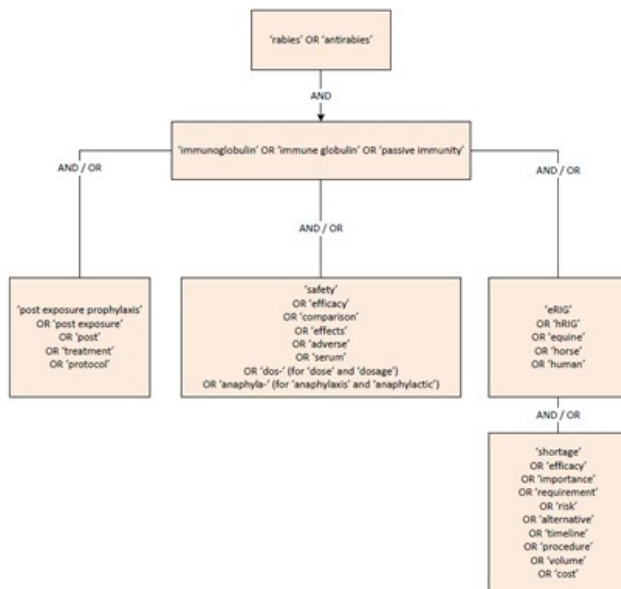
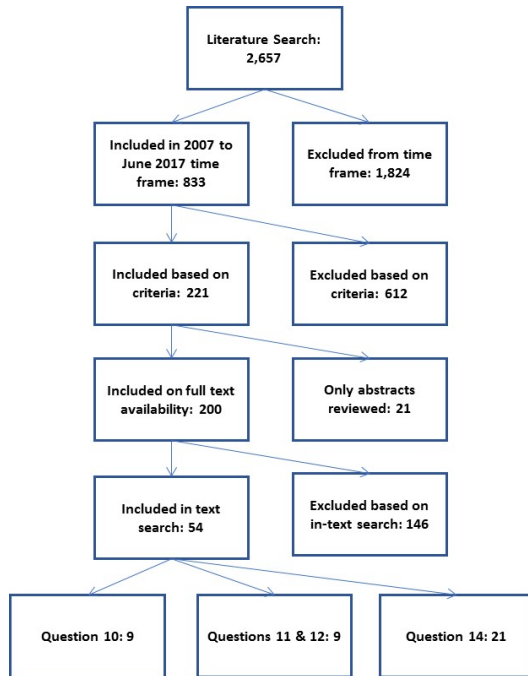


Figure 15: Search strategy for RIG



**Figure 16:** Results systematic literature review on RIG

A total of 59 recently published studies were included in the GRADE review: 18 for PrEP, 13 for PEP and 28 for RIG. Outcomes of interest for safety included any adverse event, any serious adverse event, and death. However, no published articles that were reviewed captured new information on rabies risk categories and boosters for occupational hazard or PrEP in immunocompromised individuals. Question-specific evidence profiles (Appendix II), including summaries of publications and unpublished evidence, were prepared using a standard template. All relevant publications for PICO format questions were assessed and GRADEd in terms of their risk of bias, level of indirectness, degree of imprecision, strength of association, and degree of residual confounding.

### 7.3. Results:

Detailed results of the evidence and GRADE review are included in the respective evidence profiles under Appendix II. The quality assessment of the evidence for questions 3 and 4 were combined as the publications considered usually address both aspects. The same procedure was applied for Questions 6 and 7, 11 and 12. The key results of the GRADE tables by question are summarized below.

The GRADE values for supporting evidence for recommendations on rabies immunization practices are characterized by the limited availability of high quality randomized clinical trials in this field. The key evidence frequently relies on observational studies and field data. Studies on rabies PEP regimens and RIG administration practices on this 100% fatal disease can't be carried out as placebo-controlled trials as ethically unacceptable. Because rabies is a fatal disease that affects marginalized and low-resource populations, any interventions that improve chances of survival, increase accessibility, and affordability of rabies biologics will outweigh undesirable outcomes or levels of uncertainty.

**Question 1: Does novel evidence support the use of PREP in particular sub-populations, apart from persons bearing an occupational rabies exposure risk?**

**Conclusion:** Evidence supports a moderate level of confidence that PrEP is safe and immunogenic in children and other sub-populations living in at risk areas, including when administered with childhood vaccinations or Japanese encephalitis vaccines in children and adults.

**Question 3: Can the duration of the entire course of current PREP regimens be reduced while maintaining immunogenicity and clinical protection?**

**Question 4: Can the number of doses administered in current PREP regimens be reduced while maintaining immunogenicity and clinical protection?**

Conclusion: Evidence supports a moderate level of confidence that accelerated PrEP regimens (2 visits, 1-week) are non-inferior to current WHO recommended PrEP regimens and result in an adequate level of neutralizing antibody titres of > 0.5 I.U. and an accelerated immune response upon boosters or PEP.

**Question 6: Can the duration of the entire course of current PEP regimens be reduced while maintaining immunogenicity and clinical protection?**

**Question 7: Can the number of doses administered in current PEP regimens be reduced while maintaining immunogenicity and clinical protection?**

Conclusion: Evidence supports a low to moderate level of confidence that accelerated or reduced PEP regimens are non-inferior to current WHO recommended PEP regimens and result in an adequate level of neutralizing antibody titres of > 0.5 I.U., clinical protection and improved cost-effectiveness.

**Question 8: Does novel evidence support recommendations on modified PEP protocols vs current PEP protocols for specific risk groups of rabies exposed patients, such as: Immuno-compromised patients (e.g. HIV-infected); patients concurrently using antimalarial drugs; pregnant women; bat exposures (i.e. for bat lyssavirus)?**

Conclusion: Evidence supports a very low level of confidence that modified PEP protocols for specific risk groups are non-inferior to current recommendations

**Question 10: Are there novel approaches to RIG (-sparing) injection vs current practice as part of PEP for category III exposed patients?**

Conclusion: Evidence supports a very low to low level of confidence that wound injection of RIG compared to wound injection and injection of remaining RIG IM distant from the wound is efficacious

**Question 11: Is there clinical equivalence in the safe use of eRIG compared to hRIG in category III exposed patients?**

**Question 12: Is there clinical equivalence in the efficacious use of eRIG compared to hRIG in category III exposed patients?**

Conclusion: Evidence supports a very low level of confidence that there is clinical equivalence of eRIG compared to hRIG in terms of safety and efficacy.

**Question 14: In cases of RIG shortage and constraints, can subcategories of patients be identified who should be given highest priority for RIG administration?**

Conclusion: Evidence supports a very low level of confidence that subcategories of patients can be prioritized for RIG allocation

**Potency: Currently required potency of cell culture and embryonated egg-based rabies vaccines is above 2.5 IU per dose, does this need review based on the current practice of vaccination?**

Conclusion: Evidence supports a moderate level of confidence that the immunogenicity of current rabies vaccines administered by ID route for PEP appears as least as good as that of IM vaccination regimens. While ID PrEP seems associated with lower antibody titres than IM PrEP, the observation has not been associated with any clinical relevance.

## 8. PROPOSED RECOMMENDATIONS FOR SAGE CONSIDERATION

### 8.1. PREP

Q 1 (PrEP as a preventive intervention in particular sub-populations)

1. Due to the low cost-effectiveness in most settings, PrEP as a large-scale intervention is not recommended. PrEP can be considered in areas where control in the animal reservoir is impossible (e.g. areas endemic for bat and wildlife rabies), and where there is limited access to timely and adequate PEP. This should be based on strong epidemiological evidence and local context. (See Table 4)

Q2 (need for boosters, occupational risk)

1. Individuals at a very high risk of rabies exposure from occupation, travel or limited access to timely and adequate PEP, should be considered for PrEP and/or vaccine boosters in accordance with recommended vaccine schedules (see Table 4).
2. Routine boosters are only recommended for those who face occupational exposure. If available, pre-booster serology can inform the need for a booster (see Table 4).

**Table 4: Indications for pre-exposure rabies immunization (PrEP), adapted from Müller et al. 2015**

Examples of typical individuals and populations	Likelihood and nature of exposure to rabies virus	Timely access to rabies biologics	Recommendations on pre-exposure immunization <sup>a</sup> and serologic testing
<b>Occupational exposure</b>			
Individuals involved rabies research, rabies biologics production <sup>b</sup> .	Virus may be present continuously, usually in high concentrations. Specific exposures may not be recognized.  Bite, non-bite, or aerosol exposures.	Yes	PrEP recommended. Suggested timeframes for serologic testing: After primary immunization and the every ~6 months up to every 1-2 years. Routine booster vaccination <sup>c</sup> , if antibody titre falls below 0.5 IU/ml <sup>d</sup> .
Individuals working in rabies diagnostic laboratories <sup>b</sup> , in hospitals with clinical rabies cases <sup>e</sup> , animal disease control, wildlife management, bat handling or with professional activities in caves likely to lead to direct contact with bats.	Settings or areas where rabies is enzootic and where exposure may not be recognized.  Presence of bats, particularly non-haematophagous bats. Bite, non-bite, or aerosol exposures.	Variable, mostly yes  Variable	PrEP recommended. Serologic testing every ~2 years. Routine booster vaccination if antibody titre is below 0.5 IU/ml.  PrEP recommended. No serologic testing or routine booster vaccination.
Individuals working or residing in remote areas for extended periods and involved in e.g. dog vaccination campaigns, animal disease control programmes, peace keeping, military or religious missions.	Remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures.  Partly remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures.	Variable, mostly not  Variable	PrEP recommended. Serologic testing unnecessary unless risk of exposure remains. Otherwise, test and boost if antibody titre falls below 0.5 IU/ml, or alternatively give a routine booster vaccination before departure.
Individuals involved in e.g. animal disease control with direct contact with terrestrial animals.	Settings where rabies is uncommon to rare. Exposure typically episodic with source recognized. Bite or non-bite exposures.	Variable, mostly yes	PrEP recommended. No serologic testing or routine booster vaccination.
<b>Travellers</b>			
Individuals with mainly leisure related exposures by potential direct contact, particularly with carnivores or bats, during activities over an extended period e.g. backpackers, bicycle or motorbike riders, people visiting friends and relatives. Consider cumulative exposure in frequent travelers.	Remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures.  Partly remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures.	Variable, mostly not  Variable	PrEP recommended. Serologic testing unnecessary unless risk of exposure remains. Otherwise, test and boost if antibody titre falls below 0.5 IU/ml, or alternatively give a routine booster vaccination before departure.
Individuals with leisure activities in caves leading to likely direct contact with bats.	Settings or areas where rabies is enzootic and where exposure may not be recognized.  Presence of bats, particularly non-haematophagous bats.  Bite, non-bite, or aerosol exposures.	Variable, mostly yes  Variable	PrEP recommended. Serologic testing every ~2 years. Routine booster vaccination if antibody titre is below 0.5 IU/ml  PrEP recommended. No serologic testing or routine booster vaccination.
<b>Sub-populations</b>			
Residents of remote areas where animal rabies control is impaired by difficult access, epidemiological and other factors	Settings or areas where rabies is enzootic, particularly in wildlife and where episodic exposure may not be recognized.  Bite or non-bite exposures.	Variable, mostly not	PrEP recommended. No serologic testing or routine booster vaccination.
General population	Areas where rabies is enzootic or epizootic. Exposure always episodic with source recognized.  Mostly bite, also non-bite exposures.	Yes	No PrEP recommended. PrEP for general populations is unlikely to be a cost-effective intervention and is usually more expensive than other measures to prevent human rabies deaths, such as post-exposure prophylaxis and dog vaccination campaigns.
In case of a WHO category II or III exposure to a rabid animal (or lyssavirus), post-exposure prophylaxis including thorough wound care is always required.  People who have received PrEP should be instructed accordingly.			

<sup>a</sup>A primary course of pre-exposure immunization consists of either a two-site intradermal administration of 0.1 ml of vaccine on days 0 and 7 or one vaccine dose for intramuscular administration on days 0 and 7. Administration of booster doses of vaccine depends on nature and duration of the rabies exposure risk as above.

<sup>b</sup>Assessment of relative risk and any extra monitoring of immunization status of laboratory workers is the responsibility of the laboratory supervisor (as an example, see guidelines in the current edition of the United States Department of Health and Human Services' Biosafety in Microbiological and Biomedical Laboratories).

<sup>c</sup> A routine pre-exposure booster vaccination consists of one dose of modern cell culture vaccine, ID or IM (i.e., deltoid area).

<sup>d</sup>An acceptable antibody level is 0.5 IU/ml or 1:5 virus neutralizing antibody titre (complete inhibition in the RFFIT at a 1:5 dilution, approximately equivalent to 0.1 IU/ml). Boost if the titre falls below this level, as long as the person remains at risk of viral exposure.

<sup>e</sup>Human-to-human transmission of rabies has never been confirmed outside of the transplant setting. However, rabies virus can be found in saliva, tears, and nervous tissues of human rabies cases and represents a theoretical route of transmission. Therefore, pre-exposure immunization might be indicated and can alleviate the psychological burden of fear from infection of health care staff who are regularly attending to patients with clinical rabies.

### Q 3&4 (decrease in duration/number of doses)

1. The following PrEP schedules for healthy individuals of all ages are recommended:
  - Two ID doses on days 0 and 7
  - One IM dose on days 0 and 7
2. Although a 1-day course of PrEP likely confers some protection, it is not recommended at this stage. However, if it is impossible to complete the entire course of PrEP, those who have received PrEP only on day 0 should receive a second dose as soon as possible. In the event of a potential rabies exposure prior to the second dose, full PEP should be given.
3. Individuals who are immunocompromised should receive a 3-visit course of PrEP (days 0, 7 and 21 to 28) either ID (2-site) or IM, as these individuals may have a decreased immune response to vaccine. Moreover, a 2-visit course of PrEP (days 0, 7) in immunocompromised individuals has not been studied. Where possible, serology can be used to assess seroconversion after two doses, and additional doses can be administered if needed.
4. There is limited evidence on the effect of chloroquine or other related drugs on immune response to rabies vaccine if administered ID. Individuals under treatment with chloroquine or related drugs should receive PrEP or PEP as indicated for the general population. For well-planned travel, PrEP should be given before antimalarial treatment is started.

## 8.2. PEP

### Q5 (cost-effectiveness ID vs IM)

1. More efforts are needed to reach the rural and marginalized populations most often affected by rabies. We recommend innovation to improve access, affordability of PEP, awareness and programmatic delivery.
2. ID administration, even in low-throughput clinics, is always more cost-effective

### Q6 & 7 (decrease in duration/number of doses)

1. WHO-approved and shortened PEP regimens which are described in [Table 5](#). Countries considering new or alternate regimens should take into account (a) feasibility (i.e. cost and number of doses), (b) immunogenicity and (c) clinical protection of the schedule.

**Table 5: Overview existing approved and investigational PEP regimens and criteria for evaluation of non-inferiority to WHO recommended regimens**

*Assumptions patient throughput per month: Small clinic < 10 patients; large clinic ≥ 10 patients*

*Legend: ✓ Criteria fulfilled; ○ partly fulfilled;*

*REF: Cost-effectiveness baseline reference = updated Thai Red Cross regimen (TRC)*

PEP regimens	Characteristics	Key evaluation criteria						
		Number of injection sites per visit on days 0, 3, 7, 14, 21 to 28	Immuno-genicity data	Clinical outcome data	Cost-effectiveness		Feasibility	Acceptability
					small clinic	large clinic		
<b>WHO recommended intradermal regimen</b>								
IPC regimen, 1 week	2-2-2-0-0	✓	✓	>	>	✓	✓	



WHO recommended intramuscular regimens							
Essen regimen, 14 to 28 days	1-1-1-1-0	✓	✓	≤	<	✓	✓
Zagreb regimen, 21 days	2-0-1-0-1	✓	✓	≤	<	✓	✓
Alternate immunogenic intradermal regimens							
Updated Thai Red Cross regimen, 1 month	2-2-2-0-2	✓	✓	REF	REF	✓	✓
Simplified 4-site regimen, 1 month	4-0-2-0-1	✓	○	>	>	○	✓
4-site regimen, 1-week	4-4-4-0-0	✓	○	=	<	○	○

#### Q8 (PEP for specific risk groups)

1. Rabies vaccines and RIG are safe and efficacious to use in pregnant women and should be administered using any of the recommended regimens.
2. In individuals who are immunocompromised (e.g. unmanaged HIV/AIDS), a full course of PEP with RIG is recommended in both category II and III exposures. Immunocompromised individuals who have received a complete course of PrEP should still be treated with a full course of PEP including RIG if exposed. Where available, serology and/or consultation with a specialist are advised.
3. Exposures to bats (e.g. single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva from licks, nibbling of uncovered skin, and minor scratches or abrasions without bleeding) should be treated as category III exposures that require full PEP including RIG. For exposures in which there is no wound, RIG should be injected as close to the site of exposure as anatomically feasible.

#### Q9 (change in route of administration)

1. Changes in the CCEEV and/or the route of administration during the same PEP course is acceptable in unavoidable circumstances to promote completion of the lifesaving PEP regimen. There is no evidence that restarting PEP is necessary after switching product or administration route. Additionally, the schedule for the new route should be adopted after switching route.

### 8.3. RIG

#### Q10 (RIG administration)

1. The maximum RIG dose is calculated by weight, for hRIG at 20 IU/kg and for purified eRIG F(ab')<sub>2</sub> products at 40 IU/kg body weight.
2. After calculating the RIG dose, as much RIG as anatomically possible (e.g. to avoid compartment syndrome) should be administered carefully and thoroughly into and around the wound. The maximum benefits of RIG are gained when administered directly into the wound. When the calculated volume is too small to fully infiltrate the wound (e.g. in large or multiple wounds), the RIG may be diluted with sterile normal saline to a volume sufficient for complete infiltration of all wounds.
3. It is current practice that, after completed infiltration of the wounds, the remaining RIG (if any) be administered IM at a site distant from the wound. However, updated evidence suggests that this may be of limited benefit. In settings where RIG is of low availability, the relative benefits of IM RIG injection distant to the wound should be considered against the possibility of providing the remaining RIG for local injection to other patients, to confer maximum public health benefit. This requires aseptic retention of the RIG (e.g. in smaller, individual syringes).

#### Q 11&12 (safety and efficacy eRIG)

1. Equine immunoglobulins (eRIG) are clinically equivalent to human rabies immunoglobulins (hRIG) and are considered safe and efficacious life- and cost-saving biologics. Both eRIG and hRIG neutralize the virus at the wound site within a few hours. For all RIG products meeting quality standards, the safety and efficacy profiles result in no product preference between eRIG and hRIG.

2. Considering the increase in product purity and safety, skin testing before eRIG administration is unnecessary. Thus, skin testing is not recommended and should be abandoned.

Severe adverse events or perceived lower efficacy of RIG (e.g. batches of insufficient potency or lower purification degree) should be monitored, recorded and reported, so that biological producers receive immediate feedback and can respond accordingly. A classification of adverse events is available in [Table 6](#). Post-marketing surveillance is recommended.

#### Q13 (monoclonal antibodies)

1. Monoclonal antibodies (mAbs) have demonstrated safety and efficacy in clinical trials when used as a component of PEP, and offer a potential solution to the limited availability of RIG.
2. Cocktails using two or more mAbs working synergistically show higher efficacy and increased breadth of neutralization. Ideally, the production of mAbs for supplementation of RIG should aim to be affordable and include two or more mAbs with nonoverlapping epitopes. We recommend that a registry be maintained to monitor clinical use and outcomes of mAb products.

#### Q 14 (prioritization of RIG)

1. Even if RIG is not available or affordable, prompt local treatment of all bite wounds or scratches, and for category II and III exposures a complete course of rabies vaccine is indicated.
2. For patients who can reliably document previous post exposure prophylaxis that is equivalent to a PrEP regimen, RIG is not indicated.
3. In cases of shortage or unaffordability, the following groups should be prioritized for RIG allocation:
  - Multiple bites
  - Deep wounds
  - Highly innervated parts of the body, as head, neck, hands, genitals
  - Immunocompromised patients
  - History of biting animal indicative of confirmed or probable\* rabies
  - A bite or scratch or exposure of a mucous membrane by a bat can be ascertained

\* *An animal rabies case is defined as an animal that presents with any of the following signs:*

- *Hypersalivation*
- *Paralysis*
- *Lethargy*
- *Unprovoked abnormal aggression (biting 2 or more people or animals, and/or inanimate objects)*
- *Abnormal vocalization*
- *Diurnal activity of nocturnal species*

*Cases of animal rabies are classified as follows:*

- **suspected:** *a case that is compatible with a clinical case definition of animal rabies*
- **probable:** *a suspected case plus a reliable history of contact with a suspected, probable, or confirmed rabid animal, and/or a suspect animal that is killed, died, or disappears within 4-5 days of observing illness*
- **confirmed:** *a suspected or probable case that is laboratory-confirmed\**

## 9. RESEARCH PRIORITIES

- 1) Efficacy and clinical outcomes associated with 2-visit ID PEP schedule (Day 0 and 7)
- 2) Efficacy and clinical outcomes associated with 1-week IM PEP schedule (day 0, 3 and 7)
- 3) Efficacy of PEP schedule after incomplete PrEP (e.g. emergency 1-day PrEP)
- 4) Efficacy of subcutaneous rabies vaccine administration
- 5) Immunogenicity and clinical outcomes in immunocompromised individuals to better understand factors for seroconversion
- 6) IV administration of RIG

- 7) Pharmacovigilance and reporting of any breakthrough events if a person has received PrEP with concurrent chloroquine treatment
- 8) Potential to store individually labelled vials for single-patient use to minimise wastage, in line with WHO's policy on the use of opened multi-dose vaccine vials<sup>3</sup>.
- 9) Effect of analgesics on PEP and RIG if used as a component of wound care
- 10) Pharmacovigilance for mAbs including development of a register to monitor mAb use and outcomes
- 11) Development of a policy paper or a protocol describing data and sample size needed (supported by statistical calculations) to recommend a new PEP regimen.
- 12) New vaccines: Programme-directed research, innovation and development in close collaboration with manufacturers is needed to optimize cost-effectiveness, delivery at community level, easier storage, thermostability, longer shelf-life and still retain vaccine safety and efficacy, e.g.
  - a. Can the vaccine induce protective antibody titres after one dose?
  - b. How rapidly do antibody titres develop?
  - c. Does the vaccine induce memory B cell responses that can rapidly be recalled after exposure?
  - d. Will the vaccine be cost-effective?
  - e. Will the vaccine be stable at ambient temperature?
  - f. Can the vaccine be given orally?

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<sup>3</sup> [http://www.who.int/immunization/documents/general/WHO\\_IVB\\_14.07/en/](http://www.who.int/immunization/documents/general/WHO_IVB_14.07/en/)

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## 12. LIST OF APPENDICES

**Appendix I:** SAGE WG on rabies (terms of reference, members, declaration of interest)

**Appendix II:** Evidence profiles Questions 1-14 including GRADE tables and evidence review on potency of rabies vaccine, if fractionated

**Appendix III:** Evidence to recommendation tables Questions 3, 4, 6, 7, 10, 11, 12, 13, 14

## Executive Summary

### SAGE October 2017, Pneumococcal Conjugate Vaccine Session

#### 1.0 Introduction

Currently, WHO has recommended the use of either a 10-valent or 13-valent pneumococcal conjugate vaccine (PCV10 and PCV13, respectively), for all infants worldwide. For routine immunization, WHO has recommended that PCV can be administered using either a 2p+1 or 3p+0 schedule, though 3p+1 schedules are also used in some countries[1]. A total of 141 countries have introduced PCV into their national immunization program, and 7 out of the 10 countries with the highest pneumococcal disease burden have recently introduced the vaccine[2].

Since the introduction of the first PCV (PCV7) in 2000, global reductions in pneumococcal disease burden in children under 5 years of age have been observed. The number of deaths attributable to pneumococcal disease has been halved since 2000 among HIV negative children under 5, from approximately 600,000 to 294,000 deaths in 2015. It is estimated that nearly 200,000 deaths have been averted since 2000 specifically because of PCV use[3].

Despite these demonstrated reductions, pneumococcal disease burden remains high, particularly in lower income regions. Pneumonia, from all causes, accounts for approximately 16% of childhood deaths in low and middle income countries (LMICs), compared to 5% in high income countries; pneumococcus is a leading cause of these pneumonia deaths[4]. Furthermore, the substantial costs of PCV (particularly for middle or lower middle income countries not supported by Gavi) have led to gaps in the introduction and coverage of the vaccines due to concerns about the sustainability of PCV immunization programs.

As the availability of PCV impact data by schedule and product continues to accrue, the review of such evidence is necessary to facilitate countries in making decisions on which product and schedule to use, as well as whether to conduct catch up immunization programs. The Strategic Advisory Group of Experts (SAGE) on Immunizations PCV Working Group (WG) assessed results from the Pneumococcal Conjugate Vaccine Review of Impact Evidence (PRIME) Systematic Review, modelled evidence on the impact of catch up immunization, and additional ad hoc data to update existing recommendations on

three key PCV issues: **dosing schedule, product choice, and catch up immunization**. The discussions held by the WG were framed around the following three questions:

- **Question 1: Dosing Schedule**

*How does PCV administered to healthy children in a 2p+1 schedule compare with the vaccine administered in a 3p+0 schedule, with respect to immune response in vaccinated children and impact on clinical outcomes (IPD, pneumonia, and mortality), and nasopharyngeal carriage in the vaccinated children as well as unvaccinated age groups through indirect protection?*

- **Question 2: Product Choice**

*Is the impact or effectiveness of PCV10 and PCV13 (using either WHO recommended dosing schedules) different, based on data reporting immune response following vaccination, and impact on NP Carriage and clinical outcomes (IPD, pneumonia and mortality) in vaccinated children as well as unvaccinated age groups through indirect protection?*

- **Question 3: Catch Up Vaccination**

*What additional value does catch-up vaccination with 1 or 2 doses of PCV in vaccine-naïve healthy children offer as compared with vaccination of only age eligible children (as per the vaccination schedule in the country) in relation to the overall impact on pneumococcal disease?*

The following sections of this document will provide an overview of available evidence reviewed by the WG, as well as proposed PCV policy recommendations and suggested research priorities.

## 2.0 Available Evidence Reviewed by the PCV SAGE WG

Section 2.0 briefly summarizes the key sources of primary and secondary data that served as the evidence base for the WG to revise recommendations.

## 2.1 The PRIME Systematic Review: Objectives, Approach, and General Conclusions

PRIME was a systematic review assessing primary evidence from literature assessing impact and effectiveness of each PCV dosing schedule and product. Primary evidence of catch up immunization impact was limited but assessed where available. A full report of the results from this extensive review can be found on the WHO SAGE website.

### 2.1.1 Context and Purpose of PRIME

A 2010 systematic review, referred to as the PCV Dosing Landscape Study, informed the scientific community and SAGE on PCV schedule(s) with a focus on the differences in immunogenicity and colonization/disease impact between 3- and 4-dose schedules using the 7-valent PCV (PCV7) product[5]. The available data were predominantly from high-income countries. The PCV Dosing Landscape Study contributed to the SAGE review to recommend the use of either a series of 3 primary doses without a booster or 2 primary doses with a booster given at 9 months of age or later.

A substantial number of immunogenicity and post-introduction disease and colonization impact assessments have become available since 2010, particularly from low-and-middle-income countries (LMICs) which are known to have pneumococcal epidemiologic characteristics that differ from those in higher income settings. Since 2010 two expanded serotype products, PCV10 and PCV13, have both been available, and PCV7 was removed from immunization programs in that year. The majority of the recent PCV impact data are from the use of these two WHO prequalified products, and these data have yet to be summarized for decision-making on the optimal use of PCV globally. Both the currently licensed PCV10 and PCV13 products contain antigens from serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. PCV13 also contains antigens from serotypes 3, 6A and 19A.

This update to the previous review provides further evidence to the scientific community and policy makers regarding which PCV schedule(s) and product(s) are optimal, considering both the direct and indirect effects of the vaccines.

### 2.1.2 PRIME Methods and Data Analysis:

A systematic literature review of 14 databases was conducted to include relevant data published in English from January 1, 2010-December 31, 2016, with ad-hoc additions through June 2017. All relevant citations (evaluating PCV10 and/or PCV13) included in the PCV Dosing Landscape Study

systematic review (1994-2010) were also brought into this analysis and summary document [1]. In addition, relevant unpublished data were considered.

A set of core exclusion criteria were established for all outcomes in order to ensure that effectiveness and impact estimates were comparable across studies and technically relevant to address the proposed research questions on optimal use of PCV globally. A total of 207 studies were analyzed for the final report.

*Types of Studies:*

- Included: Randomized control trials (RCTs), non-randomized trials, and observational studies reporting pre (baseline) and post vaccine introduction incidence rates for disease outcomes or prevalence for carriage
- Excluded: Incidence data from only the PCV post-introduction era, and case-series data for disease outcomes (pre-post or post- only)

*Outcomes:*

- Direct and indirect impact on invasive pneumococcal disease (IPD), pneumonia syndrome, pneumococcal nasopharyngeal (NP) carriage, as well as pneumococcal serotype specific immunogenicity measured by antibody concentrations (IgG).
- Outcomes reporting serotype specific data (IPD, immunogenicity, and NP carriage) were prioritized for review from the WG.

*Products:*

- PCV13 & PCV10

*Schedules:*

- 3+0 and 2+1 dosing schedules (2+0 and 3+1 schedule studies were included where technically relevant)

Descriptive analyses reveal the amount and variability of the data by product, schedule and outcome evaluated. Meta-analyses were done only where appropriate (immunogenicity and NP carriage), and not for all outcomes of interests. A narrative synthesis is based on the information summarized in tables with the characteristics and findings of the included studies: country, year of publication, number of participants, age range, name of vaccine, immunization schedule, comparator, study design, outcomes, magnitude of effect, and confidence interval. Additional details regarding PRIME methodology can be found on the WHO SAGE website, in the full PRIME report of results.

### 2.1.3 PRIME Findings

A more detailed summary of PRIME results can be found in subsequent sections of this Executive Summary as well as in the full PRIME report available on the WHO SAGE website. In short, findings show that both products and both 3-dose schedules are immunogenic and highly effective against disease by vaccine-serotypes as a group, in the respective vaccines.

## 2.2 Modelled Data Assessing Catch Up Vaccination Impact

Empiric evidence reporting the impact of catch up PCV vaccination at the time of introduction among children above the birth cohort is limited. To further inform the WG of how to further optimize and update the current WHO recommendations on catch up immunization for PCV, modelled evidence on the impact of catch up immunization in Kilifi, Kenya[6] and Viet Nam (Flasche, personal communication) were reviewed.

### 2.2.1 About the Model

The model assessed data only from children under 5 years of age, and only from the two settings noted above (Kenya and Viet Nam). It was assumed that catch-up given as 3 doses if started in infancy and 1 dose if started at 12m or older would confer similar protection against carriage and disease as routine use in an EPI schedule. In part, this was suggested by fitting to available data from Kilifi. Additional details about modelling data can also be found in the *WHO Technical Expert Consultation Report on Optimization of PCV Impact: Review of Evidence and Programmatic Considerations to Inform Policy*, which is a meeting report found in the SAGE October 2017 Yellow Book.

### 2.2.2 Summary of Modelled Results

Catch-up campaigns at PCV introduction accelerate direct and indirect protection against pneumococcal disease. The model predicts that in the Kilifi, Kenya setting, PCV doses given as part of a catch-up for either children aged <1 year (3 dose), <2 years (3 dose in <1y and 1 dose after) or <5 years (3 dose in <1y and 1 dose after) prevent more IPD cases per PCV dose if compared to routine PCV use. Therefore, catch-up campaigns were highly efficient uses of PCV. Furthermore, catch up immunization accelerated the rate of PCV impact by up to 3 years. Although these data assessed impact only among children under five years old, it is possible that settings of high disease burden or carriage in older children should have larger targeted age ranges. These results were robust to a range of alternative assumptions on vaccine efficacy (VE) of the routine use, VE of the catch-up doses, and the duration of protection. Additional data using a different but similar modelling approach found similar conclusions when assessing impact in Nha Trang, Viet Nam.

If the planning of a catch-up campaign introduces substantial delays in vaccine implementation, the campaign will become less efficient overall. The efficiency of PCV use for catch-up campaigns also hinges on:

**A)** The disease burden in the targeted age group (additional benefit through direct protection) and;

**B)** The contribution of these older age groups to pneumococcal transmission to others in the community, including younger children (additional benefit through indirect protection).

Catch-up campaigns may be most efficient in low income settings where a substantial disease burden and high carriage rates extend to older children.

## 3.0 SAGE PCV WG Considerations and Proposed Recommendations

Section 3.0 summarizes overall considerations and conclusions the WG derived from the available evidence described in Section 2.0, and states the proposed recommendations.

### 3.1 Background and Context

Both PCV10 and PCV13 have been shown to be safe, effective, and to demonstrate both direct and indirect effects against pneumococcal disease, when used in a three-dose schedule, either with 3 primary doses without a booster dose (3p+0) or 2 primary doses with a booster dose (2p+1). There is

substantial evidence on the disease impact of each schedule and each product in routine use among children, including head to head studies of immunogenicity and nasopharyngeal colonization outcomes; however, there are no head-to-head comparative studies of product or schedule on disease outcomes.

In the absence of consistent evidence to support a preference for a product or schedule, the country level choice will depend on factors such as local or regional programmatic considerations, disease epidemiology, serotype prevalence, cost-effectiveness, or other issues. The measured impact from single schedule or single product studies provides evidence for product and schedule performance; however, comparisons of impact between products or schedules from these single arm studies are subject to other factors that can influence the effect magnitude. Therefore, differences in observed impact on disease outcomes across these studies should not be used alone to infer conclusions about schedule or product differences.

The following recommendations relate to three priority topics that were considered by the WG, namely: (1) dosing schedule; (2) product choice; and (3) catch up vaccination. For each topic, preceding the recommendations, the WG summarizes evidence that was considered on immunogenicity, NP colonization and disease outcome studies, including serotype-specific outcomes for each. Immunogenicity was assessed by the fraction of immunized subjects achieving serotype specific antibody concentrations above the correlate of protection and by the geometric mean concentration achieved. Data from studies of 3p+1 schedules were reviewed non-systematically for serotype-specific outcomes where there were insufficient data from studies of 2p+1 and 3p+0 schedules. Due to limitations in the data reporting PCV impact on pneumonia and mortality, the WG primarily used serotype specific IPD data to develop the proposed recommendations.

### 3.2 Schedule Choice

Deliberations assessing the evidence to determine if there is a differential impact by schedule were framed around the following question:

***How does PCV administered to healthy children in a 2p+1 schedule compare with the vaccine administered in a 3p+0 schedule, with respect to immune response in vaccinated children and impact on clinical outcomes (IPD, pneumonia, and mortality), and nasopharyngeal carriage in the vaccinated children as well as unvaccinated age groups through indirect protection?***



### 3.2.1 Schedule Choice Considerations

#### Immunogenicity

There were two outcomes used to assess immunogenicity: the geometric mean concentration of antibodies (GMCs), and the proportion of participants who had an antibody response above the correlate of protection (percentage of responders).

Head to head studies demonstrate that, after the primary series, a two-dose primary schedule has lower GMCs but a similar percentage of responders compared with a three-dose primary schedule for most serotypes. For ST6A and ST6B, a three-dose primary schedule had both higher GMCs and higher percentage of responders compared to a two-dose primary schedule.

When assessing immunogenicity after the third dose of each schedule (post-booster for 2p+1 and post primary for 3p+0), a 2p+1 schedule elicited higher GMCs but a similar percentage of responders compared with a 3p+0 schedule for most serotypes, including ST6A. For ST6B, both the GMCs and percent responders indicated an advantage from a 2p+1 schedule compared to a 3p+0 schedule, post third dose.

Comparison of data across studies showed that the percentage of responders was lower in African and Asian studies than in studies from other global regions for PCV13 but not for PCV10. However, differences in immunogenicity between the two vaccines and between geographic regions observed across non-head-to-head studies may be explained by confounding factors. For example, studies evaluating a 2p+1 schedule tended to be from high income countries, often using PCV13 and with concomitant use of acellular pertussis (aP) vaccine, while those evaluating a 3p+0 schedule and PCV10 were frequently conducted in lower income countries in Africa and Asia, with the concomitant use of whole cell pertussis (wP) vaccine. Hence, differences in immunogenicity between the two vaccines and between the different regions may be explained by confounding factors such as serotype specific carriage; study population disease rates; age at vaccination; interval between doses; the adjuvant effect of whole cell pertussis vaccine; maternal pneumococcal antibodies; and maternal vaccination with diphtheria or tetanus toxoid containing vaccines.

In general, antibody responses to most serotypes increase with age at first dose, producing differences in antibody concentrations and proportions above the protective efficacy threshold both at

the post-primary and at the post-dose 3 time points. It is still uncertain the degree to which observed differences in either GMC or percent responders are clinically relevant, if at all.

### Clinical Burden of Disease

#### IPD

No head to head studies comparing the impact or effectiveness of the two schedules were available on IPD outcomes; therefore, quantitative comparisons in disease reduction across studies of different schedules should not be made. Evidence from ecological and case control studies indicates that both schedules reduce the burden of IPD caused by vaccine-serotypes as a whole in respective vaccines, both among vaccinated and unvaccinated individuals in the population.

Evidence from studies comparing different schedules across settings is confounded by many factors including use of CV7 and differences in baseline IPD incidence. Settings with outcome data on the 2p+1 schedule tend to be high income countries, using PCV13, with prior PCV7 use, and with low IPD incidence. Conversely, settings evaluating IPD impact of a 3p+0 schedule tend to be low income countries using PCV10 without prior PCV7 use, and with high IPD incidence.

#### Pneumonia Syndrome

Evidence of PCV impact by schedule on syndromic pneumonia was available but was not used by the WG to develop the proposed recommendations because of confounding in the pneumonia data and the WG's decision to prioritize review of serotype specific data. The PRIME systematic review found that the amount of evidence for each schedule varied by clinical outcome (chest x-ray confirmed pneumonia, empyema, pneumococcal pneumonia), with 2p+1 impact data more available than 3p+0 data. There is no evidence available supporting an advantage of one schedule compared to the other schedule for either vaccinated and unvaccinated age groups.

#### Mortality

Evidence of PCV impact by schedule on mortality was available but was not used by the WG to develop the proposed recommendations because of confounding in the mortality data and the WG's decision to prioritize review of serotype specific data. The PRIME systematic review found that data assessing impact of schedule on mortality (mortality rates and case fatality rates) are limited and that comparisons of PCV schedule impact on mortality could not be made. Thus no conclusions could be drawn about differential impact by schedule.

## NP Carriage

Evidence from two head to head studies assessed differential effectiveness of the two schedules. In those studies, both schedules were found to be effective in reducing overall, product specific VT NP carriage. Neither of the studies detected a significant difference in the effectiveness one schedule over another against overall VT carriage.

Evidence on differential impact of schedules on NP carriage from cross study comparisons of different schedules, conducted in various settings was inconclusive as it is confounded by many factors including use of PCV7 prior to PCV10/13 introduction, the PCV product in use, and differences in baseline carriage prevalence. As noted previously, countries evaluating 2p+1 schedules tended to be higher income, use PCV13, and have prior PCV7 use; countries using 3p+0 schedules tended to be lower income, and use PCV10 *denovo*.

### 3.2.2 Schedule Choice Recommendations

1. For PCV administration to infants, at least 3 doses of vaccine, administered **either** as 2 primary doses plus booster (2p+1) or 3 primary doses without a booster (3p+0), are recommended.
  - For countries that have yet to introduce PCV, decisions regarding the choice of schedule should take into consideration operational and programmatic issues, including timeliness of vaccination, the coverage expected to be achieved at the third dose, and pneumococcal disease age distribution patterns, if known. Low population vaccine coverage at visits occurring between 9-12 months of age or later may warrant the use of a 3p+0 schedule.
  - Once a program has been initiated, schedule switching is not necessary unless one or more factors that led to the original choice of schedule changes substantially.
2. A dosing interval of 8 weeks between the first two doses of a 2p+1 schedule and a dosing interval of at least 4 weeks for a 3p+0 schedule is recommended. However, the 8-week interval recommended for the 2p+1 schedules may be shortened if there is compelling reason to do so, such as timeliness in receipt of the second dose and/or higher coverage that may be achieved with the schedule. The dosing interval between primary doses within each schedule should not be shorter than 4 weeks.

3. The timing of the booster dose should be selected to maximize coverage. The selected age for administration of the booster dose in most programs is at 9, 12, 15 or 18 months, depending on operational and programmatic factors, including the timing of vaccination contacts in the national immunization schedule for other vaccines. There is insufficient evidence to inform optimal timing of the booster dose.

### 3.3 Product Choice

Deliberations assessing whether there was evidence indicating differential impact by PCV product were framed around the following question:

***Is the impact or effectiveness of PCV10 and PCV13 (using either WHO recommended dosing schedules) different, based on data reporting immune response following vaccination, and impact on NP Carriage and clinical outcomes (IPD, pneumonia and mortality) in vaccinated children as well as unvaccinated age groups through indirect protection?***

Data are summarized by serotype for product choice.

#### 3.3.1 Product Choice Considerations

##### Immunogenicity

*Evidence is from both single product and head-to-head studies of the two products.*

##### VT Serotypes

Both PCV10 and PCV13 induce antibodies against the serotypes common across the two vaccines. Although there are small differences in antibody response between the two products for these serotypes, in general, PCV10 and PCV13 have comparable, albeit not identical, immunogenicity. The clinical implications, if any, of these relatively small differences in immunogenicity for the common serotypes have not been established.

### Serotype 3

PCV13 induced an immune response to ST3 (documented by serotype specific IgG GMCs and the proportion of vaccine recipients with a concentration above the correlate of efficacy). PCV10 contains neither ST3 nor any cross-reactive serotypes, and therefore is not expected to induce an immune response to this serotype. Consequently, PCV10 studies, in general, do not measure immunogenicity against this serotype.

### Serotype 6A

Both PCV10 and PCV13 induce an antibody response to ST6A, a serotype included in PCV13 but not in PCV10. Evidence indicates, however, that PCV13 induces higher ST6A GMCs and percentage of responders than PCV10. The clinical significance of these immunogenicity differences cannot be inferred based on the antibody levels alone.

### Serotype 6C

ST6C immunogenicity data are rarely reported and thus could not be systematically assessed.

### Serotype 19A

Both PCV10 and PCV13 induce an antibody response against ST19A; however, evidence indicates that PCV13 induces higher ST19A GMCs and percentage of responders than PCV10. The clinical significance of these differences in immunogenicity cannot be inferred based on the antibody levels alone.

## Clinical Burden of Disease

### IPD

*There were no head to head studies comparing the impact or effectiveness of the two products on IPD outcomes. Only single product studies were assessed.*

### VT Serotypes

Available evidence indicates both products are effective in reducing overall vaccine type IPD caused by serotypes within each vaccine as a whole among both vaccinated individuals and those who remain unvaccinated in the population. Although PCV13 contains three additional serotypes, there is currently insufficient evidence to determine whether there is any differential impact on overall IPD burden (vaccine and non-vaccine type disease combined) between the two products.

### Serotype 3 IPD

As expected, PCV10 use did not result in a reduction in ST3 IPD in vaccine-eligible or non-eligible age groups, because the vaccine does not contain ST3. Evidence for direct or indirect reduction in ST3 IPD following PCV13 was inconclusive with the majority of studies showing impact on type 3 IPD in neither vaccine eligible cohorts nor in unvaccinated age groups.

### Serotype 6A IPD

Data on PCV10 impact on ST6A IPD are limited but generally supportive of a direct effect. Data assessing PCV13 impact on ST6A IPD were predominantly in settings of prior PCV7 use, with very low levels of residual 6A IPD. PCV13 showed a reduction in the residual low burden of ST 6A IPD that remained after the implementation of PCV7 in both vaccine eligible and non-eligible cohorts.

### Serotype 19A IPD

Case-control effectiveness studies of PCV10 against ST19A IPD indicate some protective effect in vaccine eligible age groups, but not all reached statistical significance; however, studies evaluating population-level impact were less conclusive. Among vaccine non-eligible cohorts, evidence from PCV10-using populations shows an increase or no change in ST19A IPD rates. Effectiveness and impact against ST19A IPD in vaccinated and unvaccinated cohort were both demonstrated for PCV13.

### Serotype 6C IPD

There are very few data on PCV10 effects against ST6C IPD. Some studies, though not all, showed a significant impact of PCV13 on ST6C IPD.

### Pneumonia Syndrome

Evidence of PCV impact by product on syndromic pneumonia was available but was not used by the WG to develop the proposed recommendations because of confounding in the pneumonia data and the WG's decision to prioritize review of serotype specific data. The PRIME systematic review of pneumonia evidence reviewed PCV impact data by product on syndromic pneumonia (including chest x-ray confirmed pneumonia, empyema, pneumococcal pneumonia). PRIME found these data were subject to confounding, however, evidence demonstrate impact from both products, both on directly vaccinated populations and unvaccinated age groups. There are currently no data supporting differential impact on overall pneumonia between the two products

### Mortality

Evidence of PCV impact by product on mortality was available but was not used by the WG to develop the proposed recommendations because of confounding in the mortality data and the WG's decision to prioritize review of serotype specific data. The PRIME systematic review found that comparisons of PCV product impact on mortality could not be made, and thus no conclusions could be drawn about differential impact by product.

### NP Carriage

*Limited head to head evidence was available to compare differential impact or effectiveness between PCV10 and PCV13*

### VT Serotypes

Both products were found to be effective and have impact on carriage of serotypes included in the respective vaccines as a whole; however, quantitative comparisons across studies of individual products were difficult because of substantial confounding by schedule, local epidemiology and prior PCV7 use. PCV10 was found to decrease overall VT carriage among unimmunized populations. Data reporting on indirect effects in populations that have been using PCV13 for at least three years are limited; however, recent data from the UK indicate PCV13 also demonstrates indirect effects against overall VT carriage (Miller et al, personal communication), in line with observed herd effects in unvaccinated age groups. NP carriage with vaccine serotypes is reduced by both PCV products but non-vaccine type replacement is well described such that overall pneumococcal carriage can remain unchanged. It is currently unknown whether the net effect of VT reductions and replacement with NVTs in carriage and disease would direct choice of one product over another and further investigation is needed.

### Serotype 3

No significant direct or indirect effects were found for PCV10 on ST3 carriage, as expected. No conclusive direct effect of PCV13 on ST3 NP carriage was found, as results were mixed. No data were available assessing indirect effects of PCV13 on ST3 NP carriage.

### Serotype 6A

Direct effects on ST 6A carriage, for both products, were observed but there was insufficient evidence to conclude whether the magnitude of impact differed between products. Possible indirect effects against ST6A carriage have been demonstrated for PCV10 in studies where there was no prior use of PCV7. No evidence on indirect effects is available for PCV13 because carriage had already been substantially reduced due to prior PCV7 use where this was studied.

#### Serotype 19A

PCV10 use was associated with statistically significant increases in ST19A carriage in some studies and non-significant increases or reductions in ST19A carriage in other studies with low pre-study carriage; statistically significant reductions in 19A carriage were observed from PCV10 in settings of high baseline carriage, though non-vaccine related reduction in 19A carriage, i.e. natural temporal variation, cannot be excluded. Evidence on indirect effects of PCV10 suggests a non-significant increase in ST19A carriage in settings where the vaccine is used.

PCV13 studies demonstrated more consistent reductions in ST19A carriage in children age-eligible for vaccination in routine use settings. Analyses of PCV13 indirect effects are not available.

#### Serotype 6C

No clear conclusion can be drawn as availability of results for impact of vaccination on ST6C colonization were limited for both products and generally underpowered. Only one PCV13 study had sufficient power and it showed substantial reduction.

### *3.3.2 Product Choice Recommendations*

1. Both vaccines have impact against overall vaccine-type disease and carriage. PCV13 may have additional benefit in settings where disease attributable to ST19A or ST6C constitutes a significant public health problem; however, there is at present no supportive evidence of different net impact on overall disease burden between the two products.
2. The country-level product choice should consider programmatic characteristics, vaccine supply, vaccine price, local/regional vaccine serotype prevalence, antimicrobial resistance patterns among vaccine serotypes.
3. Given the relative comparability of existing PCV products and programmatic challenges that may be associated with product switching, once a program has been initiated product switching is



not recommended unless one or more factors that led to the original choice of product changes substantially (see Recommendations 1 and 2).

4. Interchangeability between PCV10 and PCV13 has not been studied in the 2 or 3-dose *primary* series; however, limited evidence suggests that products confer comparable immunogenicity for the *booster* dose regardless of which product was used in the primary series. Therefore, when a 2- or 3-dose primary immunization series is initiated with one of these vaccines, ideally the remaining doses needed to complete the primary series should be administered with the same product. If it is not possible to complete the primary series with the same product, the other vaccine should be used, rather than miss a primary or booster dose. There is no evidence to suggest that restarting the vaccination series is necessary if a product switch occurs, therefore restarting the series is not recommended even for the primary series.

### 3.4 Catch Up Vaccination

Deliberations assessing whether there was evidence assessing impact of catch up vaccination were framed around the following question:

***What additional value does catch-up vaccination with 1 or 2 doses of PCV in vaccine-naïve healthy children offer as compared with vaccination of only age eligible children (as per the vaccination schedule in the country) in relation to the overall impact on pneumococcal disease?***

#### 3.4.1 Catch Up Considerations

Evidence regarding the impact of catch up immunization is limited across different age groups; however, the available evidence suggests PCV immunization, at the time of national introduction, for children outside the birth cohort accelerates both direct and indirect protection and thereby hastens the impact of PCV. Modeling of NP carriage and IPD in Kilifi, Kenya demonstrated that at the time of PCV introduction a catch-up campaign in those under 5 years of age can accrue a greater benefit per dose administered than would smaller campaigns in more narrow age strata, or compared with routine infant vaccination alone. Limited evidence exists on the effectiveness of PCV as a means of response to pneumococcal disease outbreaks or to supplement ineffective routine vaccination in humanitarian crises.

Based on available evidence, any catch up vaccination program confers additional direct and indirect benefits compared with routine immunization alone. If logistically feasible, catch-up campaigns

at PCV introduction can enhance the benefit per dose of the PCV program in settings with high VT carriage and disease beyond infancy. After PCV introduction vaccination, PCV catch up campaigns may also be desirable in settings with a weak routine vaccination program or when rapid disease control is sought. Example situations include settings of vaccine serotype disease outbreaks caused by VT pneumococci or humanitarian emergency settings with high risk of pneumococcal disease. Limited evidence is available to determine whether a single dose is sufficient or whether 2 doses are required for catch up vaccination beyond infancy. The benefits of a catch up campaign are lessened if the resources needed for the campaign diverts resources and negatively impacts PCV coverage in the birth cohort, if the resources for the campaign result in delayed introduction of PCV in the birth cohort, or if the epidemiologic setting is one where there is only moderate vaccine serotype carriage and disease in those in the catch up age cohort. The relative benefit of conducting a catch up campaign at the time of introduction also depends on the cost and vaccine supply.

#### *3.4.2 Catch Up Recommendations*

1. Catch-up vaccination as part of PCV introduction will accelerate both direct and indirect protection and therefore accelerate PCV impact on disease, particularly in case of high VT carriage prevalence and disease burden in children aged 1 to 5 years old.
2. Catch-up vaccination with PCV can be done with 1 dose of vaccine for those initiating vaccine at age 24 months and older. For those who are 12-23 months at the time of first vaccination some programs have used 2 PCV doses separated by at least 8 weeks, and others have used 1 dose. For those initiating vaccination at age 6 months or under, a 3 dose regimen should be offered. For infants aged 7-11 months, some programmes have used 2 doses, and others have used 3 doses. If there is limited availability or capacity for catch-up immunization, the youngest children should be prioritized to receive catch-up doses of PCV because of the higher pneumococcal disease risk.
3. Unvaccinated children up to 5 years of age who are at high risk for pneumococcal infection based on a medical condition (e.g. HIV infection, sickle cell disease) should receive at least 2 PCV doses separated by at least 8 weeks to assure immunogenicity.
4. In areas/communities where low vaccination coverage has permitted sustained vaccine serotype pneumococcal transmission (or disease), especially those with coverage below 50%, catch up campaigns (also termed periodic intensification of routine immunization) can be used to reduce the disease burden.

5. Catch-up vaccination to replace missed doses among individual children should be encouraged with particular focus on children at highest risk of pneumococcal disease.
6. In humanitarian or emergency situations, age-appropriate schedules of PCV vaccination should be implemented, certainly for children under 1 year of age, and usually for children up to 5 years of age as indicated by the situation, through the use of the framework for vaccination in humanitarian emergencies. Immunization of children over age 5 may be indicated in certain situations.
7. Vaccination may be considered in response to outbreaks of confirmed VT pneumococcal disease, based on the characteristics of the outbreak, including the outbreak size, duration and age group affected.

### 3.5 Surveillance and Research Recommendations

Based on current evidence and remaining evidence gaps, the WG proposes several recommendations to guide future surveillance and research efforts.

#### 3.5.1 Surveillance Recommendations

1. High quality, long-term, post-introduction, serotype-specific pneumococcal surveillance is needed in a representative number of settings.
2. **Methodology of disease surveillance:** Pneumococcal surveillance can be conducted as population-based or only in sentinel health facilities (which is not population-based). While population-based surveillance is required to document disease impact and serotype replacement, non-denominator based IPD surveillance in sentinel sites provides additional information on the distribution of serotypes in the PCV routine use era and a qualitative measure of PCV impact. Population-based surveillance may not currently be feasible in a sufficient number of representative countries and sites, so high quality sentinel site surveillance can provide useful complementary data. In addition to disease surveillance, periodic carriage surveillance could offer insight on the case-carrier ratio and ongoing circulation of vaccine serotypes. Pneumococcal surveillance does not need to be conducted in every country, but SAGE encourages countries to conduct high-quality surveillance with the ambition for surveillance and laboratory capacity to be strengthened everywhere.
3. **NP colonization surveillance:** Since pneumococcal colonization is a critical driver of population level disease and PCV impact, periodic monitoring of carriage is an important adjunct to disease surveillance. It offers a means to interpret pneumococcal disease and syndromic surveillance

findings, and provides important insights into case-carrier ratios, ongoing circulation of vaccine serotypes, and a means to monitor the PCV program implementation.

4. ***Diseases under surveillance:*** Pneumococcal surveillance can monitor not only IPD, but also other syndromes caused by pneumococcus, such as meningitis, pneumonia, and sepsis. At a minimum, we recommend that meningitis be monitored due to the severe nature of the disease, the need for identification of etiology for clinical management, and the higher yield of pathogens from cerebrospinal fluid, compared with the yield from blood cultures which are usually obtained from children with pneumonia and sepsis.
5. ***Duration of surveillance:*** Surveillance should be sustained indefinitely during the post-introduction period. The minimum duration is 5 years following PCV introduction, as evidenced by the time required for a plateau in IPD serotype replacement and PCV impact on overall IPD as concluded by a previously published global analysis. However, changes in distribution and pneumococcal disease impact are still being seen in many settings up to 17+ years following PCV introduction and use.
6. ***Location of surveillance:*** Surveillance should be conducted in a representative number of settings to monitor changes in disease following the use of different PCV products, in different dosing schedules, and in different geographic and epidemiologic settings with different pneumococcal burden and transmission.
7. WHO should periodically review global pneumococcal surveillance data to identify specific evidence gaps that need to be addressed through additional surveillance or special studies, including periodic cross-sectional studies on NP carriage prevalence.

### *3.5.2 Schedule Choice Research Recommendations*

1. Additional data from head-to-head studies of schedules are needed to address differences in biological outcomes such as NP carriage, immunogenicity, duration of protection, and transmission dynamics, including herd immunity.
2. Coverage achieved by different PCV schedules, including the timeliness of vaccination, and the age of vaccination should be evaluated.
3. Serotype specific quantitative immune correlates of protection against invasive pneumococcal disease should be investigated from different epidemiologic settings. These can be carried out by using data from serotype specific vaccine effectiveness studies, with nested immunogenicity data.

4. Studies to evaluate the serotype specific duration of protection from different schedules are needed, especially to inform modeling efforts on schedule optimization.
5. Modeling studies should be undertaken to systematically evaluate key drivers of the relative benefits of 2p+1 vs 3p+0 schedules. Such drivers may include local epidemiology of carriage and disease, demographic structure, vaccine efficacy, timeliness and booster dose coverage. These models should further help quantifying scenarios under which one schedule can achieve a discernably higher impact than the other.

### *3.5.3 Product Choice Research Recommendations*

1. Field data and modeling are needed to better understand the drivers of, and predictors of pneumococcal serotype replacement in disease. Specifically, potential differences in product-specific serotype replacement need to be characterized to better understand their differential impact on pneumococcal disease.
2. Head to head studies comparing immunological and carriage impact of future and existing PCV products are needed to adequately inform product and schedule choices for maximum control of pneumococcal disease. Assessment of PCV impact on carriage has additional value in predicting herd effects of vaccination and pneumococcal circulation, whereas measuring immunogenicity is important for establishing correlates of protection against IPD and carriage.
3. Studies are needed to understand the effects of maternal antibodies and maternal immunization with vaccines containing diphtheria and/or tetanus toxoid proteins on infant vaccination with PCVs containing pneumococcal polysaccharides conjugated to CRM, diphtheria, or tetanus toxoid proteins. These assessments should also include the effect of maternal vaccination on early infant PCV and diphtheria, tetanus, and pertussis (DTP) immunization in terms of optimizing timing of the first infant dose.
4. Data are needed on PCV product interchangeability to inform the effects of product switching during the primary immunization series (i.e. when programs switch PCV products) and on the use of schedules intentionally using different products to optimize impact.

### *3.5.4 Catch Up Research Recommendations*

1. Further assessment is needed of pneumococcal epidemiology in outbreaks, and outbreak response opportunities with PCV.
  - a. A better understanding of ST1 epidemiology is needed for directing immunization efforts to prevent or control outbreaks of this serotype. Also review of historical data on

pneumococcal outbreaks, particularly of ST 1, may be useful to define outbreak thresholds and age groups for vaccination

2. Further assessment is needed of the benefits or limitations of developing and using PCV products containing single or a limited number of outbreak-associated serotypes as a tool for controlling pneumococcal outbreaks.
3. Studies should be conducted in settings where outbreaks or humanitarian emergencies have recently occurred to evaluate risk of pneumococcal disease, including pneumonia, and assess impact of PCV use in these settings.
4. A systematic analysis of evidence comparing 1-dose versus 2-dose catch-up vaccination at the time of vaccine introduction should be conducted. Data to compare 1-dose vs 2-dose catch-up vaccination at the time of vaccine introduction should be collected for systematic analysis.
5. Additional data are needed, through modeling or impact studies, on the relative benefit and cost of catch-up vaccination at the time of PCV introduction or switch to PCVs containing different serotypes or valencies.

#### 4.0 Concluding Remarks

The review of available PCV evidence and conclusions of the WG highlight the sufficient amount of evidence indicating that both products and schedules have overall benefit, as well as the lack of head to head evidence that would be valuable in determining whether a particular product or schedule has added benefit, particularly for disease outcomes. Furthermore, there are few empiric, primary data available to analyze the effects of catch up vaccination in children above the birth cohort.

The nuances of analyzing pneumococcal epidemiology and the presence of several key confounding factors make assessing PCV impact particularly challenging. As countries continue rapidly introducing these vaccines, and as new conjugate and non-conjugate pneumococcal vaccines continue to advance through the product development pipeline, optimizing research endeavors to better quantify the benefits, and possible limitations, of pneumococcal vaccination is vital to direct program optimization.

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# **WHO Technical Expert Consultation Report on Optimization of PCV Impact: Review of Evidence and Programmatic Considerations to Inform Policy**

Department of Immunizations, Vaccines, and Biologics

WHO HQ Salle C, June 12-13, 2017

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*This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization*

## **Executive Summary**

A Technical Expert Consultation on optimizing pneumococcal conjugate vaccine (PCV) impact was held at World Health Organization (WHO) Headquarters June 12-13, 2017. Since licensure and prequalification in 2000, PCVs have been introduced in 141 countries and 190,000 pneumococcal deaths have been averted from 2000 to 2015. WHO recommends that the two prequalified PCV products, 10-valent (PCV10) and 13-valent (PCV13), should be administered either in a three primary doses (3p+0) or two primary doses with a booster (2p+1) schedule. Catch up vaccination is recommended as a mechanism to accelerate herd protection.

An increasing amount of evidence has accumulated since the last PCV position paper update in 2012, including from low and middle-income countries. The meeting served to review new evidence that could inform the Strategic Advisory Group of Experts Working Group for PCVs (SAGE PCV WG) of possible differences in impact and effectiveness by product and schedule for both routine infant immunization and catch-up immunization. Throughout the meeting, participants identified critical data gaps and developed a prioritized list of future PCV research directions.

Both primary evidence and modeled data were reviewed in the consultation to formulate overarching conclusions, identify data gaps, and prioritize future research questions. The meeting discussed evidence presented from PCV Review of Impact Evidence (PRIME)—an extensive systematic review of PCV impact data which was created in part to serve as an evidence base for SAGE PCV WG. The empiric evidence reviewed on immunogenicity, nasopharyngeal carriage, pneumonia, invasive pneumococcal disease, and mortality is discussed in a separate report available on the WHO SAGE website. The systematic review found a lack of available evidence to conclude a strong preference for either PCV product or schedule due to both



confounding factors across different environments and a distinct lack of head to head studies which directly compared products and/or schedules.

The participants reviewed data and discussed the programmatic implications related to a 3p+0 or 2p+1 schedule or shifting from a 3p+0 to a 2p+1 schedule. The evidence for the added value of introducing catch-up campaigns, including the age groups to be targeted, based on mathematical models, was also discussed. To fully capture the global impact of PCVs, comprehensive modeling work for both schedules and product choices in the future will require empiric evidence from a wider range of geographic regions.

Representatives from high, middle and low-income countries highlighted the drivers of decision making regarding choice of PCV product, dosing schedule, and the use of a catch-up campaign through presentations and a panel discussion. While each country shared unique experiences, common themes that influenced decisions across all settings included the importance of cost-effectiveness, the availability of local impact data, vaccine supply, and cold chain storage capacity.

The conference culminated with individual participants identifying the three highest priority research questions needed to make or affirm policy recommendations. The majority of participants recommended research topics that centered on product choice and schedule. Additionally, the participants consistently cited serotype replacement and serotype distribution as an emerging concern and pressing research gap. The presented evidence and prioritized research recommendations were taken into consideration at the PCV SAGE WG meeting, which occurred directly after the consultation.

## **I. Introduction**

A technical expert consultation on the optimization of pneumococcal conjugate vaccine (PCV) impact was convened on June 12<sup>th</sup> and 13<sup>th</sup> 2017 at the World Health Organization headquarters in Geneva, Switzerland. The objectives of the meeting were to review available evidence regarding PCV impact in routine use settings, provide inputs to inform the subsequent deliberations of the Strategic Advisory Group of Experts Working Group (SAGE WG) for PCV, and to identify and prioritize policy relevant data gaps.

The PRIME systematic review reported evidence of PCV impact by product and dosing schedule. Emerging modelled and primary data from research institutions were also presented. In addition, key programmatic considerations related to each of the PCV products and schedules were highlighted. Country policy makers also discussed the evidence that may be required by national governments to sustain the use of PCVs in their national immunization programs. The consultation culminated in an interactive session that synthesized the evidence presented and prioritized the remaining gaps in policy-relevant evidence to optimize the global impact of PCVs.

## **II. Current PCV Recommendations & Considerations for Policy[1]**

The current PCV recommendations from the 2012 WHO position paper, were summarized, focusing on three specific issues, namely: (1) choice of schedule; (2) choice of product; and (3) catch up vaccination at the time of introduction

The existing recommendations propose a schedule consisting of three primary doses (3p+0) or, as an alternative, two primary doses plus a booster (2p+1) for either PCV product. It is recommended that the country-level choice of product should be based on locally relevant factors such as serotype distribution, vaccine supply, cost effectiveness, and cold chain volume. Given the lack of evidence on the interchangeability between PCV10 and PCV13, WHO recommends completing a dosing schedule with the same PCV product, whenever possible. The position paper encouraged the use of catch-up vaccination as a mechanism to accelerate herd protection through the provision of two catch-up doses at an interval of at least two months to unvaccinated children 12-24 months of age and high-risk children aged 2-5 years.

Since the publication of the 2012 position paper, more data exist from a wider range of epidemiological settings with PCV10 and PCV13 administered in both the 3p+0 and 2p+1 schedule. Data on mortality, morbidity, and nasopharyngeal carriage may enable more informed recommendations on the optimal use of PCV. A recent large-scale outbreak of pneumococcal meningitis in a PCV-using country[2], primarily affecting adolescents and adults, has raised questions about the optimal schedules to promote longer term protection and/or enhance the indirect effects of vaccination.

In addition, there are a number of programmatic issues that need to be considered when updating policy recommendations:

1. Some countries find it difficult to accommodate additional parenteral vaccines into existing schedules because of concerns about multiple injections at the same visit, leading to increased interest in adopting schedules with vaccine doses in the second year of life and scale-up of vaccine delivery programs for that age group.
2. The proportion of total vaccine expenditures spent on PCV in countries (median of 37% of overall national vaccine costs)[3] is a financial challenge, especially for middle-income countries who do not benefit from Gavi support. Many of these countries also have low child mortality, and thus have difficulties justifying the introduction of the vaccine in their national programs on the basis of mortality impact alone.
3. Many countries will be transitioning out of Gavi support over the next 3-5 years and there are concerns about these countries sustaining PCV in their national program, necessitating a robust case be made to national policy-makers.

### **III. Overview of Current Status of PCV Use Globally**

Updated estimates of deaths and cases due to pneumococcus and Hib have been developed, have been endorsed by the WHO Immunization and Vaccines Implementation Research Advisory Committee (IVIR-AC), and are under country consultation[4]. Dr. Kate O'Brien discussed current pneumococcal disease burden and the evolving global use of PCV. Among HIV-negative children, a total of 294,000 (192,000 – 366,000) deaths are estimated to have occurred in 2015, a decrease from approximately 600,000 deaths in 2000. From 2000 to 2015 it was estimated that approximately 190,000 pneumococcal deaths have been averted as a result of PCV use[4,5]. Many GAVI-eligible countries carry the highest pneumococcal disease burden, and most have been able to introduce PCV. However, introduction efforts and coverage levels must accelerate to achieve the Sustainable Development Goal (SDG) target of reducing under-five child mortality rates to at least 25 per 1000 live births[6].

Despite this progress, pneumonia remains a major contributor to child mortality, causing approximately 16% of deaths in low and middle-income countries and around 5% of deaths in high income countries[7]. Of the 10 countries with the highest numbers of pneumococcal deaths, 7 have recently introduced PCV, indicating opportunities for future significant declines in pneumococcal mortality in the upcoming years. In addition to countries with high burden of disease, future PCV work should consider focusing on large countries with moderate mortality rates and small countries with high mortality rates.

PCV product and schedule use appear to vary by geographic region. As of September 2017, 101 countries had adopted the use of PCV13 while 33 countries were using PCV10, and 8 used both[8]. While the majority of non-GAVI countries are following a 2p+1 schedule, most GAVI eligible countries have implemented a 3p+0 schedule

because this aligns with the other primary immunization schedule and is expected to facilitate higher vaccination coverage in countries with weaker health systems. Almost all Gavi-eligible countries in Africa are using a 3p+0 schedule, while currently two countries in the South-East Asia region are using a 2p+1 schedule[8].

#### **IV. Broader Economic Impact of PCV**

Dr. David Bloom presented a keynote address on the potential broader social and economic value of PCV immunization and discussed how the improved health resulting from vaccination can lead to economic growth. There is an increasing need to change the paradigm from looking solely at the effect of income on health to also looking at the effect of health on income. While economists and policy makers in the past have undervalued the economic benefits of vaccinations, data were presented that indicate a 2% improvement in health can be associated with a ten-year gain in life expectancy, which in turn can be associated with a 0.5-1 percentage point of annual per capita income growth.

A challenging research priority will be to ascertain and quantify the broader full benefits of vaccinations—such as productivity gains, decreases in antimicrobial resistance, increases in social equity, and reduction in comorbidities. Due to both the direct and indirect benefits, the economic loss resulting from neglecting to invest in vaccines are substantially higher than the costs of immunization, making it an attractive investment. Dr. Bloom argued that economists should shift away from simple assessments of cost-effectiveness and move towards benefit-cost analyses because the latter can quantify both health and non-health outcomes into more easily understood monetary value.

#### **V. Key drivers of mathematical models & implications for interpreting empiric data**

Much of the observed impact of PCVs has been due to indirect effects in unvaccinated segments of the population, particularly when assessing impact in high income countries. The extent of indirect effects from PCVs relies primarily on two opposing forces: the protection of unvaccinated individuals through reduced transmission of vaccine targeted serotypes (herd protection), and increases in the incidence of pneumococcal disease attributable to non-vaccine serotypes (serotype replacement). Mathematical models for pneumococcal transmission have performed reasonably well in predicting herd protection overall; however, a limited understanding of the key drivers of serotype specific replacement has hindered more precise prediction of the role of individual serotypes after PCV implementation.

Serotype replacement and herd protection are key to the evaluation of product and schedule choice. Critical evidence gaps that limit our understanding of those forces and hence limit the predictive capacity of models include a better understanding of serotype specific replacement in dependence of PCV formulation, the difference in time-profile of waning vaccine protection against pneumococcal carriage after 2p+1 and

3p+0 schedules, and the sources of transmission of vaccine serotype pneumococci to infants.

The potential impact of pneumococcal catch-up campaigns at the time of PCV introduction is largely driven by the time that cohort introduction takes to achieve its full population impact and hence the additional preventable disease burden that a catch-up can target. These are in turn determined by the fraction of vaccine type pneumococcal disease occurring in older children and their contribution to the transmission of pneumococci as well as the vaccine efficacy of PCV if delivered through a campaign to both young and older children and the number of doses required to achieve such protection. Recent modelling indicated that by directly protecting older children and accelerating herd protection in settings with high disease and carriage rates beyond infancy, such as Kilifi, Kenya, catch-up campaigns may prevent more cases of IPD per vaccine dose administered than the routine vaccination programme and hence present a highly efficient option for PCV use[9]. In a setting with moderate carriage prevalence, like Nha Trang, Vietnam, herd-effects establish sooner after the start of routine PCV use[10]. Hence, catch-up campaigns still substantially accelerate direct and indirect effects in lower carriage settings, but may only prevent similar or fewer cases of IPD per dose than the routine vaccination programme.

## **VI. PCV Review of Impact Evidence (PRIME): Systematic Review**

PRIME is an extensive systematic review of PCV effectiveness and impact data led by the Johns Hopkins International Vaccine Access Center, in collaboration with WHO, the Centers for Disease Control and Prevention, the Institute of Child Health, and Agence de Medecine Preventive. It serves as an evidence base for the SAGE WG to inform their recommendations. PRIME assessed evidence on potential differences in impact by PCV product and dosing schedule, the value of catch-up vaccination, and the indirect effects of vaccination through five outcomes: Immunogenicity, Nasopharyngeal Carriage (NP Carriage), Pneumonia, Invasive Pneumococcal Disease (IPD), and Mortality. The PRIME systematic review concluded that there were no definitive preferences for a particular schedule or product. Available data assessing impact of catch up immunization were very limited. The full report of PRIME results, available on the WHO SAGE website, explains findings for each outcome in detail.

Though analyses for each outcome differed and each had a unique set of analytical challenges to consider, there were two key messages in the discussions that followed each presentation:

- 1) The PRIME systematic review highlighted the importance of distinguishing between a lack of available evidence on product or schedule differences and having sufficient evidence indicating that there is no significant difference in impact between products or schedules.

2) For many outcomes, the lack of head to head studies served as a major data limitation that prevented investigators from drawing clear conclusions about differences in impact by schedule or product. Single arm trials and observational studies were confounded by methodologic limitations, making it difficult to draw inferences based on quantitative comparisons across studies.

		Schedule	Product	Catch up
Mortality	Is there sufficient evidence for a conclusion?	No	No	No
	Preference			
	Data Gaps	Head to head studies	Head to head studies	Head to head studies
IPD	Is there sufficient evidence for a conclusion?	Limited evidence available due to confounding from prior PCV use and lack of head to head studies	Limited evidence available due to confounding from prior PCV use and lack of head to head studies	No
	Preference	No preference	PCV13 may have advantage in settings where IPD from 19A and 6C are common; otherwise, no preference	
	Data Gaps	Head to head studies More 3p+0 evidence	Head to head studies More PCV10 evidence	Head to head studies
Pneumonia	Is there sufficient evidence for a conclusion?	Limited evidence available due to confounding from prior PCV use and lack of head to head studies	Limited evidence available due to confounding from prior PCV use and lack of head to head studies	No
	Preference	No preference	No preference	
	Data Gaps	Head to head studies More 3p+0 evidence	Head to head studies More PCV10 studies	Head to head studies
Immunogenicity	Is there sufficient evidence for a conclusion?	Yes	Yes	No
	Preference	Immunogenicity measured post-primary series is higher in a 3p+0 schedule, but booster in 2p+1 exhibits higher immunogenicity	PCV13 elicits higher immune response (proportion of children reaching correlate of protection) for ST3, 6A, 19A. However, clinical	

		compared to post-dose 3 in 3p+0 schedule. Clinical significance of these differences in immunogenicity is uncertain	significance of these differences in immunogenicity is uncertain	
	<b>Data Gaps</b>	Head to head studies	Head to head studies More data on immunogenicity on PCV10 for 3, 6A, 19A	Head to head studies directly comparing immunogenicity after 1 catch up dose to immunogenicity after 2 catch up doses
<b>IP Carriage</b>	<b>Is there sufficient evidence for a conclusion?</b>	Limited evidence available due to confounding by baseline carriage, prior PCV7 use, and lack of sufficiently powered studies	Limited evidence available due to confounding by baseline serotype-specific carriage and a lack of sufficiently statistically powered studies	No
	<b>Preference</b>	No preference	No preference	
	<b>Data Gaps</b>	Head to head studies and studies in settings with comparable baseline carriage rates.	Head to head studies PCV10 studies with prior PCV7 use, PCV13 studies without prior PCV7 use.	Head to head studies

**Figure 1.** PRIME Analysis Summary Table by outcome. Green indicates enough adequate evidence available; yellow indicates limited evidence available; red indicates not enough evidence available to draw conclusion

## VII. Programmatic Considerations

Current PCV coverage levels and the timeliness of achieving the coverage levels with the 3p+0 or 2p+1 schedule were discussed. Additionally, experts from a range of geographic and resource settings shared their country-level experience regarding PCV use and impact, as well as the key programmatic factors that influenced national immunization policies.

### *Vaccine Coverage*

The relative coverage with three doses of PCV using either a 3p+0 or 2p+1 schedule were predicted, using DTP3 (as a proxy for the 3p+0 schedule) and Measles-Containing-Vaccine First-Dose, MCV1 (as a proxy for the booster dose in a 2p+1 schedule) as reference points. In countries using a 3p+0 schedule, the DTP3 and PCV3 coverage were generally comparable in a majority of countries; only 16% of the countries analyzed had a >10% coverage difference between DTP3 and PCV3, and 32%

had a >5% coverage difference. Additionally, in countries using a 2p+1 schedule, the MCV1 and PCV3 coverage levels were also similar in a majority of countries; only 32% of the countries analyzed had a >10% coverage difference between MCV1 and PCV3. Thus, in countries still to introduce PCV, the potential coverage that may be achieved could be estimated reasonably accurately using the coverage with DTP3 or MCV1, provided the third dose is provided along with these two doses, respectively. Many countries that introduced PCV in a 3p+0 schedule have low MCV2 [Measles-Containing-Vaccine Second-Dose] coverage during the second year of life, so a switch in dosing schedule from PCV 3p+0 to PCV 2p+1 where the third dose is provided in the second year of life could reduce a country's PCV3 coverage.

The timing for a child to receive the third dose of PCV using data on timing of DTP3 and MCV1 from coverage surveys was also assessed. Country programs vary extensively in their timeliness and coverage[11][12]. Therefore, the country level decision to switch from three primary doses to two doses and a booster should be based on local data and could be estimated using data from national coverage surveys.

### *Transmission Dynamics*

The minimum population size needed to self-sustain transmission of an infectious disease without importation – the Critical Community Size (CCS) – is a critical value for understanding persistence dynamics and estimating the probability of geographically-localized fadeout or elimination of a pathogen. While the CCS has been demonstrated for pathogens inducing sterilizing immunity, immunity that results in prevention of acquisition in the future (such as measles), it is challenging to apply the same methodology to *S. pneumoniae*, due to its low case-to-colonization ratio and inconsistent surveillance across different settings. Dr. Ben Althouse presented results from a stochastic, individual-based, age-structured mathematical model of pneumococcal colonization, including biologically realistic acquisition and transmission dynamics, calibrated to settings with various forces of infection. For each setting, CCS was estimated by varying the population size probability of disease extinction with multiple stochastic realizations. Dr. Althouse found that the number of children in a given population needed for self-sustained transmission for more than 50% of all stochastic realizations is on the order of 1,000 to 10,000, with this number depending on the force of infection and acquired immunity through natural colonization. This relatively small CCS can be explained by the long duration of pneumococcal carriage in infants and toddlers, who are the transmission reservoirs. The CCS highlights the potential importance of subnational variation in PCV coverage whereby relatively small pockets of unvaccinated individuals can continue carrying and transmitting pneumococcus despite being surrounded with adequately-vaccinated populations. Assuring high and homogeneous vaccination coverage with PCV will be needed to maintain vaccine serotype pneumococcal transmission at the lowest possible levels.



### *Drivers of Decision-Making Regarding PCV Schedules*

A panel discussion was held to get country perspectives on the rationale and factors that influenced decisions on PCV introduction, the choice of schedule and product, and evidence that may be required to sustain PCV in their national programs.

In 2010, the United Kingdom became the first country to use PCV in a 2p+1 dosing schedule, and Dr. Elizabeth Miller reflected on the factors that led to the decision to use this schedule. She indicated that a 3p+0 schedule was not considered in the UK. This was due to the fact that when 3p+0 was used with the Hib vaccine, there was an increase in incidence after a few years, which required the UK to add a booster dose. Studies did not indicate a major difference in immunogenicity between the 2p+1 and 3p+0 dosing schedules, while the 2p+1 schedule was found to be more cost-effective. PCV 13 was chosen as the product because it was licensed for use in a 2p+1 schedule and because of a concern about the prevalence of serotype 19A disease resulting from serotype replacement following PCV 7 use.

Dr. Peter McIntyre reported on the considerations leading to Australia's decision to utilize a primary 3p+0 dosing schedule, with 3+1 for children at higher risk of IPD. In 2000, Indigenous children in northern and central Australia had the highest reported rates of IPD in the world, with high serotype diversity (serotypes in PCV7 only accounted for 35-40% of IPD) and early onset of meningitis. From 2001, conjugate pneumococcal vaccines were funded for children with medical conditions placing them at higher risk of IPD (3 +1 schedule) and for all Indigenous children (3+0 schedule), with those living in 4 jurisdictions of highest IPD incidence also recommended to receive a dose of 23 valent polysaccharide vaccine (PPV23) at 18-24 months. In 2005, PCV7 was funded universally on a 3p+0 schedule, due to primarily for cost reasons, with Indigenous and high-risk schedules continued. Impact evaluations for the PCV7 era demonstrated that the 3p+0 schedule had a similar impact to that reported by countries using 3p+1 or 2p+1 schedules. There was strong emergence of serotype 19A in non-Indigenous children, which accounted for almost 50% of IPD by 2010 when PCV13 became available. In contrast, among Indigenous children receiving PPV23, serotype 19A decreased. However, with additional serotypes in PCV13, there was deemed insufficient extra benefit to warrant continuing 23PPV; 3+0 was used generally and 3+1 for high risk children for PCV13, based on the PCV7 experience. However, 3 dose vaccine failures (primarily 19A and 3) in the second year of life with PCV13 have prompted serious consideration of moving to a 2p+1 schedule – this change is now out for public consultation (September 1 2017). Delay of the third dose to 12 months led to some concern about breakthrough meningitis between 4 and 12 months of age but the reduction in total and severe IPD (primarily pneumonia with empyema) in the second year of life and greater herd impacts was felt to justify this.

Dr. Narendra Arora reported that the Indian National Technical Advisory Group on Immunization (NTAGI) opted for the 2p+1 PCV schedule over a 3p+0 schedule due to data presented during the WHO PCV Consultation in 2016, where available data, mainly

from PCV 7, indicated that this schedule may be superior to the 3p+0 schedule. Because the country required 20 million doses for introduction, the option of multi-dose vials and the consequent lower volume of cold chain storage capacity requirements were the key factors in opting to use PCV13, available in a 4-dose presentation with preservative. However, in the longer term, given the size of the birth cohort in India and since a single manufacturer may not be able to meet the demand, the national program is open to using more than one product in the country.

Dr. Bikash Lamichhane reported on Nepal's experience with a 2p+1 PCV10 dosing schedule, with a modified schedule of 6w, 10w, and 9 months (i.e. 4 weeks, rather than 8 weeks, between the two priming doses). The country-level decision to introduce PCV in phases with a 2p+1 schedule was based on studies in Nepal that revealed that 2p+1 conferred higher antibody levels than a 3p+0 schedule following the third dose. This suggested a longer duration of protection, which was assessed as important in Nepal because IPD data indicated a predominance of disease due to serotype 1, and the age of peak incidence was above 9 months of age. Additionally, the second dose is given at 10 weeks of age rather than the usual 14 weeks of age because of concerns from health care workers about the feasibility and acceptability of delivering three parenteral vaccines in a single visit at 14 weeks of age. While the coverage with the third dose was low in the initial phases, the coverage levels are increasing and expected to be similar to MCV1.

Dr. Betuel Sigauque explained that the decision to switch from PCV10 to PCV13 in Mozambique was driven by the Ministry of Health's preference for the 13-valent formulation requested in its initial application to Gavi. While PCV10 was initially used in Mozambique, this was driven by supply constraints rather than epidemiology or cost; thus, once the supply was sufficient, the country decided to switch to PCV13. PCV13 was preferred because it was expected to cover about 85% of prevalent serotypes, whereas PCV10 was expected to cover 65%. A technical advisory group reviewed local data on colonization, IPD, and serotype prevalence and replacement, and recommended the switch in product from PCV10 to PCV13. Their decision was based primarily on local data indicating that while PCV10 had a large impact on reducing IPD and pneumonia, there was also an increase in ST19A carriage and disease which could warrant switching to a vaccine that contains that serotype.

Dr. Lucia de Oliveira, a representative from Pan American Health Organization (PAHO), clarified details surrounding major budgetary constraints that led to the discontinuation of PCV13 in Venezuela's national immunization program. While PCV13 was introduced in 2014 in Venezuela, a severe financial crisis caused the Health Ministry to discontinue PCV's inclusion in the national immunization program in an effort to sustain the less expensive vaccines in the program. This is the first case in the history of EPI in the Americas that a country has discontinued the use of a recommended vaccine.

The Ministry of Health is eager to reintroduce the lowest-cost PCV product when funds become available.

The Philippines, Bangladesh, and Tanzania have all faced similar financial challenges either because they are not eligible for Gavi support (Philippines) or are approaching GAVI-transition (Bangladesh and Tanzania). Representatives from these countries discussed their thoughts and concerns for sustaining the use of PCVs in their respective countries. Dr. John Erasmo of the Philippines said that the universal roll-out of PCV has been hindered by the high cost of the vaccine. Hence, vaccination is currently limited to those registered to be in the lowest income bracket in the country. While the country has a goal of nationwide PCV13 introduction, the desire to also introduce the dengue vaccine in some regions of the country requires careful considerations in the prioritization of the two vaccines and how to allocate limited national resources for the introduction of these vaccines. Both Dr. Samir Saha of Bangladesh and Dr. Dafrossa Lyimo of Tanzania expressed concerns on sustaining the vaccine post GAVI-graduation given the high costs involved. To sustain the use of PCVs, both emphasized the need for local data to communicate the value of PCV to those making decisions on allocation of national budgets. Dr. Saha pointed out that the decision to introduce the vaccine in Bangladesh was based on projected mortality reductions from mathematical modelling. However, for sustaining the vaccine using domestic resources, empiric data on mortality reduction may be required. In Tanzania, the decision to introduce PCV was based on high rates of pneumonia hospitalizations. Policy-makers are tracking hospitalization and outpatient visits and reduction in these parameters and resultant cost savings through prevention of disease would be important in convincing policy-makers to sustain the vaccine in the national program. She also noted that there was a strong community demand for the vaccine, which may help with sustaining the vaccine in the program.

## **VII. Key Evidence Gaps & Conclusions**

The final session concluded with a prioritization of key policy-relevant questions and future research directions. Participants were assigned to break out groups to discuss the following six policy-related topics:

- 1) Choice of Schedule
- 2) Choice of Product
- 3) Catch Up Vaccination
- 4) Impact of maternal immunization with tetanus-diphtheria containing vaccines
- 5) Impact of PCV on antimicrobial resistance
- 6) Prevention of and response to outbreaks

For the first three issues, the participants were asked to consider the data presented from PRIME during the consultation, identify the key evidence gaps and convert them in policy-relevant research questions. The remaining three groups were asked to identify and prioritize the policy relevant evidence gaps and research questions.

The feedback from participants corresponding to each group is briefly summarized below.

#### *Choice of Schedule*

In determining the policy recommendations on choice of schedule, the highest priority research areas identified were: (1) serotype-specific vaccine effectiveness studies, with head-to-head studies of different schedules where possible; (2) completeness and timeliness of different dosing schedules; and (3) data on the long-term impact of schedule on disease transmission and dynamics. Specifically, there was an interest in gathering studies that assessed the impact on disease in the second year of life by dosing schedule. The participants also prioritized the need for data on the duration of protection provided by different schedules on nasopharyngeal carriage and disease, particularly in low- and middle-income countries.

#### *Choice of Product*

The highest priority research gap identified for product choice was to accumulate quality, long term surveillance post introduction to better understand the correlation between antibody responses and vaccine impact, as the serotype specific correlates of protection need to still be fully established. An additional priority includes increasing the amount of studies that evaluate the effects of product interchangeability during primary immunization on immunogenicity, NP carriage, and disease. Head to head studies comparing future PCV products with existing products were also stressed. Many participants cited serotype replacement data as one of the most pressing research gaps. Assessments of the effects of dosing schedule or product interchangeability on serotype replacement should be conducted.

#### *Catch up vaccination*

The priority research gap to inform future deliberations about catch-up vaccination was to conduct cost-benefit analyses of catch-up campaigns. Most of the currently available catch-up data relies on disease transmission models, so there is a need to collect empiric data to parameterize and validate the models.

#### *Outbreaks*

The highest priority research gap identified was the need for epidemiologic data on pneumococcal disease outbreaks and of pneumococcal disease in emergency settings. It is also important to gather impact data on the strategic use of PCV in high risk settings, specifically: (1) in the meningitis belt in order to determine the optimal routine immunization schedules to reduce the risks of outbreaks and on strategies for outbreak response with vaccination; and (2) in refugee populations to determine optimal vaccination strategies in these settings.

#### *Antimicrobial Resistance*

The added economic value as a result of implementing PCV in the face of the emerging threat of antimicrobial resistance (AMR) should be studied through models. Additionally, data on the degree by which PCV use reduces the rates of antibiotic use and AMR in low- and middle-income countries should be collected.

*Maternal Immunization*

To understand how maternal vaccination with vaccines containing antigens that are also used as the protein carrier of PCVs alters an infant’s immune response to PCV, the participants identified the importance of quantifying any blunting effect and its clinical consequences. These would be assessed through immunogenicity and clinical outcomes, especially in LMICs. Additionally, it will be important to understand decay rates for maternal antibodies and how that could affect timing of the first dose

*Other outcomes*

Participants described the need for future randomized implementation trials to quantify the true and wider impact of schedule, product, and catch-up choice—looking beyond the traditional immediate impact assessments on disease and estimating longer term consequences like cognitive function and increased school performance and productivity.

*Overall conclusions of priority evidence gaps and research questions*

The following matrix describes overall rankings of different priority research questions across all of the break-out groups. The priority 1 category reflects the research questions cited by the most participants at the meeting.

Priority	PCV evidence gaps/research questions
1	A. High quality evidence of the impact of long-term PCV use on serotype-specific disease and carriage, for both products and both schedules in various epidemiological settings with emphasis on head-to-head (H2H) studies where possible <sup>1</sup>
	B. Data on the long-term impacts of 2p+1 vs 3p+0 schedules on serotype-specific disease and carriage in the second year of life and beyond with emphasis on H2H studies where possible
	C. Impact of the completeness and timeliness of different dosing schedules on serotype-specific carriage/transmission and disease outcomes with emphasis on H2H studies where possible <sup>2</sup>

<sup>1</sup> Experts acknowledged that H2H studies of licensed products or different schedules that evaluate disease outcomes are highly unlikely, as are long term H2H studies with either disease or carriage outcomes. It may be possible to evaluate disease outcomes by comparing provinces within the same country, but this would not represent the classical H2H study. H2H studies looking at carriage outcomes are more likely/feasible.

<sup>2</sup> Only small H2H studies comparing schedules would likely be possible, and specific transmission scales would be needed to evaluate this aspect

	<p>D. Immunogenicity, carriage and disease data (including serotype replacement) on the interchangeability of PCV products (to inform product switching and to inform countries using more than one product)<sup>3</sup></p> <p>E. A clearer understanding of the relationship between serotype-specific immune response to vaccination and disease outcomes, including serotype-specific correlates of protection</p> <p>F. Serotype distribution of residual disease and replacement data for carriage and invasive pneumococcal disease (IPD) after more than 5 years of PCV use in L/MIC<sup>4</sup> settings, by dosing schedule for both products, including data on the role of changes in the age distribution of disease and colonization</p>
<b>2</b>	<p>G. Head to head studies comparing future pneumococcal vaccine products to licensed PCVs with respect to immunologic and carriage outcomes</p> <p>H. Cost-benefit analysis of catch-up campaigns</p> <p>I. Epidemiology of pneumococcal disease in outbreaks and in high-risk settings such as humanitarian emergencies</p> <p>J. Estimate the economic impact of antimicrobial resistant (AMR) pneumococcal infections and the economic impact of PCV use on AMR pneumococcal disease (including indirect effects)</p>
<b>3</b>	<p>K. Impact data on the strategic use of PCV in high risk settings or outbreak situations, (which could include evaluating the value of catch-up campaigns in these settings and/or the use of adult PCV campaigns to prevent outbreaks in the meningitis belt)</p> <p>L. Impact of PCV use on rates of AMR pneumococcal infections and on rates of antibiotic usage in L/MICs</p> <p>M. Understand the clinical and biological relevance for infants of maternal vaccination with tetanus, diphtheria and pertussis vaccines, and impact on infant immune response (including blunting of the infant response as function of maternal vaccinations and decay of maternal antibodies)</p> <p>N. Empiric evidence of the impact of catch-up campaigns on carriage as a means to validate models of transmission</p> <p>O. High quality evidence of the extent of cross-serotype protection for both PCV products, post-introduction</p>
<b>4</b>	<p>P. Relative cost-benefit of different dosing schedules and products, especially for GAVI graduating countries</p> <p>Q. Economic costs of pneumococcal disease in outbreaks and in refugee/humanitarian crisis settings</p> <p>R. Define a pneumococcal outbreak and thresholds that would trigger a response of the strategic use of PCV, specifically applicable to the meningitis belt and refugee/humanitarian crisis settings</p> <p>S. Effect of concomitant vaccine administration at 9 months of age with PCV and YF, MenCV, MCV and RTS,S on immune response to antigens in all co-administered products, by PCV product (which have differing carrier proteins that may have implications for immunogenicity in the presence of other antigens)</p>

<sup>3</sup> Evaluating disease outcomes in the context of the use of multiple PCV products in a single individual would be challenging. However, it may be possible to do an analysis of vaccine failures, e.g. whether a higher proportion of vaccine failures is seen in children who received more than one product during their primary vaccine series

<sup>4</sup> Low- and middle-income countries (L/MICs)

	T. Develop a clearer understanding around the specific circumstances in which a country should use a catch-up campaign
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## **IX. Concluding Remarks**

The WHO Technical Expert Consultation on Optimization of PCV Impact reviewed the available impact evidence with the intent of shaping SAGE recommendations to optimize future PCV use. While both products and schedules show clear overall impact against vaccine-type serotypes as a whole, differential impact between products or schedules could not be ascertained due to the lack of available head to head studies, and the presence of significant confounders that complicate interpretation of comparisons. Programmatic issues and the cost of the vaccines were identified as major factors that influenced country-level decisions regarding product choice and schedule. Future research priorities were also identified and included conducting more head to head assessments of PCV impact, particularly for IPD and pneumonia outcomes, as well as further analyses of reduced dosing schedules, transmission dynamics, serotype replacement, and PCV impact on controlling outbreaks or AMR. A Strategic Advisory Group of Experts on Immunization (SAGE) Working Group on PCVs met directly after the technical consultation to discuss the evidence presented in relation to current WHO policy on PCV use and draft revisions of the recommendations. Updated recommendations based on evidence reviewed in this consultation will be presented to SAGE by the PCV Working Group, and discussed at the October 2017 SAGE meeting.

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## Conclusions of the SAGE Working Group on Measles and Rubella

21-22 June 2017, Geneva

### WHO Policy Recommendation on Target Immunity Levels for Elimination: Considerations for Defining Age-specific Target Levels

#### FOR DECISION

In light of the following considerations, SAGE is asked to provide recommendations on what level of population immunity is needed to achieve herd immunity in defined age groups.

#### Definitions

“Age-specific immunity levels” are the proportion of people in specified age groups that are immune to a particular pathogen (whether due to vaccination or natural infection).

“Target immunity levels” are age-specific immunity levels, usually defined to interrupt transmission by driving R below 1.

“Reproduction number” is the mean number of secondary cases generated by each infectious case. If this is less than 1, transmission is eventually stopped and elimination can be achieved.

#### Note

Results included in this document are based on yet unpublished results. Please do not share.

#### Background

The current target of the World Health Organization (WHO), as provided in the *Global Measles and Rubella Strategic Plan 2012-2020*, is to

*“achieve at least 95% coverage with both the first and second routine doses of measles vaccine (or measles-rubella-containing vaccine as appropriate) in each district and nationally.”*

The plan further states that

*“high coverage with two doses of MCV serves as the foundation required to ensure high population immunity against measles”*

and that

*“measles and rubella elimination require achieving and maintaining high levels of*

*population immunity. For measles, vaccination coverage will need to reach and remain at or exceed 95% with each of the two doses of MCV (for countries yet to introduce RCV), MR or MMR vaccines at the district and national levels.”*

Where this cannot be achieved the plan recommends Supplementary Immunization Activities (SIAs):

*“Countries not able to achieve high and homogenous vaccination coverage with the first and second dose of MCV through their routine immunization systems will need to use SIAs). These can be summarized as a one-time “catch-up” SIA targeting a broad age group (often 9 months to 14 years of age) to immunize the most susceptible children, followed by periodic “follow-up” SIAs targeting children born since the previous one regardless of vaccination status, with special efforts made to reach children who have never been vaccinated against measles.”*

Strictly speaking, any target based on child vaccination coverage only applies to current and future birth cohorts and their immunity going forward. To assess the ability of a country or region to achieve and maintain elimination, it is necessary to look at immunity levels across age groups. These levels are determined by historical routine vaccination coverage, but also by vaccination campaigns and outbreaks leading to corresponding levels of natural immunity. For this reason, in the late 1990s, the WHO European Region derived age-specific target immunity profiles, or the levels of immunity necessary in different age groups to achieve elimination.<sup>1</sup> These profiles are widely applied within and occasionally outside Europe. Based on a basic reproduction number (or number of secondary cases produced by a typical infective in a totally susceptible population) of 11 and assumed mixing patterns based on pre-vaccination data from England and Wales, it was recommended that at least 85% of 1–4 year olds, 90% of 5–9 year olds and 95% of 10 year olds and older possess immunity against measles. These immunity levels should be distinguished from recommendations on vaccination coverage levels. Coverage targets generally need to be higher than immunity targets because vaccine effectiveness is not 100%, and they generally apply to young children. Gaps in immunity can exist despite high routine coverage if coverage targets were not met in the past, or because of population migration.

The recommendations for the WHO European Region were derived from models that used estimated contact patterns that were consistent with the age distribution of cases in high-income countries. As such, it was not clear whether the recommendations are relevant beyond the specific context of the European Region, or whether different target levels were to be recommended elsewhere. We here report results from a re-

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<sup>1</sup> Ramsay M. *A strategic framework for the elimination of measles in the European region*. 1997.

assessment of age-specific target immunity levels that take into account recent observations of age-specific contact patterns in different settings around the world.

### Diary-based studies on contact patterns

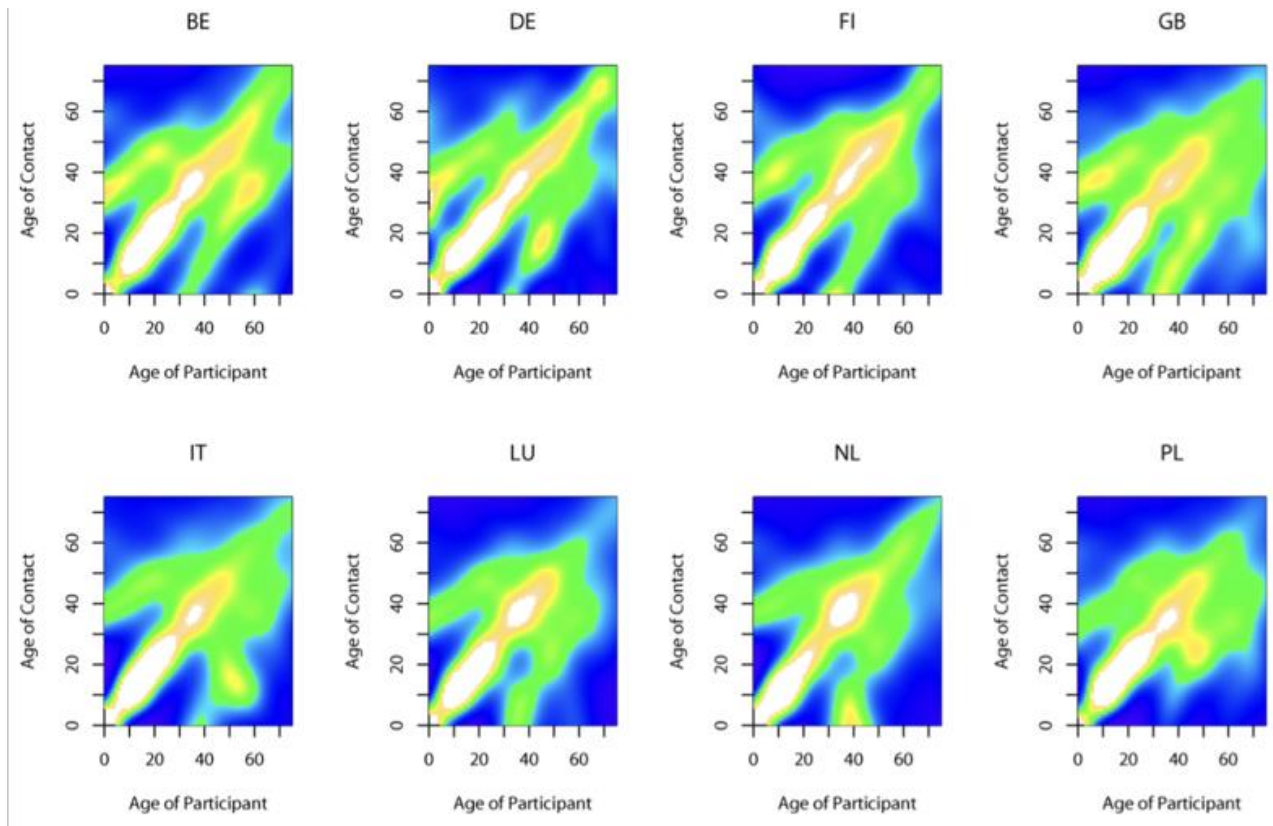


Figure 1. Age-specific contact patterns in 8 different European countries, shown as heat maps (brighter colours: more contact). Shown is the reported age of participants (bottom axis) and the reported age of their contacts (left axis). Countries: Belgium, Germany, Finland, Great Britain, Italy, Luxembourg, Netherlands, Poland. Reproduced from Mossong et al.<sup>2</sup>

Much work over the past decade has gone into better quantifying the amount of transmission-relevant contact occurring between different age groups (Figure 1). Diary-based studies have been conducted across Europe, as well as in Viet Nam, China, Uganda and elsewhere.<sup>2</sup> While other methods for measuring social contact patterns exist, contact data from diary studies have become the de facto standard in studying age-specific infectious disease dynamics. Mathematical models of transmission based on

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<sup>2</sup> Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Med* 2008;5(3):e74. URL: <http://dx.doi.org/10.1371/journal.pmed.0050074>. doi:10.1371/journal.pmed.0050074.

these observed patterns have consistently outperformed those based on homogeneous mixing.<sup>3</sup>

### Age-specific immunity scenarios

We first investigated reproduction numbers in 8 countries (Finland, Germany, Italy, Netherlands, Poland, Taiwan, Uganda, United Kingdom and Viet Nam) under previously recommended target immunity levels (85% in under-5 year olds, 90% in 5–9 year olds and 95% in all older age groups). If homogeneous mixing is assumed, all countries except Uganda would interrupt transmission with immunity at these levels, their median reproduction numbers  $R$  being less than 1 (Fig. 2). Only Uganda, which has a large proportion of children in the population (35% of the population less than 10 years of age) was found to have a reproduction number significantly greater than 1 (median: 1.05) if immunity was at the previously recommended target immunity levels.

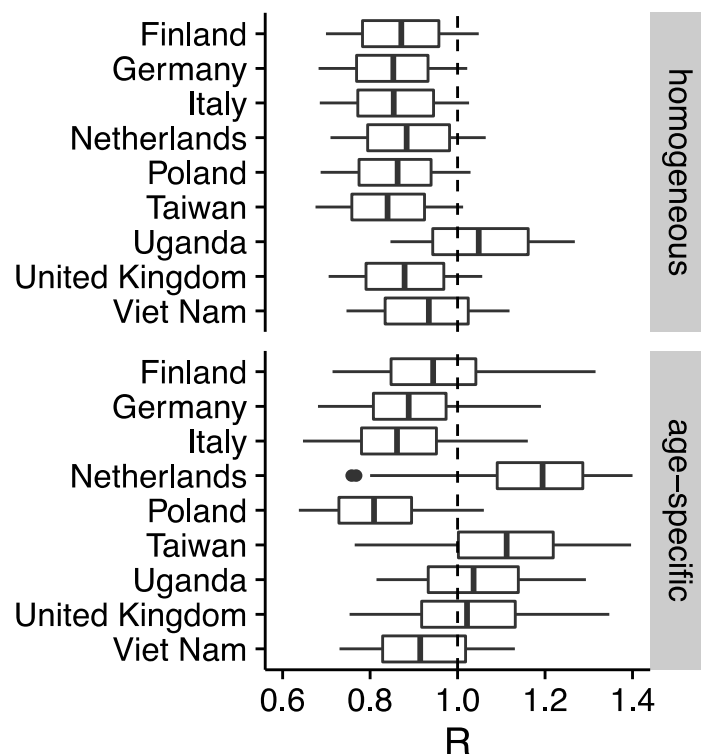


Figure 2. Estimates of what the reproduction numbers of measles would be in a scenario of immunity at current target levels, under assumptions of homogeneous (top) versus age-specific (bottom) mixing.

<sup>3</sup> Wallinga J, Teunis P, Kretzschmar M. Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. *Am J Epidemiol* 2006;164(10):936–44. URL: <http://dx.doi.org/10.1093/aje/kwj317>. doi:10.1093/aje/kwj317.

Using the same immunity levels but with age-specific mixing as observed in diary studies, the Netherlands, Uganda, the United Kingdom and Taiwan would have estimated reproduction number greater than 1 (Figs. 2 and 3A), indicating that continued outbreaks would be possible. Germany, Italy, Finland and Viet Nam would have more than 10% probability of reproduction numbers greater than 1 at these levels.

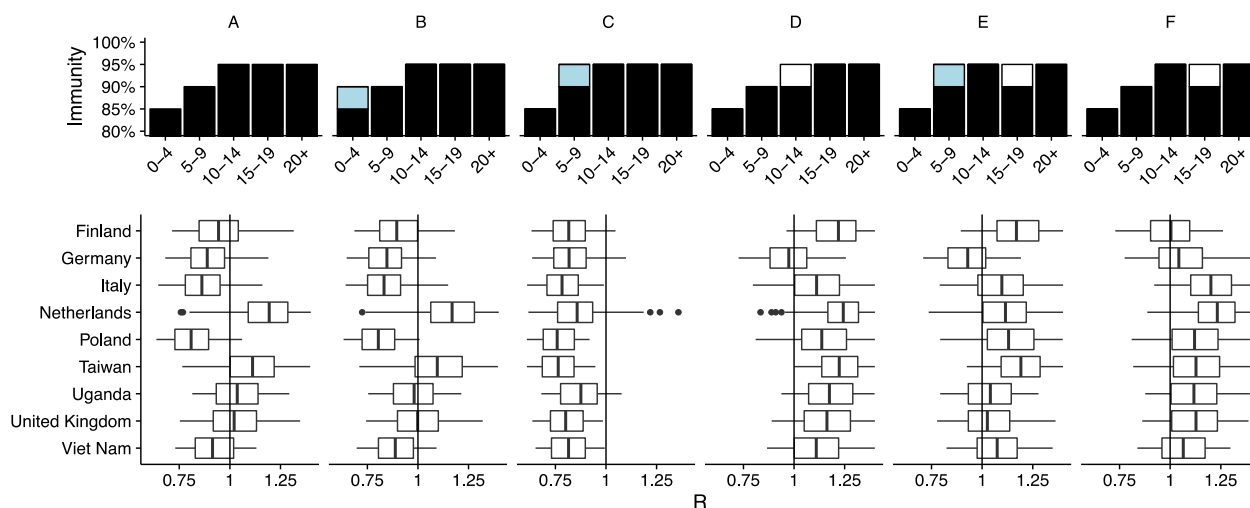


Figure 3. Estimates of what the reproduction numbers of measles would be in different scenarios, with age-specific mixing as measured in diary studies. Top: Scenarios of immunity levels. Bottom: Estimated reproduction numbers. Left to right: A) Current target levels. B) 5% higher immunity in under 5 year olds. C) 5% higher immunity in 5–9 year olds. D) 5% lower immunity in 10–14 year olds. E) 5% higher immunity in 5–9 year olds and 5% lower immunity in 15–19 year olds. F) 5% lower immunity in 15–19 year olds.

With alternative scenarios, the reproduction numbers changed (Fig. 3, scenarios B to F). Raising immunity in under-5-year olds (scenario B) by 5% to 90% would reduce the estimated reproduction numbers slightly. In this scenario, all countries that would have reproduction numbers greater than 1 under the previously recommended target immunity levels would still have had reproduction numbers equal to or greater than 1. Only in Germany and Italy would the estimated probabilities of having a reproduction number greater than 1 drop to below 5%. On the other hand, raising immunity in 5-to-9-year olds by 5% to 95% (scenario C) would sharply reduce reproduction numbers. In this scenario, all countries would have a median estimated reproduction number well below 1, and only the Netherlands (10%) and Uganda (13%) would be estimated to have a probability greater than 5% of having a reproduction number greater than 1.

Scenarios in which a gap in immunity is introduced in older generations resulted in significantly higher reproduction numbers. Reducing immunity levels in 10-to-14-year olds by 5% to 90% compared to the previously recommended target immunity levels (scenario D) would increase the median reproduction numbers in all scenarios except Germany to above 1. Even if immunity in 5-to-9-year olds was increased to 95% at the same time, all countries would retain a high probability of having a reproduction

number greater than 1 (Germany 30%, all other above 50%). Reducing immunity in 15-to-19 year olds by 5% to 90% from the previously recommended target immunity levels (scenario E) would increase the probabilities of a reproduction number greater than 1 to greater than 50% in all countries. Reducing immunity in all over-19 year olds by 5% to 90% from the previously recommended target immunity levels (scenario F) would increase the probabilities of a reproduction number greater than 1 to greater than 90% in all countries.

### **Evaluating age-specific immunity levels from serological studies**

To validate our approach, we derived predictions from serological studies conducted in the late 1990s and early 2000s with observed case data in the following period. Reproduction numbers estimated using age-specific mixing based on these serological data were weakly correlated with the number of cases in the 10 subsequent years as per WHO figures (Spearman rank coefficient between estimated R and cases per capita: 0.49). Out of 17 countries in which serological studies were conducted as part of the ESEN2 study in the early 2000s<sup>4</sup>, eight reported more than 5 measles cases per million per year in the following 10 years. Of these, Spain (3419 cases over the course of 10 years) had a median estimated reproduction number of 0.54 and probability 0 of a reproduction number greater than 1. Israel (1792 cases) had a median estimated reproduction number of > 0.9, and a probability greater than 20% of a reproduction number greater than 1. The United Kingdom (6601 cases) had a median reproduction number of 1.1, with a probability of 62% of a reproduction number greater than 1. The other five countries (Belgium: 1066 cases, Bulgaria: 24,416 cases, Cyprus: 111 cases, Ireland: 1687 cases, Romania: 20,570 cases) all had median estimated reproduction numbers greater than 1 and, correspondingly, high probabilities of a reproduction number greater than 1.

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<sup>4</sup> Andrews N, Tischer A, Siedler A, Pebody RG, Barbara C, Cotter S, et al. Towards elimination: measles susceptibility in Australia and 17 European countries. *Bulletin of the World Health Organization* 2008;86:197–204. URL: <http://www.who.int/bulletin/volumes/86/3/07-041129/en/>.

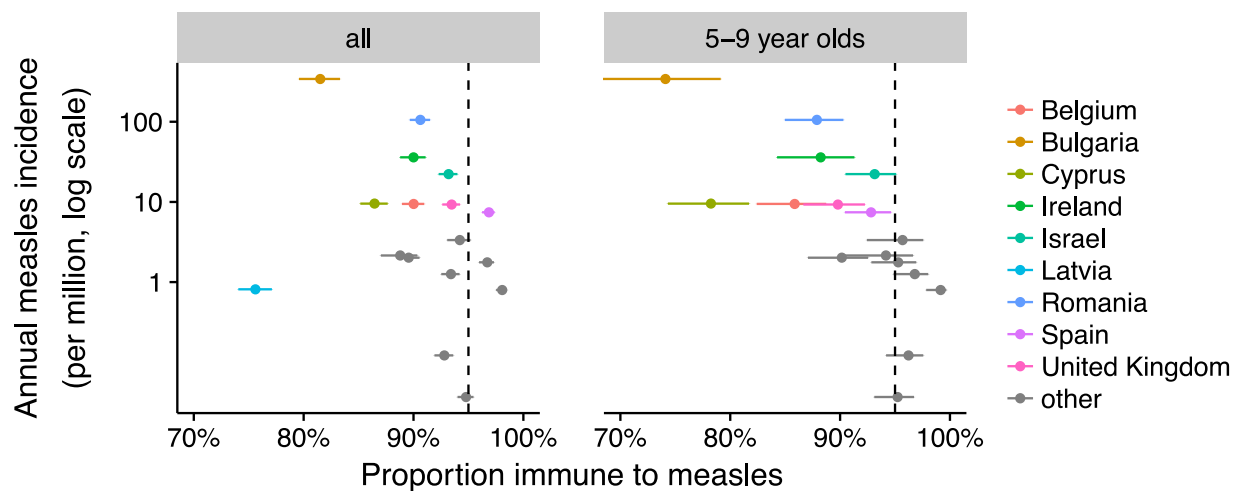


Figure 4. Estimates derived from serological studies conducted around the year 2000 compared to reported rate of cases across the following 10 years. Shown is the proportion estimated immune to measles from serological studies in the whole population (left) and 5-to-9 year olds (right). Countries with estimated mean reproduction numbers greater than 2 and/or more than 5 cases per million per year in the 10 years following the serological study are highlighted in colour. Not shown in right panel: Latvia (proportion of 5–9 year olds estimated immune: 62% (95% confidence interval, 57%–67%), 0.8 cases per million per year).

Five other countries (Hungary, Latvia, Lithuania, Malta and Sweden) had median estimated reproduction numbers greater than 1, but did not report many cases the following 10 years (maximum: 131 in Sweden). Of these, Cyprus and Latvia were estimated to have reproduction numbers well above 1, while the others were closer to one, with probability of the reproduction number being less than 1 greater than 15% in all cases except Lithuania (median reproduction number: 1.4, 16 cases).

There was a negative correlation between population-level immunity levels as determined from serology and outbreaks (Spearman rank coefficient between estimated population-level immunity and cases per capita: -0.38; Fig. 4, left), with several outbreaks in countries reporting high levels of immunity (Israel, Spain and the United Kingdom). The correlation is stronger when considering only immunity in 5-to-9 year olds (Spearman rank coefficient between estimated immunity in 5-to-9 year olds and cases per capita: -0.62; Fig. 4, right). Of the 6 countries (Czech Republic, Hungary, Luxembourg, Malta, Slovakia, Slovenia and Sweden) that found a proportion greater than 94% of 5-to-9 year olds immune in the serological studies, none experienced a significant outbreak in the subsequent 10 years. Immunity in all other age groups was also negatively correlated with cases per capita over the next 10 years, but at lower levels of correlation (0-to-4: -0.42; 10-to-14: -0.50; 15-19: -0.42, 20+: -0.06).

## Limitations

This study has several limitations. It relied on broad estimates of the basic reproduction number, derived from pre-vaccination era dynamics. While these numbers are well-established values in mathematical epidemiology, recent studies have produced both lower and higher estimates, depending on the method used and the type of setting investigated<sup>5</sup>. For example, settings with high population density, large birth cohorts and massive in-migration from endemic areas may have higher basic reproduction number. Moreover, the reproduction numbers we estimated from serological studies did not always correctly predict where outbreaks could be expected. In particular, Israel, Spain and the United Kingdom experienced large numbers of cases in the following 10 years in spite of reproduction number estimates which would indicate interruption of transmission. Three potential causes for this discrepancy are that: First, decreases in vaccination coverage as well as the presence/absence of vaccination campaigns may have changed the risk of outbreaks during the 10 years following the serological studies. Second, samples used for the serological studies were a combination of residual and population-based samples and may not be representative of population-level antibody levels. For example in Spain, a disproportionate number of cases occurred in young adults, but there was nothing in the serological data to suggest that this might be expected. Moreover, if those lacking immunity are preferentially in contact with each other because they cluster socially or geographically, outbreaks could occur in these groups, and population-level serology might not provide a good estimate of realised immunity levels in outbreak settings. In Israel, outbreaks occurred in orthodox religious communities with very low vaccination coverage. Third, mixing levels between 5-to-9 year olds might be even stronger than suggested by the diary-based studies underlying the contact matrices used here. This would be in line with findings from the pre-vaccination era in England and Wales showing a sharp increase in age-specific incidence at the age of school entry, coincident with the age of first exposure to a school setting. Israel, Spain and the United Kingdom were all found to have levels of immunity in 5-to-9 year olds of 90–95% in serological studies, and yet experienced significant outbreaks in the following 10 years. It is conceivable that even these levels might be too low to guarantee interruption of transmission of measles virus, especially in the presence of sub-national variation in immunity.

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<sup>5</sup> Guerra, F. M.; Bolotin, S.; Lim, G.; Heffernan, J.; Deeks, S. L.; Li, Y. & Crowcroft, N. S. The basic reproduction number ( $R_0$ ) of measles: a systematic review. *The Lancet Infectious Diseases, Elsevier, 2017*



## **Conclusions:**

Based on the study, the authors propose that target immunity levels be recommended for elimination based on the original levels derived for WHO European Region, but with a requirement of higher immunity of 95% in 5–9 year olds.

## **Draft Recommendations**

The following recommendations are proposed by the SAGE WG on Measles and Rubella for considerations by the SAGE based on the evidence presented above.

1. Achieving homogeneous immunity of at least 95% through coverage of at least 95% with 2 doses of MCV remains the primary goal for measles elimination.
2. Countries should include immunity targets in addition to coverage targets as part of necessary strategies for achieving measles elimination
  - Neglecting immunity gaps in older age groups could make it difficult and costly to achieve elimination
  - Neglecting immunity gaps particularly in school-aged children could increase disease burden and mortality among infants younger than 1 year of age as school-aged children could be the transmitters of infection (as siblings in school or in the future as parents).
3. Recommend immunity levels of 95% in all age groups from 5 years
  - in particular when conducting follow-up campaigns, in addition to ensuring high coverage in children 1-4 years of age, the campaigns should address possible immunity gaps in the 5-9 year olds in order to prevent outbreaks”.

## Annex 1: Estimating reproduction numbers from mixing patterns and immunity profiles

The basic reproduction number  $R_0$  can be calculated as the spectral radius (or largest eigenvalue) of the next-generation matrix (NGM)  $K$ ,<sup>6</sup>

$$R_0 = \rho(K)$$

We can write the elements of the next-generation matrix  $K$  as

$$k_{ij} = q\delta_i p_{ij}$$

where  $q$  is a scale factor that, in the simplest case, is the probability of infection upon contact multiplied with the duration of infectiousness,  $\delta_j$  is the rate at which individuals in age group  $j$  make contact with others, or the number of people they meet per unit time (assumed independent of population age structure),  $p_{ij}$  is the probability that a contact made by an individual in age group  $j$  is with someone in age group  $i$ . Given a value of  $R_0$  and a contact matrix, we can use these two equations to calculate  $q$ , then calculate the elements of the reproduction matrix  $M$  taking into account immunity levels

$$m_{ij} = q \delta_i p_{ij} (1 - r_j)$$

where  $r_j$  is the proportion of people in age group  $j$  that is immune and the reproduction number  $R$  as the spectral radius of  $M$ ,  
 $R = \rho(M)$  (7)

which is the equivalent of  $R_0$  when taking into account current immunity levels in the population.

An assumption of homogeneous mixing would be equivalent to assuming that  $\delta_i = \delta$  (each individual has the same number of contacts, no matter which age group they are in) and  $p_{ij} = n_j$  (the probability of a contacts of group  $i$  being with group  $j$  is equal to the proportion of individuals that are in group  $j$ ).

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<sup>6</sup> Diekmann, O.; Heesterbeek, J. A. P. & Roberts, M. G.

The construction of next-generation matrices for compartmental epidemic models.  
*J R Soc Interfac.*, **2010**, *7*, 873-885

## Conclusions of the SAGE Working Group on Measles and Rubella

21-22 June 2017, Geneva

### WHO Policy Recommendation on administration of MCV to infants <6 months of age.

#### FOR DECISION

In light of the following considerations, SAGE is asked to provide recommendations on the vaccination of infants <6 months of age with measles-containing vaccine (MCV).

#### Background

Countries are experiencing measles outbreaks with high incidence in children younger than 9 months of age, an age group in which measles can be severe. Thanks to the success of the immunization programme in reducing measles incidence, many mothers now have measles antibodies induced by vaccination rather than natural disease. Antibody levels after vaccination are generally significantly lower than those after natural disease, leading to lower measles antibodies in infants born to women with vaccine-derived immunity.

In 2015, the National Institute for Public Health and the Environment (RIVM) in the Netherlands conducted a systematic literature review of the immunogenicity, effectiveness and safety of measles vaccination below 9 months of age. Based on this, and other evidence, current recommendations are to give the first dose of measles or MR vaccine at 9m, moving to 12m when coverage is high and the risk of measles in infancy is low, that is when overall incidence is close to elimination. In addition, SAGE (October 2015) recommended that:

*“In the following situations, a supplementary dose of MCV should be given to infants from 6 months of age :*

- 1. during a measles outbreak as part of intensified service delivery;*
- 2. during campaigns in settings where the risk of measles among infants < 9 months of age remains high (e.g. in endemic countries experiencing regular outbreaks);*
- 3. for internally displaced populations and refugees, and populations in conflict zones;*
- 4. for individual infants at high risk of contracting measles (e.g. contacts of known measles cases or in settings with increased risk of exposure during outbreaks such as day-care facilities);*
- 5. for infants travelling to countries experiencing measles outbreaks;  
for infants known to be HIV-infected or exposed (i.e. born to an HIV-infected woman)*

*Measles vaccine immunogenicity and effectiveness are lower at 6 months than at later ages, and there are concerns about the long-term effectiveness of an early 2-dose schedule and its potential for later blunting of immunity. MCV administered before 9 months of age should therefore be considered a supplementary dose and recorded on the child’s vaccination record as “MCV0” unless the country has data showing high seroconversion when vaccination is carried out before 9 months of age. Children who receive a MCV0 dose should also receive MCV1 and MCV2 at the recommended ages*

*according to the national schedule. Available evidence on safety and immunogenicity of rubella and mumps-containing vaccines support their use from 6 months of age. Countries using MR or MMR in their national schedule should use the combined vaccine rather than measles-only formula"*

*"In areas where there is a high incidence of both HIV infection and measles, an initial dose of MCV may be offered as early as age 6 months (recorded as MCV0). The 2 routine doses of MCV (MCV1 and MCV2) should then be administered to these children according to the national immunization schedule." (see 2017 measles vaccine position paper)*

*Because immunogenicity and effectiveness are lower than for doses administered at a later age and concern about the long-term effectiveness of an early 2-dose schedule, MCV administered at 6 months of age should be considered a supplementary dose and recorded on the child's vaccination record as "MCV0". Children who receive a MCV0 dose should then receive at least two doses of measles-containing vaccines at the recommended ages according to the national schedule. Available evidence on safety and immunogenicity of rubella and mumps-containing vaccines support their use from 6 months of age. Countries using measles rubella (MR) or measles, mumps and rubella (MMR) in their national schedule should use the combined vaccine rather than measles-only formulations in children aged <1 year. SAGE recognizes that this is an off-label use and recommends that national programmes do not restrict the use of either vaccine in the <1 year age group".*

However, recent outbreaks show that many cases occur in children less than 6 months of age. The key question is how can these children be better protected while maintaining robust population immunity? Should vaccination of infants below 6 months of age be recommended, and if so, in what settings?

The MR SAGE WG addressed the above questions in two ways:

1. A review of the epidemiology of measles in infants <6 months of age through the analysis of case-based surveillance data between 2011 and 2016;
2. An updated systematic review on the immunogenicity (humoral and cellular), duration of immunity, vaccine effectiveness, blunting of response to MCV2 after early MCV1, and safety of vaccination of infants <6 months of age.

Summary of the findings of epidemiological analyses and the systematic review are in the two reports below. More detailed reports of these two studies are available in the web as background documents for the session.

## 1. Epidemiology of measles in infants younger than 6 months: analysis of surveillance data 2011-2016

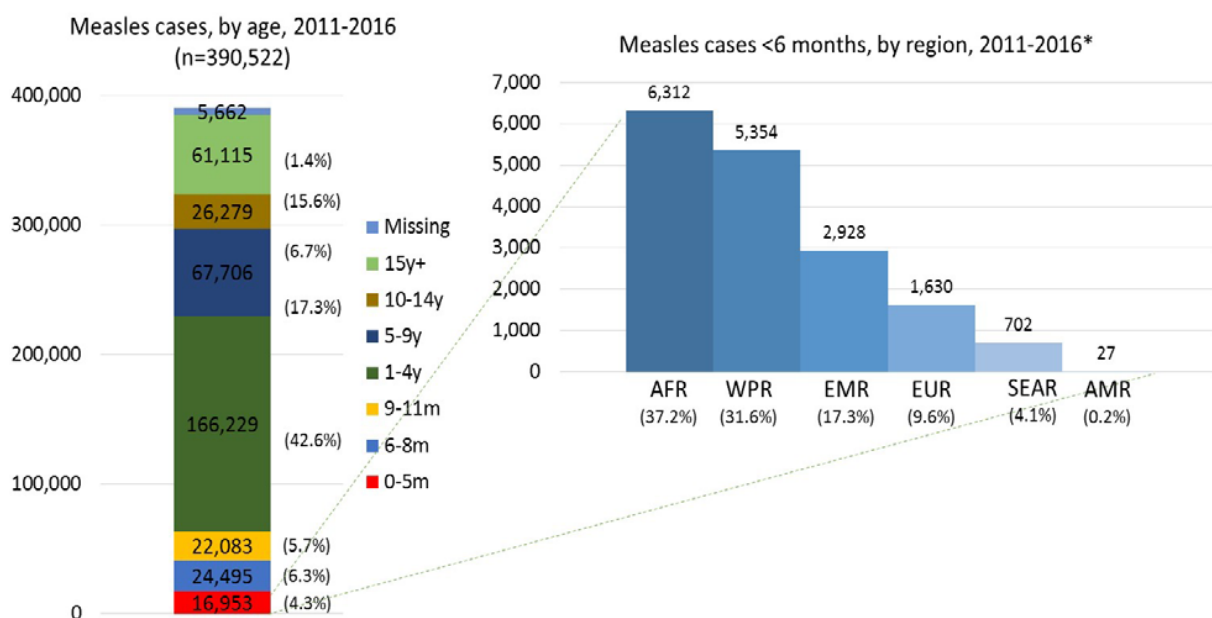
An analysis of the epidemiology of measles in infants younger than 6 months was conducted by the U.S. CDC and WHO using case-based measles surveillance data from 2011 to 2016. The specific research questions for this analysis were:

1. What is the burden of disease due to measles among infants less than 6 months old?
2. What epidemiological circumstances and country situations are associated with a significant proportion of measles cases in children <6 months old?

The analyses were conducted using case-based measles surveillance data that were available at WHO-HQ for years of onset 2011-2016, except for the South-East Asia Region (SEAR) for which surveillance data were available only for 2014-2016. Confirmed measles cases were defined as either laboratory confirmed or epidemiologically linked to a confirmed case. Data from several countries were excluded from analysis due to small numbers of confirmed cases (n=32 countries excluded) or case ages that were only reported in full years (n=36 countries excluded; 30 in the European Region [EUR], 6 in the South-East Asian Region [SEAR]).

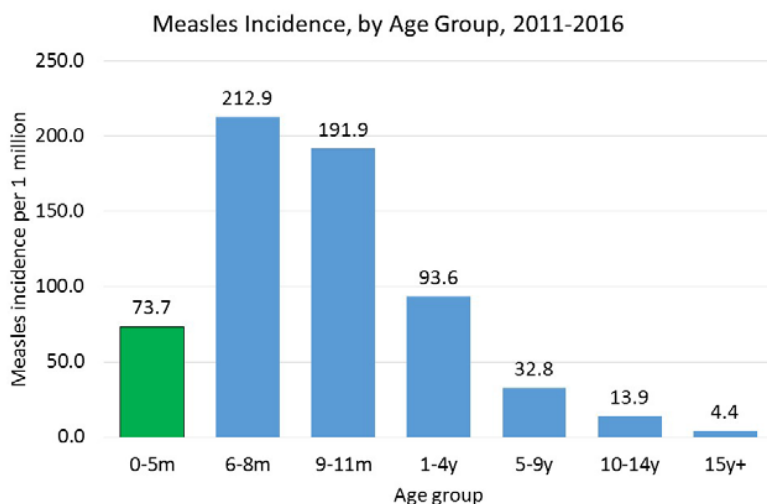
### Epidemiology of measles among infants <6 months

Out of a total of 390,522 confirmed\* measles cases of all ages during 2011-2016 in the countries included in this analysis, 16,953 (4.3%) were among infants <6 months (Figure 1). The largest numbers of measles cases <6 months were in countries in the African Region (AFR; 6,312 cases, 37.2%) and the Western Pacific Region (WPR; 5,354, 31.6%). This figure is an under-representation of the actual number of infant cases in the South-East Asian Region (SEAR) and the European Region (EUR) because most countries in those regions were excluded due to case ages only reported in full years.



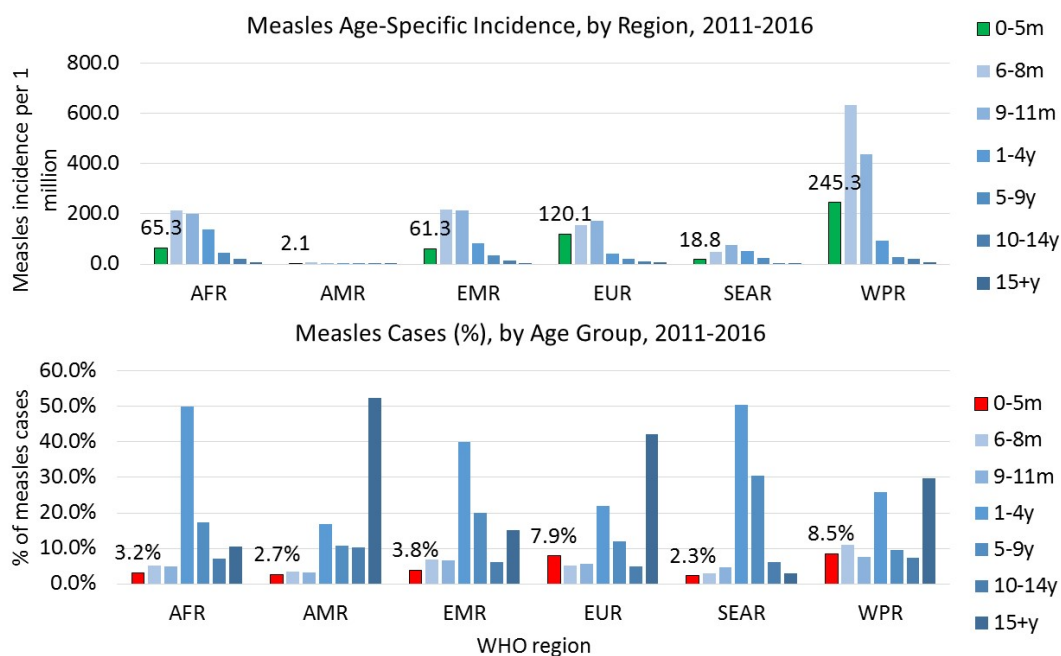
**Figure 1.** Ages of confirmed measles cases, and cases age <6 months by region, 2011-2016.

Compared to other age groups, infants <6-months were disproportionate among measles cases. Although infants <6 months comprise 1.2% of the total population of the countries included in the analysis, they comprised 4.3% of all measles cases in these countries.



**Figure 2.** Age-specific average annual measles incidence per 1 million population, 2011-2016.

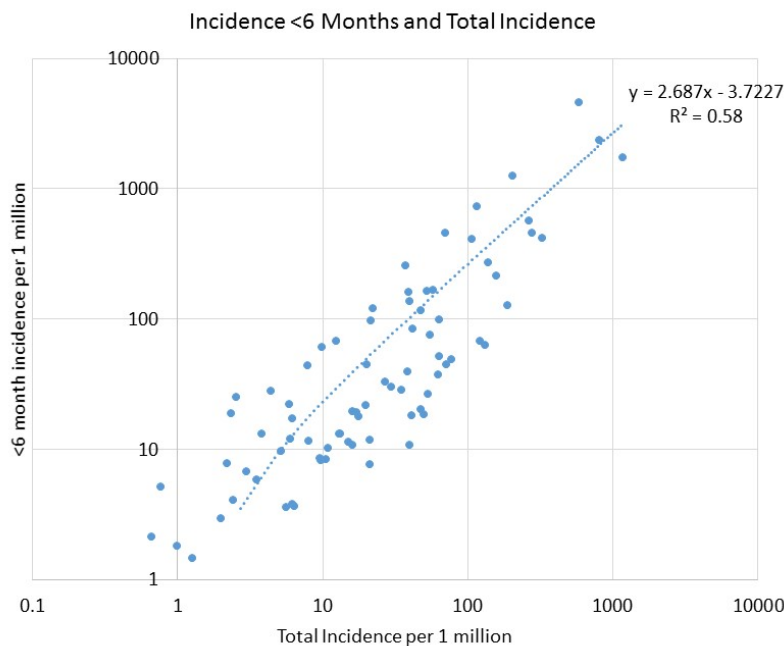
Average annual measles incidence among infants <6 months during 2011-2016 was 73.7 confirmed cases per 1 million population (Figure 2). Age-specific incidence was highest among 6-8-month-olds (212.9 per 1 million), followed by 9-11-month-olds (191.9 per 1 million). The age-specific incidence for infants <6 months was higher than that of older age groups including 5-9 years, 10-14 years, and ≥15 years.



**Figure 3.** Age-specific incidence and percent of cases by age group, stratified by region, 2011-2016.

Compared to the <6-month incidence across all regions (73.7 cases per 1 million), the two regions with the highest <6-month incidences were EUR (120.1 per 1 million, figure based on 9 out of 39 EUR countries) and WPR (245.3 per 1 million) (Figure 3). The lowest <6-month incidence occurred in the Region of the Americas (AMR; 2.1 per 1 million).

Across all WHO regions, the highest age-specific incidence was among the 6-8 month age group and the 9-11 month age group (Figure 3). In EUR and WPR regions, the incidence among infants <6 months was higher than the incidence among older children aged 1-4 years. The percentage of all measles cases that were <6 months was highest in EUR (7.9%) and WPR (8.5%), notably the same two regions with the highest <6 month incidences. In the other regions, the percentage of measles cases that were <6 months ranged from 2.3% to 3.8%.



**Figure 4.** Correlation between incidence <6 months and total incidence (all ages), 2011-2016.

There was a strong and generally linear correlation between incidence in the <6 month age group and total incidence among all ages ( $R^2 = 0.58$ ,  $p < 0.0001$ ) (Figure 4). In countries where overall incidence was high, <6-month incidence also tended to be high.

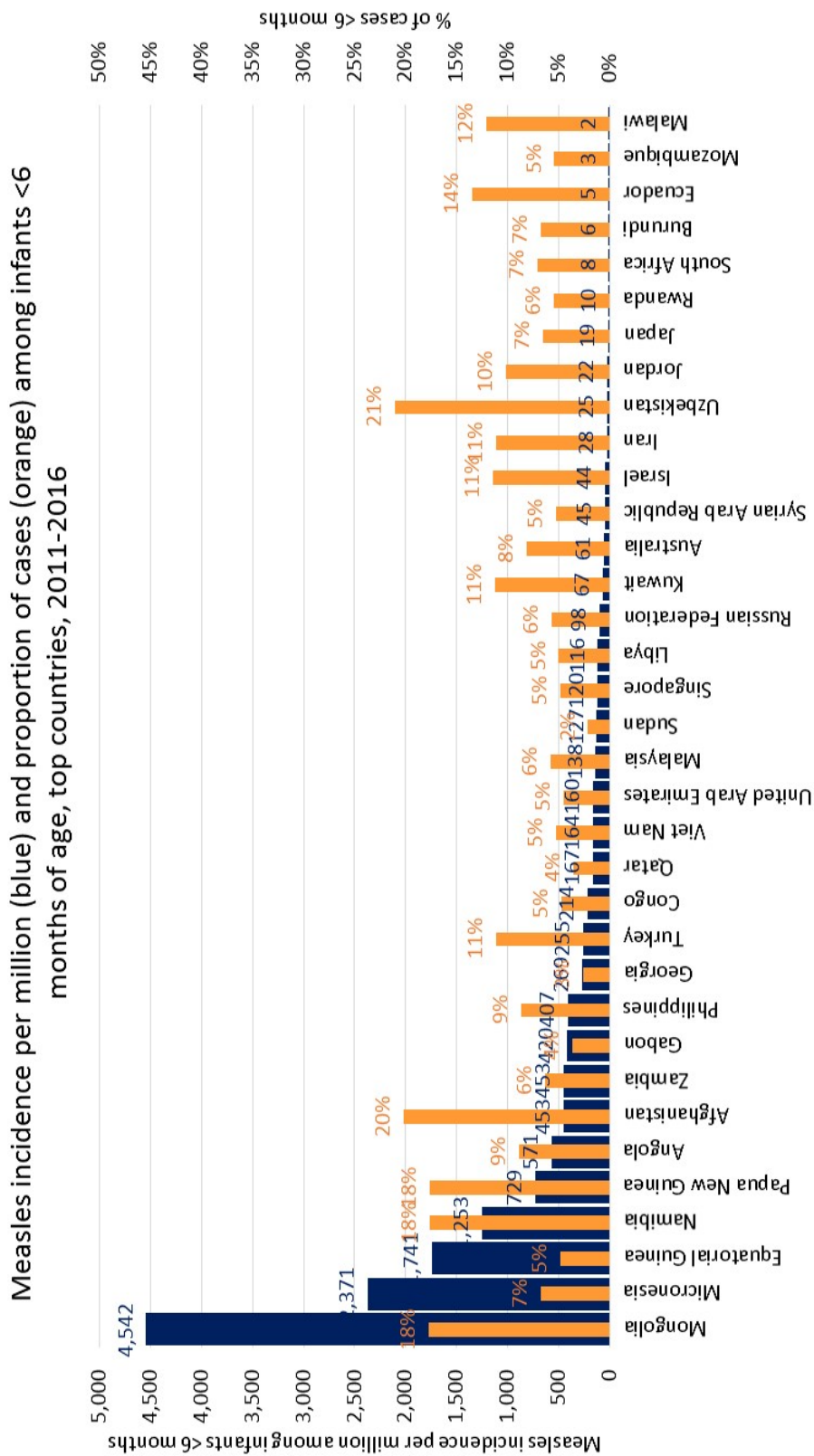


Figure 5. Measles incidence per 1 million and proportion of cases among infants <6 months of age, top countries, 2011-2016.



The countries with the highest <6-month average annual incidence during 2011-2016 were Mongolia, Micronesia, Equatorial Guinea, Namibia, and Papua New Guinea (Figure 5; shown in blue bars). All of these countries had large outbreaks at some point during 2011-2016. The percentage of all confirmed cases that were <6 months ranged from 0% (Djibouti, not shown in Figure) to 21% (Uzbekistan). The average proportion of cases that were <6 months old in a country was 5.2%, and the median was 3.5% (Q1 - Q3: 2.3% - 6.1%).

### **Bivariate (unadjusted) analysis of associations between country/programmatic characteristics and measles among infants <6 months**

In order to estimate associations between country/programmatic characteristics and measles among infants <6 months, we used three types of regression models to estimate associations with: 1) incidence per million among infants <6 months (a continuous variable), 2) proportion of cases among infants <6 months (a continuous variable), and 3) a pre-determined cut-off for a “high” proportion of cases among infants <6 months ( $\geq 5\%$  versus  $< 5\%$ ).

In bivariate unadjusted regression analyses, some characteristics were found to be associated with at least one of the measures indicating disproportionately more measles among infants <6 months compared to other ages. Specifically, countries with the following characteristics had either increased proportions of cases among infants <6 months or higher incidence among infants <6 months: WPR, upper-middle income,  $\geq 95\%$  MCV1 coverage, 80-89% or 90-94% MCV2 coverage, and MCV2 introduced. Several of the country/programmatic characteristics that we analyzed had no statistically significant associations with any of the three measures of measles among infants <6 months of age, including age at MCV1 or MCV2 administration, year of MCV1 or MCV2 introduction, number of years since last SIA, birth rate, and population density.

### **Multivariate (adjusted) analysis of associations between country/programmatic characteristics and measles among infants <6 months**

In multivariate regression, variables were included in a fully adjusted model if they were significantly associated in at least one of the regression models. The only variable that was significant when adjusting for all other variables was  $\geq 95\%$  MCV1 coverage, which was associated with a higher proportion of cases among infants <6 months.

### **Limitations**

This epidemiologic analysis of measles case-based surveillance data has several limitations. First, data from several countries were excluded from these analyses because they contained incomplete age data. This included a majority of EUR countries, and almost all SEAR countries. Consequently, some countries with recent large outbreaks (e.g., Romania) were not included in this analysis. It would be beneficial to be able to include such countries in the analysis. Second, the quality of some of the data used in this analysis may be sub-optimal. The sensitivity of the case-based surveillance data is unknown. Sensitivity of surveillance data may vary by age groups even within the same country, but we were not able to measure or estimate that. There may be reporting bias in which younger cases are more likely to be reported (younger infants may be more likely to have severe disease and require medical care). Vaccination coverage data estimates are based on countries' administrative data and WHO/UNICEF estimates, and the quality probably varies in different regions and/or countries. Third, surveillance data from India do not represent a truly case-

based surveillance system, so those data were included in the epidemiologic analysis, but were not included in the regression analysis. Fourth, this was an ecologic analysis at the country level rather than an analysis of individual-level data. This limits our ability to investigate how individual level characteristics such as family composition or maternal immunization affect infants. Our results can only be generalized at the country level. Fifth, due to its observational nature, results from this study can imply only association, and not causation.

## **Conclusions**

During 2011-2016, there were almost 17,000 confirmed measles cases among infants <6 months in the countries included in our analysis. There was a significant linear correlation between incidence in the <6 month age group and total incidence among all ages. Multivariate adjusted analysis showed the only variable significant associated with a higher proportion of cases among infants <6 months of age was high MCV1 coverage.

Future research should attempt to determine the source of measles transmission to infants <6 months. Family structures and transmission patterns should be studied to determine whether these infant cases are primary or secondary cases in families, whether nosocomial transmission to infants is a problem, and the role of maternal immunity sourced from vaccination or infection. Answering these questions will help to determine whether infants <6 months must be protected directly through vaccination, or whether they can be protected indirectly by reducing or eliminating transmission in older children and adults. Outbreak investigations in which these data can be collected should be supported in representative communities.

## 2. Systematic literature review and meta-analyses of the benefits and risks of measles vaccination below 6 months of age

Laura Nic Lochlainn, Susan Hahné, RIVM, 8<sup>th</sup> September 2017

A comprehensive systematic review and meta-analysis of measles containing vaccines (MCV) administered to infants <9 months of age was conducted in 2015 by the National Institute for Public Health and the Environment (RIVM) in the Netherlands.<sup>1</sup> The authors concluded that humoral immunogenicity was dependent on age of MCV, as well as on the vaccine strain and presence of maternal antibodies. Based on this systematic review and meta-analysis, and other evidence, SAGE made recommendations that infants from 6 months of age receive a supplementary dose of MCV under certain conditions<sup>2</sup>.

However, recent outbreaks have found many cases of measles are occurring in children less than 6 months of age. As a result, countries have requested information on the benefits and risks of providing MCV <6 months of age. Therefore, RIVM conducted an updated systematic review and meta-analysis with the following primary questions:

- What is the immunogenicity, duration of immunity, efficacy and effectiveness of MCV (M, MR and MMR) when given to infants younger than 6 months of age (as compared infants aged 6-8 months).
- Does a dose of MCV administered <6 months of age blunt the immune response to a subsequent dose of measles vaccine?
- Is the safety profile for infants vaccinated with MCV <6 months of age comparable with infants vaccinated with MCV at 6-8 months of age?

An initial literature search was carried out on 01 June 2015 for any articles published in relevant databases reporting MCV <9 months.<sup>1</sup> An updated search was carried out on 13 April 2017 for articles published after 01 January 2015 reporting MCV <6 months.

Data on the following outcomes were extracted from included studies: immunogenicity (humoral and cellular), vaccine efficacy or effectiveness (VE), duration of immunity, blunting and safety. Where appropriate, results were stratified by age at administration of MCV in months. Where sufficient data was available, results were pooled by meta-analyses. Heterogeneity between results of different studies were examined with forest plots and quantitatively using the I<sup>2</sup> statistic. Where possible, random effects meta-regression was employed. The quality of all included studies was assessed using the GRADE methodology.

From the initial literature search carried out in June 2015, 867 references were identified and 18 met criteria for inclusion in the updated review. Following the updated literature search in April 2017, an additional 186 references were identified and one met criteria for inclusion. Therefore, a total of 19 studies from both searches were included. The majority of included studies (n=16) were from Africa, while two were from Asia and one from Europe.

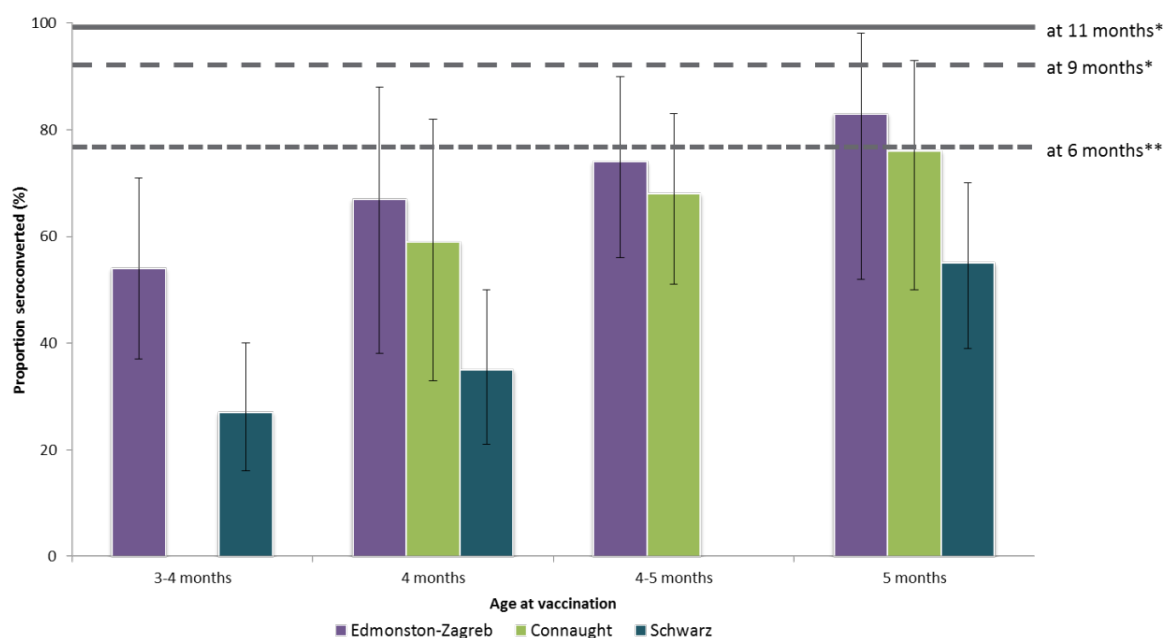
<sup>1</sup> Nic Lochlainn, L. et al., 2015 Measles vaccination below 9 months of age: Systematic literature review and meta-analyses of effects and safety. Available at:

[http://www.who.int/immunization/sage/meetings/2015/october/2\\_MCV\\_below\\_9\\_months\\_Effect\\_safety\\_28092015.pdf](http://www.who.int/immunization/sage/meetings/2015/october/2_MCV_below_9_months_Effect_safety_28092015.pdf)

<sup>2</sup> World Health Organization. "Measles vaccines: WHO position paper, April 2017—Recommendations." Vaccine (2017).

The pooled estimates for seroconversion following MCV <6 months were derived from five studies and found that MCV at 4 months of age increased from 50% (95% CI 29-71) to 67% (51-81%) following MCV at 5 months of age.<sup>3,4,5,6,7,8</sup> As a reference, the proportion seroconverted following MCV1 at 6 months of age (of 76%)<sup>1</sup>, at 9 months of age (92%)<sup>9</sup> and at 11 months of age (98%)<sup>9</sup> were included in Figure 1 where it can be seen that seroconversion rates following MCV1 <6 months of age are lower than the reference values.

The proportion of infants seroconverting was found to be further dependent on the vaccine strain used, with a seroconversion rate of 83% achieved at 5 months with the Edmonston-Zagreb strain (Figure 1).



**Figure 1: Pooled estimates of the proportion seroconverted by age of MCV (4-5 months), derived from five studies. Error bars present 95% confidence intervals.** \*This horizontal line represents the proportion of infants seroconverted following MCV at 6 months (small dashed line) Nic Lochlainn et al., 2015<sup>1</sup>. \*\*The horizontal lines represent the median proportion of infants seroconverted following MCV at 9 months (wide dashed line) and 11 months (filled line) Moss and Scott, 2009<sup>9</sup>.

<sup>3</sup> Anonymous. Measles immunity in the first year after birth and the optimum age for vaccination in Kenyan children. Collaborative study by the Ministry of Health of Kenya and the World Health Organization. Bull World Health Organ. 1977;55(1):21-31.

<sup>4</sup> Khanum S, et al., Comparison of Edmonston-Zagreb and Schwarz strains of measles vaccine given by aerosol or subcutaneous injection. Lancet. 1987;1(8525):150-3.

<sup>5</sup> Ndumbe PM, et al., Comparison of Edmonston-Zagreb, Connaught and Schwarz measles vaccines in Cameroonian infants aged 3-8 months. Vaccine. 1995;13(3):276-80.

<sup>6</sup> Rogers S, et al., Immunogenicity of standard dose Edmonston-Zagreb measles vaccine in highland Papua New Guinean children from four months of age. J Trop Med Hyg. 1991;94(2):88-91.

<sup>7</sup> Jensen TG, et al. Trials of Edmonston-Zagreb measles vaccine in Guinea-Bissau: serological responses following vaccination with Edmonston-Zagreb strain at 4-8 months versus vaccination with Schwarz strain at 9-12 months of age. Vaccine. 1994;12(11):1026-31.

<sup>8</sup> World Health Organization. Expanded Programme on Immunisation: Seroconversion after measles immunisation - Tanzania. WER. 1981;30:3.

<sup>9</sup> Moss, W.J. and Scott, S. 2009 "WHO Immunological Basis for Immunization Series Module xx: Measles." Geneva, Switzerland.

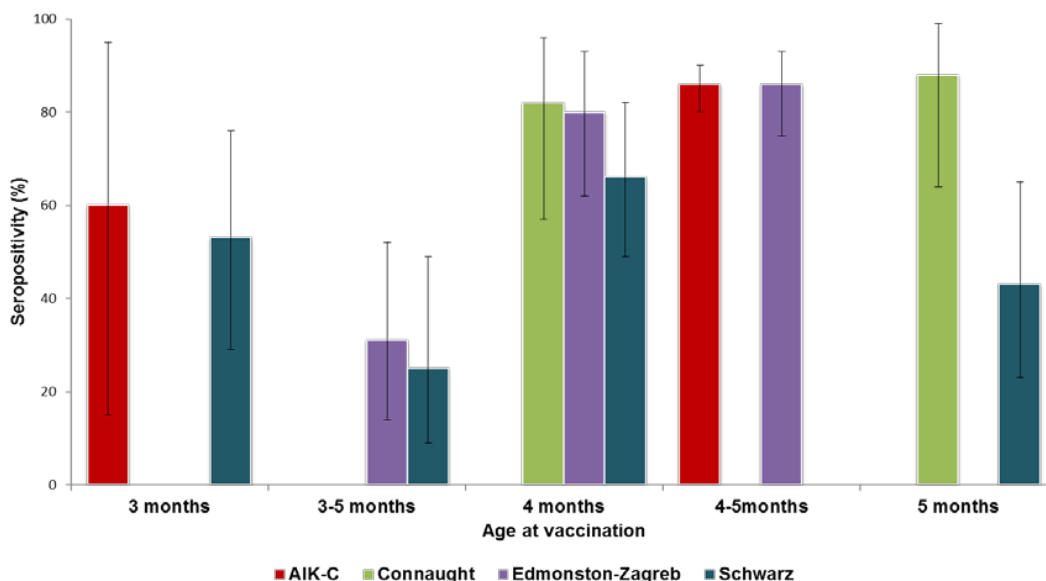
GMTs were found to be higher following MCV <6 months compared to ≥6 months of age, but results for MCV <6 months were derived from only two studies.<sup>10,11</sup>

There was no evidence to assess measles avidity following MCV <6 months of age.

One study was found comparing cellular immunity among unvaccinated infants and infants vaccinated with MCV1 at 4 months and 9 months of age. They study found infants vaccinated at 4 months had higher IFN-γ memory T-cell responses at 9 months compared to the unimmunized group. They also found that the presence of maternal antibodies had no effect on memory T-cell responses nor did the number of MCVs the infants received.<sup>12</sup>

Estimates of the proportion seropositive by age of MCV ranging from 3 to 5 months, pooled across strain and titre were derived from eight studies.<sup>13,14,15,16,17</sup>

Seropositivity was found to increase with age and to be strain dependent (Figure 2). The overall pooled estimate for seropositivity following MCV <6 months was 68% (95%CI 58-78).



**Figure 2: Pooled estimates of the proportion seropositive by age of MCV (3-5 months) and vaccine strain derived from seven studies. Error bars present 95% confidence intervals.**

<sup>10</sup> Ko B, et al.,. Neutralising antibody responses to two doses of measles vaccine at 5 and 13 months of age in the United Kingdom. *Commun Dis Public Health*. 1999;2(3):203-6.

<sup>11</sup> Whittle HC, et al. Effects of dose and strain of vaccine on success of measles vaccination of infants aged 4-5 months. *Lancet*. 1988;1(8592):963-6.

<sup>12</sup> Njie-Jobe J, et al. Immunological impact of an additional early measles vaccine in Gambian children: responses to a boost at 3 years. *Vaccine*. 2012;30(15):2543-50.

<sup>13</sup> Martins C, et al. Measles virus antibody responses in children randomly assigned to receive standard-titer edmonston-zagreb measles vaccine at 4.5 and 9 months of age, 9 months of age, or 9 and 18 months of age. *J Infect Dis*. 2014;210(5):693-700.

<sup>14</sup> Kiepiela P, Coovadia HM, Loening WE, Coward P, Botha G, Hugo J, et al. Lack of efficacy of the standard potency Edmonston-Zagreb live, attenuated measles vaccine in African infants. *Bulletin of the World Health Organization*. 1991;69(2):221-7.

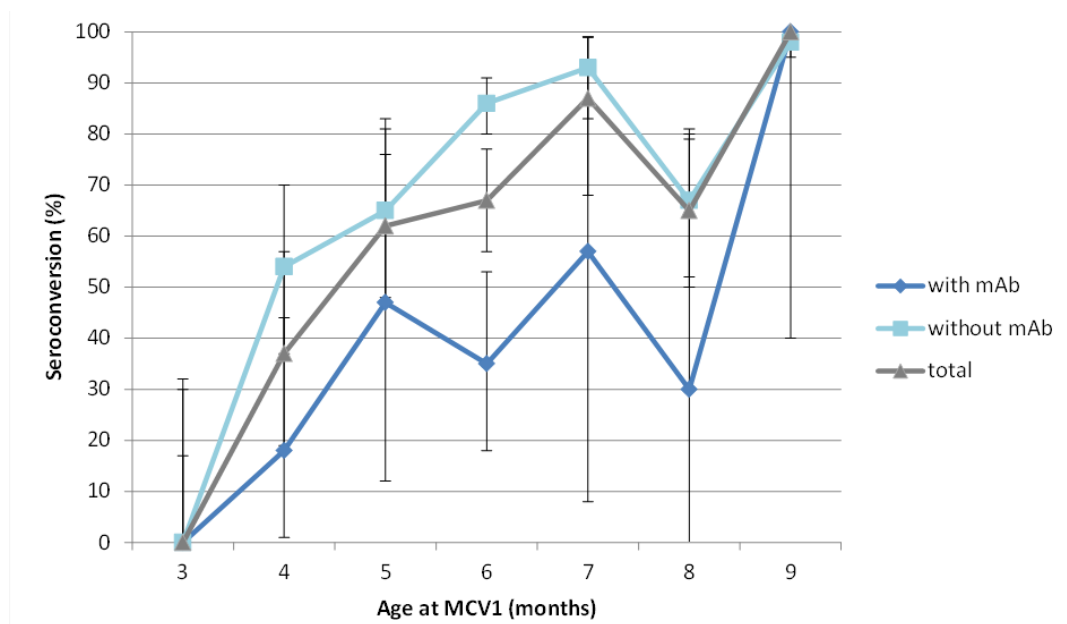
<sup>15</sup> Sakatoku H, Nakano T, Arai S, Afari EA. Antibody response to measles immunization in rural Ghanaian infants. *J Trop Pediatr*. 1994;40(5):291-3.

<sup>16</sup> Tidjani O, Grunitsky B, Guerin N, Levy-Bruhl D, Lecam N, Xuereff C, et al. Serological effects of Edmonston-Zagreb, Schwarz, and AIK-C measles vaccine strains given at ages 4-5 or 8-10 months. *Lancet*. 1989;2(8676):1357-60.

<sup>17</sup> Martins CL, et al. Protective efficacy of standard Edmonston-Zagreb measles vaccination in infants aged 4.5 months: interim analysis of a randomised clinical trial. *BMJ*. 2008;337:a661.

For vaccine efficacy and effectiveness and safety, there were two eligible studies following MCV1 <6 months which had small sample sizes. One study reported vaccine effectiveness of 54% (95%CI 0-84%) among infants vaccinated with MCV1 below 5 months (n=5), and vaccine effectiveness of 37% (95%CI 0-74%) among infants vaccinated with MCV1 at 6-8 months (n=11).<sup>18</sup> The second study reported vaccine efficacy among infants vaccinated with MCV1 at 4.5 months of 91% (95%CI 62-98) (n=43), vaccine efficacy against measles related hospitalisation was 100% (95%CI 46-100)] and against measles related death [100% (95%CI -42-100)]. However, the follow-time was very short.<sup>17</sup> Only two studies were identified reporting duration of immunity following MCV <6 months and ≥ 6 six months of age. One study infants who responded to MCV1 had significantly higher responses four to six weeks following MCV2 at 13 months, compared to those who did not respond to MCV1.<sup>Error!</sup> *Martins et al.*, examined the GMTs of infants following vaccination with MCV1 at 4.5 months and MCV2 at 9 months using standard-titer Edmonston-Zagreb. Overall, they found that at 24 months, infants vaccinated early maintained high protective antibody levels.<sup>Error! Bookmark not defined.</sup>

The effect of maternal antibodies following MCV <6 months was examined as a secondary question in this review. Results of the meta-analysis of the proportion seroconverted stratified by presence of maternal antibodies found that the proportion seroconverted is higher in infants without maternal antibodies compared to those with maternal antibodies (Figure 3).



**Figure 3: Proportion seroconverted by month of MCV, stratified by presence of maternal antibodies.**

Seventeen of nineteen included studies were observational. Therefore, for all outcomes, the quality of evidence was found to be moderate, low or very low but of importance.

<sup>18</sup> Hull HF, et al., Measles mortality and vaccine efficacy in rural West Africa. *Lancet*. 1983;1(8331):972-5.

**Conclusions:**

The authors concluded that humoral immunogenicity following MCV<6 months of age was dependent on age of MCV and levels of maternal antibodies. In addition, they concluded that there was limited evidence available for cellular immunity, vaccine effectiveness, duration of immunity, safety and blunting. This paucity of data, together with heterogeneity between studies, warrants caution when interpreting the results.

In order to obtain reliable evidence to inform decisions, the authors recommend conducting a trial, with a long follow-up after subsequent doses of MCV in an endemic area with MCV at 4-6-9 months, or observational case-control studies in high endemicity areas where MCV has been given at 6 months of age in the past e.g. South Africa or Papua New Guinea. Finally, seroepidemiological studies in low and middle income countries could provide a better understanding of population immunity towards measles and other vaccine preventable diseases.

**SAGE WG Conclusions and Recommendations:**

- The data from the systematic review are insufficient to recommend vaccination under 6 months of age.
- The current policy on vaccination of infants from 6 months of age is already broad and inclusive, so there is no need to expand the current recommendations.
- Findings support the importance of sustained high population immunity achieved through high coverage as the primary strategy for protecting infants under 6 months of age, supported by high quality surveillance and coverage monitoring.
- Further research is needed to address the substantial information gap and to better understand the transmission source, the disease burden and the role of factors such as maternal immunity and blunting among affected infants less than 6 months of age. Community-based outbreak investigations to determine actual sources of infection for children <6 months of age are encouraged. A better understanding of measles virus transmission to young infants (e.g. from school-age siblings or parents) would enable effective targeting of these transmission drivers.
- Improved data quality and tools to be able to interpret data according to data quality, completeness of surveillance and other contextual factors at country and region levels are needed.
- Clinical trials in infants <6 months may be informative to improve the evidence concerning effectiveness, safety and long term effects on the effectiveness of subsequent MCV doses (i.e. MCV1 and MCV2). In addition, studies in countries which have introduced MCV1 at 6 months could add to the body of evidence

## **Should an additional dose of measles-containing vaccine be recommended for HIV-infected adolescents and adults?**

### **Introduction**

At the October 2015 meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization, SAGE recommended that an additional dose of measles-containing vaccine be administered to HIV-infected children receiving highly active antiretroviral therapy (HAART) following immune reconstitution. In considering this recommendation, SAGE requested evidence on the need for revaccination of HIV-infected adolescents and adults. This report summarizes the available evidence and provides the basis for policy recommendations.

For the purposes of this review, HIV-infected adolescents and adults refer to individuals not infected through mother-to-child HIV transmission. Although an increasing number of perinatally-infected children are surviving into adolescence and adulthood, HIV infection commonly precedes exposure to measles vaccine or wild-type virus in these individuals. Consequently, immune responses to measles vaccine develop in the context of a compromised immune system. This temporal sequence is inverted in HIV-infected adolescents and adults who acquire HIV infection later in life through sexual or other modes of HIV transmission after exposure to measles vaccine virus. This latter group of HIV-infected adolescents and adults is the focus of this review.

### **Current recommendations on measles vaccination of HIV-infected adolescents and adults**

Current recommendations on measles vaccination of HIV-infected adolescents and adults support vaccination of those who are potentially susceptible and not severely immunosuppressed. The World Health Organization's position paper on measles vaccines published in April 2017 states:

“Given the severe course of measles in patients with AIDS, measles vaccination should be routinely administered to potentially susceptible, asymptomatic HIV-infected children and adults. Vaccination may even be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to conventional definitions.”

The Advisory Committee on Immunization Practices in the United States recommends two doses of MMR in HIV-infected adults without immunologic evidence of severe immunosuppression and measles immunity.

“Adults with human immunodeficiency virus (HIV) infection and CD4+ T-lymphocyte count  $\geq 200$  cells/ $\mu\text{l}$  for at least 6 months who do not have evidence of measles, mumps, or rubella immunity should receive 2 doses of MMR at least 28 days apart. Adults with HIV infection and CD4+ T-lymphocyte count  $< 200$  cells/ $\mu\text{l}$  should not receive MMR.”

No current guidelines recommend measles revaccination of HIV-infected adolescents or adults after immune reconstitution with HAART.



## **Burden of measles in HIV-infected adolescents and adults**

Outside of case reports and small case series, limited data exist on the burden of measles in HIV-infected adults, although large measles outbreaks have occurred in populations with a high prevalence of HIV infection, including South Africa (2009-2011) and Malawi (2010). Eight cases of measles inclusion body encephalitis were reported in immunocompromised, HIV-infected adults in South Africa. No published data are available on the incidence of measles or disease severity in HIV infected versus non-infected adults in the same population to determine if HIV-infected persons are at higher risk of disease or death.

## **Systematic review of measles seroprevalence and measles vaccine immunogenicity and safety in HIV-infected adolescents and adults**

To provide SAGE with evidence on the need for revaccination of HIV-infected adolescents and adults, we conducted a systematic review of measles seroprevalence and measles vaccine immunogenicity and safety in HIV-infected adolescents and adults. This systematic review consisted of a search of Medline (Ovid), Embase, Cochrane Library, PubMed, LILACS, INDMED, and WHO GHIL databases to identify studies published from the date of establishment of each database to March 16, 2017. The search terms were adapted for each database and included HIV-related keywords in conjunction with measles vaccine-related keywords. References of included studies and relevant reviews were further reviewed to capture pertinent publications not identified in the database search. Search results from each database were merged and duplicates removed. The records were imported into Covidence online software (Veritas Health Innovation) to facilitate screening and full-text review. Titles and abstracts were reviewed by two independent reviewers to exclude irrelevant studies. The remaining studies underwent full-text review by two independent reviewers using pre-specified inclusion and exclusion criteria. Disagreements between reviewers were adjudicated to achieve consensus. Exclusion criteria included review articles, studies in non-human species or studies published in non-English languages. We further excluded studies limited to children younger than 18 years of age or those who were perinatally-infected. Relevant data were extracted independently by two reviewers using standardized data extraction forms and imported into Stata statistical software version 14 (StataCorp). Due to significant heterogeneity in study methodology and outcome reporting, meta-analysis was not considered appropriate. This heterogeneity included differences in the time between exposure to measles virus (wild-type or vaccine) and immunological testing, assay methodology, thresholds to determine seropositivity, and the proportion of participants receiving antiretroviral therapy (ART). The database search identified 1,133 unique publications of which 30, published between 1991 and 2017, were judged to meet inclusion criteria (Figure 1).

## **Measles seroprevalence in HIV-infected adolescents and adults**

Twenty-seven studies involving 9,607 HIV-infected adolescents and adults reported estimates of the proportion who were measles seropositive (Figure 2). History of measles or measles vaccination was generally poorly documented. The median measles seroprevalence was 92% (IQR: 85.2 %-95.0%). Ten studies included an HIV-uninfected comparison group but no study reported statistically significant differences in measles seroprevalence between HIV-infected and HIV-uninfected participants (Figure 3). Three of seven studies that quantified measles antibody levels reported significantly lower antibody levels in HIV-infected participants compared to HIV-uninfected controls, although the clinical and public health impact of these differences is unclear. Eleven studies reported younger age or more recent birth cohort as a

significant risk factor for measles seronegativity, consistent with the hypothesis that measles seroprevalence is higher among HIV-infected populations with a higher risk of exposure to wild-type measles virus.

### **Immunogenicity of measles-containing vaccines in HIV-infected adolescents and adults**

Six studies involving 109 seronegative HIV-infected adults evaluated the immunogenicity of measles-containing vaccine. There was significant heterogeneity across these studies: the dates of publication ranged from 1993 to 2016 and follow-up ranged from 3 weeks to 24 months post-vaccination. Measles vaccine immunogenicity, defined by seropositivity at end of follow up, ranged from 0% to 56% (median 39%). Immunogenicity appeared to be higher in more recent studies conducted after the widespread introduction of ART, but the published data did not allow for more direct assessment of the impact of ART on measles vaccine immunogenicity in HIV-infected adolescents and adults. Of the three immunogenicity studies with an HIV-uninfected comparison group, only one study detected a statistically significant lower seroprevalence among HIV-infected adults ( $p=0.002$ ; Belaunzaran-Zamudio et al., 2009).

Three of six studies on MCV immunogenicity included interim time points after vaccination that demonstrate waning of vaccine-derived immunity among HIV-infected adults. One study reported similar antibody responses 3 months after vaccination between HIV-infected and uninfected participants (81% vs 86% seropositive) but significantly lower rates of seropositivity by 12 months among HIV-infected adults (35% vs 81%). However, similar cellular immune responses as measured by antigen-specific T-cell proliferation were observed at all time points (Belaunzaran-Zamudio et al., 2009).

### **Safety of MCVs in HIV-infected adolescents and adults**

Four studies assessed the safety of measles-containing vaccines in HIV-infected adolescents and adults and no severe adverse events were reported. Our search identified one well-publicized case report of fatal pneumonitis possibly attributable to measles vaccine virus. A 21-year-old man with AIDS and undetectable CD4+ T-lymphocyte count presented 11 months after receiving a second dose of measles vaccine. He was found to have characteristic multinucleated giant cells with intranuclear and intracytoplasmic inclusions on lung biopsy and measles vaccine virus was identified in lung tissue.

### **Evidence to inform SAGE recommendations**

1. The quality of evidence is low that measles seroprevalence does not differ between HIV-infected and uninfected adolescents and adults as it is based on cross-sectional observational studies.
2. The quality of evidence is very low on the immunogenicity of measles vaccine in HIV-infected adolescents and adults.
3. There is confidence in the conclusion that an additional dose of measles-containing vaccine is not warranted for HIV-infected adolescents and adults receiving antiretroviral therapy.

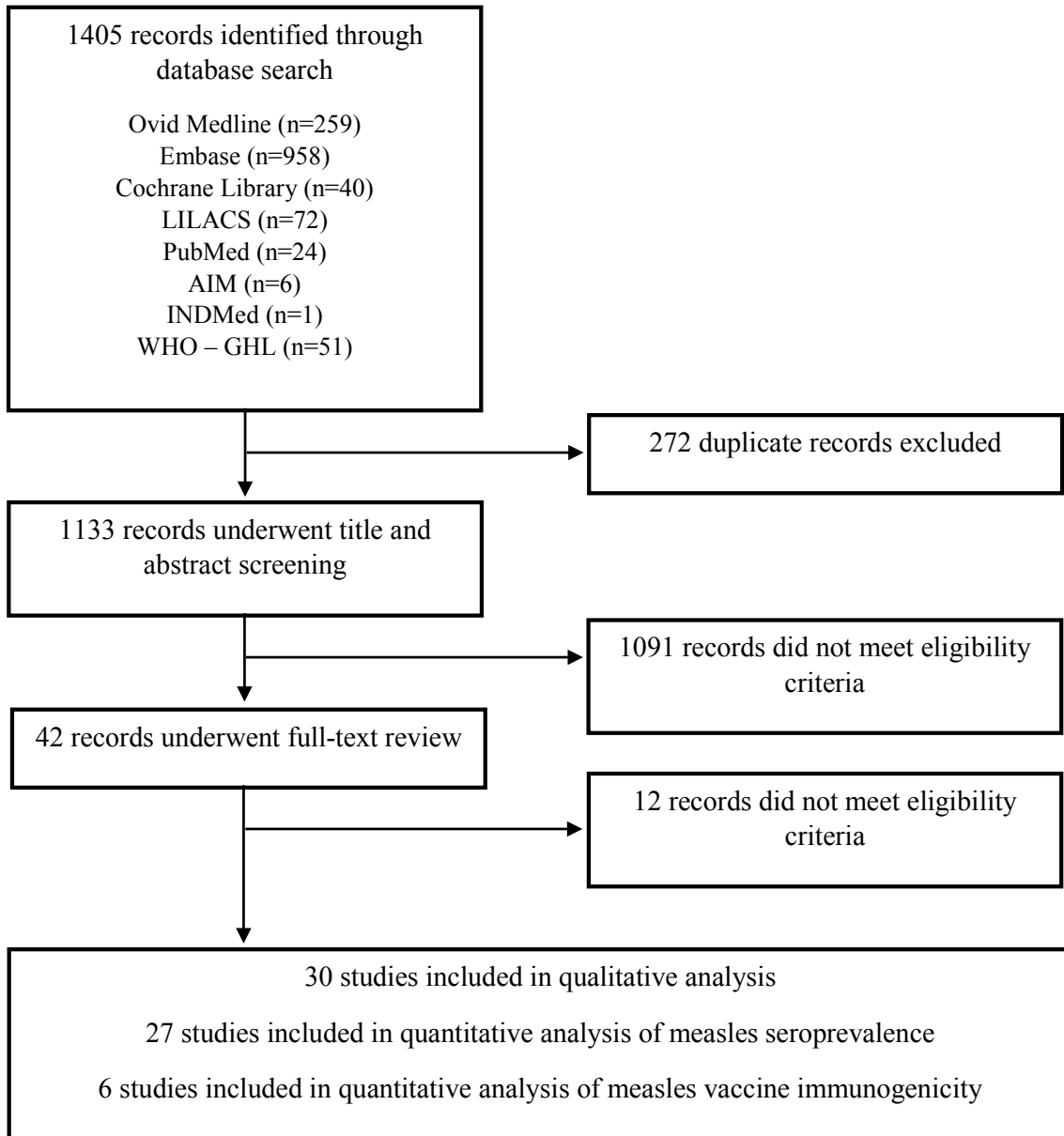
### **Draft Recommendations**

Current World Health Organization recommendations are that measles vaccination should be routinely administered to potentially susceptible, asymptomatic HIV positive children and

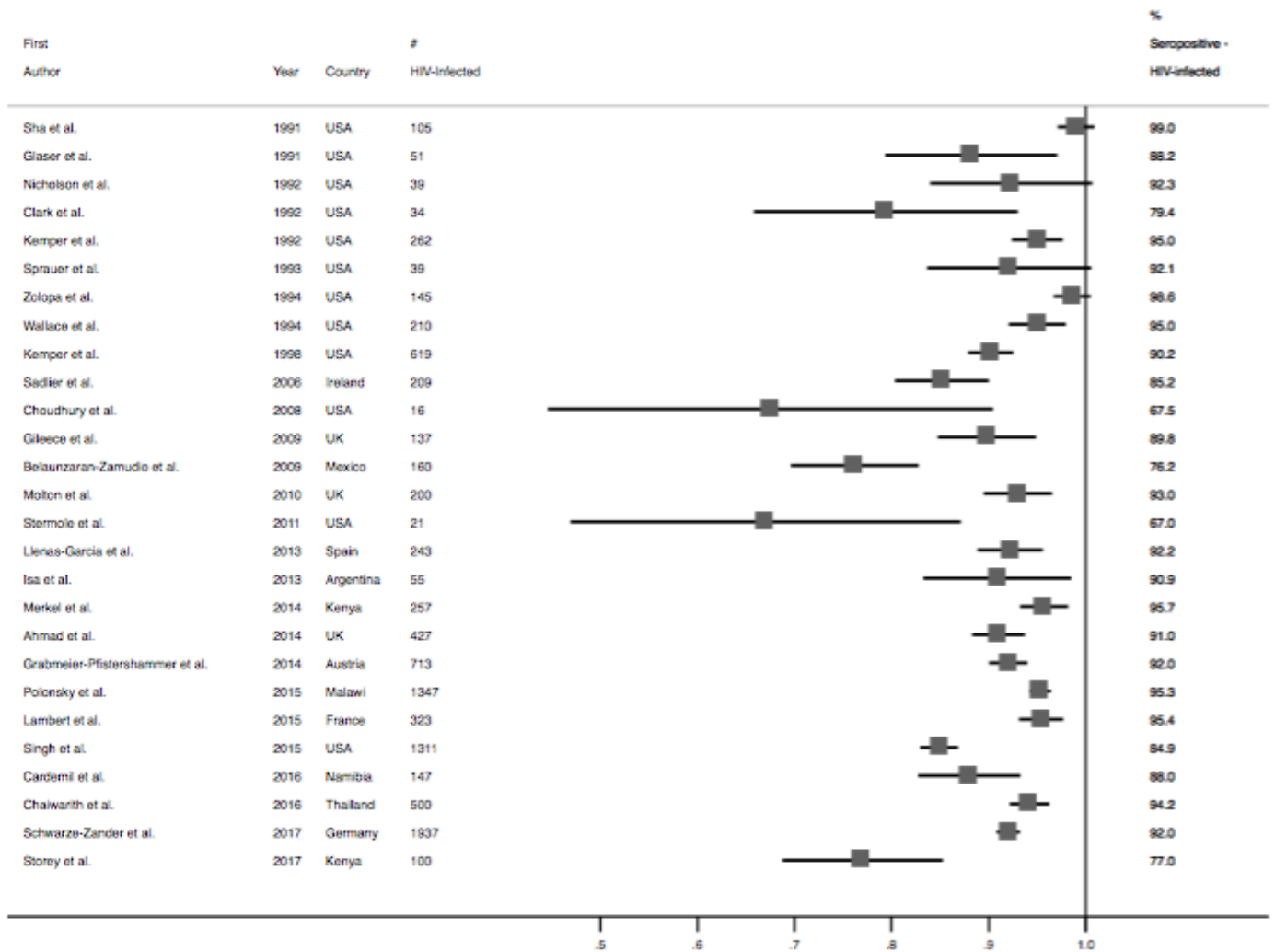
adults. Vaccination may be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to conventional definitions.

1. Studies of measles seroprevalence and measles vaccine immunogenicity among HIV-infected adults do not support the need for an additional dose of measles vaccine following immune reconstitution with HAART.
2. Measles susceptible adults, whether HIV infected or not, may require targeted vaccination efforts to achieve regional measles elimination goals.

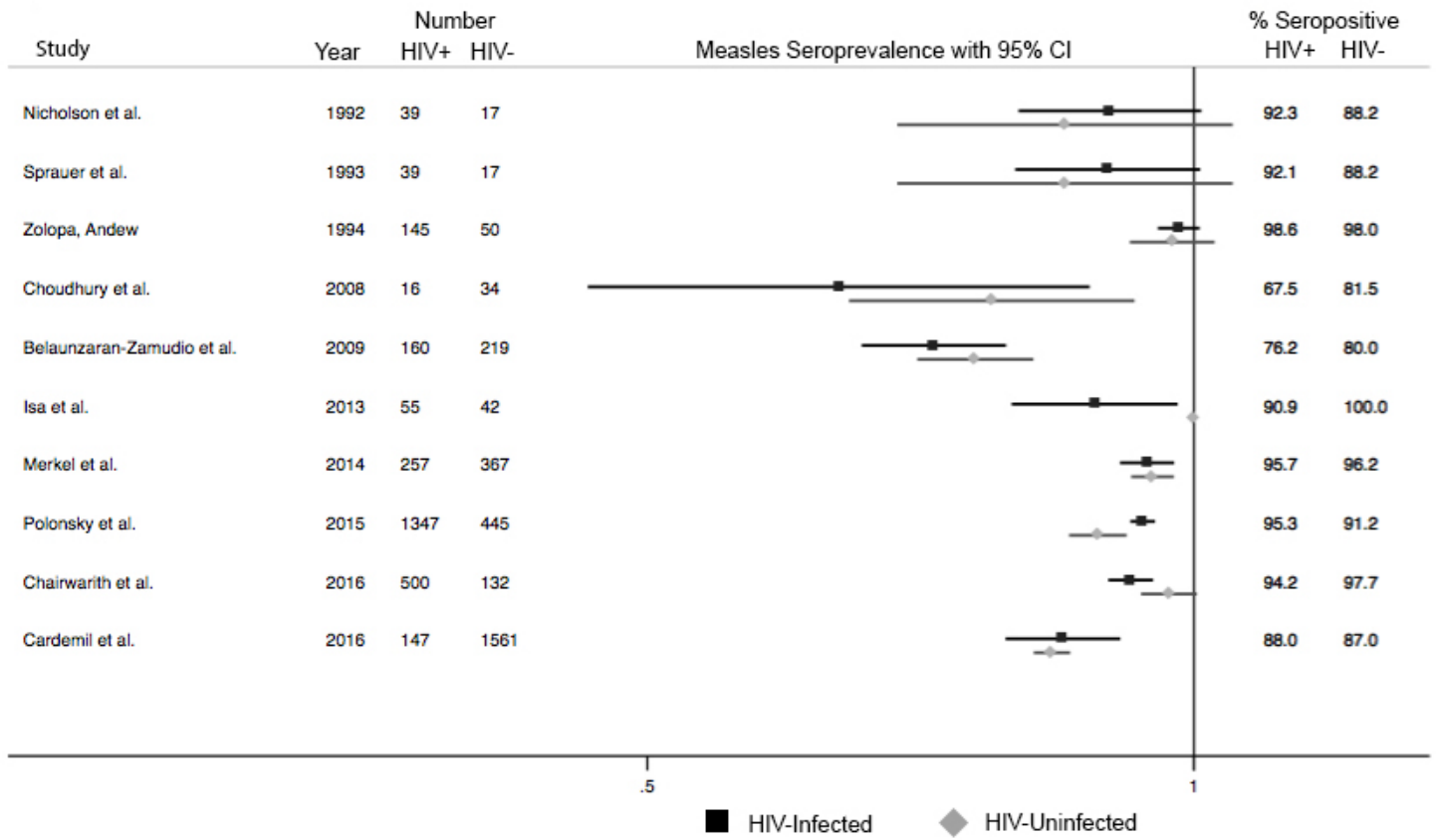
**Figure 1: Systematic review flow chart**



**Figure 2: Measles seroprevalence in HIV-infected adolescents and adults**



**Figure 3:** Measles seroprevalence in HIV-infected and uninfected adolescents and adults



**Figure 4:** Measles vaccine immunogenicity and safety in HIV-infected adolescents and adults

	<b>Number of HIV-Infected Adults Vaccinated</b>	<b>Number of HIV-Uninfected Adults Vaccinated</b>	<b>% HIV+ receiving ART</b>	<b>End of Follow-Up</b>	<b>Number of HIV+ Seropositive End of Follow-Up</b>	<b>Number of HIV- Seropositive End of Follow-Up</b>	<b>p-value</b>	<b>Interim Time-Points</b>	<b>Severe Adverse Events</b>
<b>Sprauer, 1993</b>	3	2	NR	3 weeks	0 of 3 (0%)	1 of 2 (50%)	p>0.05	-	None
<b>Wallace, 1994</b>	6	0	NR	1 year	2 of 6 (33%)	-	-	4 of 6 (67%) HIV+ seropositive at 3 months	None
<b>Belaunzaran-Zamudio, 2009</b>	26	21	84.6%	1 year	9 of 26 (35%)	17 of 21 (81%)	p = 0.002	21 of 26 (81%) HIV+ seropositive at 3 months 19 of 22 (86%) HIV- seropositive at 3 months	None
<b>Stermole, 2011</b>	7	0	NR	Max of 24 months	3 of 7 (43%)	-	-	-	NR
<b>Singh, 2015</b>	40	0	NR	Mean of 7.2 months	21 of 40 (53%)	-	-	-	NR
<b>Chaiwarith, 2016</b>	27	2	100%	48 weeks	15 of 27 (56%)	1 of 2 (50%)	p>0.05	20 of 27 (74%) HIV+ seropositive at 8-12 weeks 2 of 2 (100%) HIV- seropositive at 8-12 weeks	None

NR = not reported

## **Measles Seroprevalence in HIV-infected and HIV-uninfected adolescents and adults**

**Population:** HIV-infected adolescents and adults

**Intervention:** None

**Comparison:** HIV-uninfected adolescents and adults

**Outcome:** Measles seroprevalence

<b>PICO Question:</b> Is the seroprevalence of measles antibodies different among HIV-infected and HIV-uninfected adults?				
		Rating	Adjustment to rating	
<b>Quality Assessment</b>	No of studies/starting rating		10 observational studies	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious <sup>1</sup>	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	<b>Final numerical rating of quality of evidence</b>			<b>2</b>
<b>Summary of Findings</b>	<b>Statement on quality of evidence</b>		Evidence supports a low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.	
	<b>Conclusion</b>		We have a low level of confidence in the conclusion that that measles seroprevalence is not lower in HIV-infected than uninfected adolescents and adults.	

<sup>1</sup> No study showed a statistically difference in measles seroprevalence between HIV-infected and uninfected adults.

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## **Immunogenicity of MCV in HIV-infected and HIV-uninfected adolescents and adults**

**Population:** HIV-infected adolescents and adults

**Intervention:** Measles vaccination

**Comparison:** HIV-uninfected adolescents and adults

**Outcome:** Measles seroprevalence at end of follow-up

<b>PICO Question:</b> Is the immunogenicity of MCV different among MCV-naïve HIV-infected and HIV-uninfected adolescents and adults?				
		Rating	Adjustment to rating	
<b>Quality Assessment</b>	No of studies/starting rating		3 observational <sup>1</sup>	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	Serious inconsistencies <sup>2</sup>	-1
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not present	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	<b>Final numerical rating of quality of evidence</b>			<b>1</b>
<b>Summary of Findings</b>	<b>Statement on quality of evidence</b>		Evidence supports a very low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.	
	<b>Conclusion</b>		We have a very low level of confidence in our conclusions regarding the relative immunogenicity of MCV in HIV-infected and uninfected adolescents and adults.	

<sup>1</sup> Although these were clinical studies in which measles vaccine was administered to HIV-infected and uninfected adults, there was no randomization, placebo, nor masking of HIV-infection status.

<sup>2</sup> Two of 3 studies found a significant difference in immunological response between HIV-infected and HIV-uninfected vaccinees. There is significant heterogeneity in the methodology, point estimates and conclusions.

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## **Safety of MCV in HIV-infected and HIV-uninfected adolescents and adults**

**Population:** HIV-infected adolescents and adults

**Intervention:** Measles vaccination

**Comparison:** HIV-uninfected adolescents and adults

**Outcome:** Occurrence of adverse and serious adverse events

<b>PICO Question: Is the safety of MCV different among MCV-naïve HIV-infected and HIV-uninfected adolescents and adults?</b>				
		Rating	Adjustment to rating	
<b>Quality Assessment</b>	No of studies/starting rating		3 observational <sup>1</sup>	2
	Factors decreasing confidence	Limitation in study design	Serious limitations <sup>2</sup>	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not present	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	<b>Final numerical rating of quality of evidence</b>			<b>1</b>
<b>Summary of Findings</b>	<b>Statement on quality of evidence</b>		Evidence supports a very low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.	
	<b>Conclusion</b>		We have a very low level of confidence in our conclusion that the safety of MCV is not different in HIV-infected adolescents and adults as compared to HIV-uninfected	

<sup>1</sup> Although these were clinical studies in which measles vaccine was administered to HIV-infected and uninfected adults, there was no randomization, placebo, nor masking of HIV-infection status.

<sup>2</sup> Rare, serious adverse events, such as infection with measles vaccine virus, would not have been detected in these studies.

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# Report on BCG vaccine use for protection against mycobacterial infections including tuberculosis, leprosy, and other nontuberculous mycobacteria (NTM) infections

Prepared by the SAGE Working Group on BCG Vaccines and WHO Secretariat

22. September 2017

## List of abbreviations

AFR. <i>african region</i>	MDR-TB. <i>multidrug-resistant TB</i>
AMR. <i>antimicrobial resistances</i>	MDT. <i>multi-drug therapy, multidrug therapy</i>
BCG. <i>bacillus calmette-guérin</i>	MICs. <i>middle income countries</i>
BUD. <i>buruli ulcera disease</i>	MICS. <i>multiple indicator cluster surveys</i>
CFU. <i>colony forming units</i>	MOTT. <i>mycobacteria other than tuberculosis</i>
DHS. <i>demographic health surveys</i>	NRA. <i>national regulatory authority</i>
DRDR. <i>drug resistance determining regions</i>	NS. <i>needle and syringe</i>
DSJI. <i>disposable-syringe jet injectors</i>	NTM. <i>non-tuberculous mycobacterial</i>
DST. <i>drug susceptibility testing</i>	OPV. <i>oral polio vaccine</i>
EID. <i>early infant HIV diagnosis</i>	PB. <i>pauci-bacillary</i>
EMR. <i>eastern mediterranean region</i>	PEP. <i>post-exposure prophylaxis</i>
EUR. <i>european region</i>	PMTCT. <i>prevention of mother to child transmission</i>
G2D. <i>grade-2 disabilities</i>	POC. <i>point-of-care</i>
GLP. <i>global leprosy programm</i>	PQ'd. <i>prequalified</i>
GTB. <i>global TB programme</i>	PTB. <i>pulmonary tuberculosis</i>
HBsAg. <i>hepatitis B surface antigen</i>	R&D. <i>research and development</i>
HCWs. <i>health care workers</i>	SAGE. <i>strategic advisory group of experts on immunization</i>
HICs. <i>high income countries</i>	SDGs. <i>sustainable development goals</i>
IRIS. <i>immune reconstitution inflammatory syndrome</i>	SEAR. <i>south east asian region</i>
IUATLD. <i>international union against TB and lung disease</i>	TB. <i>tuberculosis</i>
JRF. <i>WHO/UNICEF Joint Reporting</i>	UHC. <i>universal health coverage</i>
LBW. <i>low birth weight</i>	VENICE. <i>vaccine european new integrated collaboration effort</i>
LICs. <i>low income countries</i>	WPR. <i>western pacific region</i>
LMICs. <i>lower-middle income countries</i>	WUENIC. <i>WHO/UNICEF estimates of national immunization Coverage</i>
MB. <i>multi-bacillary</i>	XDR-TB. <i>extensively drug-resistant TB</i>
MDGs. <i>millennium development goals</i>	

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## 1. Executive summary

**Background:** Bacillus Calmette-Guérin (BCG) vaccines continue to be the only vaccines in use for prevention of tuberculosis (TB). BCG vaccines were first used in 1921, subsequently rolled out in developed countries and since 1974, have been included in the WHO Expanded Programme on Immunization (EPI). The use of BCG in routine infant vaccination programmes (estimated coverage at 90%) is estimated to globally prevent 117,132 TB deaths per birth cohort in the first 15 years of life. Although BCG vaccines until now are not specifically indicated for prevention of leprosy, there is evidence that BCG vaccination has also contributed to the significant decline in leprosy incidence. Further, BCG has been found to be effective against other mycobacterial infections such as Buruli ulcer disease. Finally, BCG vaccination has also been reported to have beneficial non-specific effects (NSE), in particular reducing all-cause infant mortality in certain settings.

**Disease burden:** In spite of high vaccination coverage with BCG in 2015, there were an estimated 10.4 million new TB cases (142 per 100,000 population) reported worldwide. Of those, an estimated 1.8 million people died, including 210,000 children. About 1.2 million people (11%) developed HIV-associated TB and 480,000 multi-drug resistant TB. In addition, a quarter of the world's population has latent tuberculosis infections. Prevention of TB-related deaths relies mainly on two strategies: firstly, BCG vaccination of infants preferably at birth, and secondly, treatment of latent TB infection, mainly in HIV-infected persons and young childhood contacts of TB patients. Although the fight against leprosy has gained considerable success, more than 200,000 cases were notified in 2016 and the annual case detection rate is only slowly declining. The South-East Asia region (SEAR) accounts for 75% of the global leprosy burden and reported 161,263 new leprosy cases in 2016 but cases are reported in all regions.

**Current WHO recommendations:** WHO published the last BCG position paper in 2004 and recommended that, in settings where TB is highly endemic or where there is high risk of exposure to TB, a single dose of a BCG vaccine should be given to all infants at birth. A systematic review at the time showed little evidence that revaccination with BCG afforded additional protection, and revaccination was therefore not recommended. In low TB burden settings, many countries were advised to consider moving to limiting BCG vaccination to selective risk groups based on guidelines from the International Union against TB and Lung Disease (IUATLD). In an additional guidance note published in 2007, WHO provided specific guidance for children who are HIV infected or HIV exposed. It was recommended that BCG vaccine should not be given to children who were known to be HIV-infected. There are currently no formal WHO recommendations on the use of BCG vaccine to prevent *M. leprae* (leprosy) or other mycobacterial infections such as *M. ulcerans* (Buruli ulcer being the third most common mycobacterial disease in the world).

**Implementation:** Most countries have opted to recommend universal BCG vaccination at birth. Only a few countries recommend BCG later during childhood. In some countries with low TB endemicity (mainly western European countries, North America and Australia), only specific subpopulations at high risk for TB are vaccinated with BCG. Changes in available evidence, TB incidence, HIV prevalence, vaccine shortages, and perceptions of risks and benefits of BCG can all alter vaccine policy within a country and across regions. In 2016, the global BCG vaccine coverage estimate was 90% reported from 169 countries, and all WHO regions have an average BCG vaccine coverage greater than 86%. Timeliness analyses, however, reveal that BCG vaccination is often not administered at birth but rather is frequently delayed to later in the first weeks of life and in some countries is administered together with the first diphtheria-tetanus-pertussis (DTP) containing vaccine at six weeks of age or even later.

**Demand and supply:** BCG vaccines are produced worldwide and several large countries are self-sufficient producing BCG vaccine for their own needs (e.g. China, India and Indonesia); nevertheless, over recent years a serious shortage of BCG vaccine supply has emerged, forcing WHO and UNICEF to prioritize supplies of prequalified BCG vaccines to the populations most in need. BCG vaccine supply for 2017 is estimated to be 1.5 times greater than the forecasted demand.

However, there is limited flexibility in the supply due to national product registration constraints and supply is still concentrated to a few large manufacturers with prequalified products serving most countries.

Different BCG vaccine seed strains have evolved over time due to mutations and deletions during replication at different manufacturing sites. As a result, BCG products differ substantially in their genetic and phenotypic properties. Worldwide, the most commonly used vaccine strains are: Russian BCG-I/Bulgaria (approx. 100 countries), Danish 1331, and Tokyo 172-1.

**Impact:** Neonatal BCG vaccination provides protection against the more severe types of disseminated TB, such as miliary TB and tuberculous meningitis, to which infants and young children are particularly susceptible. However more recent evidence suggest consistent protection against pulmonary TB for up to 10 years and more recently some evidence of moderate protection for 20 years in settings that include Brazil, Saudi Arabia and Europe. A systematic review of published trials did not find an association with vaccine strains. However, there is a report of a large trial and one observational study which suggest an association between BCG strain and protective efficacy which suggests that further studies are warranted. Unpublished modelling data comparing BCG administration at birth and 6 weeks of age estimates that delaying BCG vaccination to age 6 weeks may lead to a 1.8% increase in TB deaths. Evidence indicates that BCG given at birth is also effective for preventing leprosy, conferring higher protection than against TB. Several studies suggest it might prevent other mycobacterial infections including Buruli ulcer.

The evidence for benefits of BCG revaccination against TB and leprosy is still limited and does not support this practice. BCG vaccination is safe in immunocompetent children. However, vaccination of immunocompromised, including vaccination of HIV infected infants is not recommended. However delays in ascertaining HIV status of newborns continue to occur thus BCG is often administered to HIV infected infants whose status is still unknown at the time of vaccination. While robust evidence is missing, reduction in HIV mother to child transmission rates, earlier diagnosis of neonatal HIV infection and earlier antiretroviral treatment initiation are expected to reduce the risk of BCG adverse events in HIV infected children.

Review of economic analyses in the literature show that universal BCG vaccination remains cost-effective in countries where TB incidence is high. However in countries where the TB incidence is low, selective BCG vaccination of high-risk populations can be considered, when an efficient surveillance system is in place. There are no cost-effectiveness studies for BCG vaccination against leprosy and other mycobacterial infections. BCG revaccination is not considered cost-effective since no increased effectiveness has been observed. In 2014, SAGE concluded that the available data suggest the current WHO recommended schedule for BCG vaccination at birth has a beneficial effect on all-cause infant mortality.

**New vaccine pipeline:** Many activities have taken place with respect to the development of new TB vaccine candidates, with three vaccine candidates currently in phase IIb or III clinical trials. Most approaches focus on adolescent and adult vaccination after BCG “priming” of newborns. It is therefore important to understand if available BCG vaccines vary in their priming and protective efficacy. A new sub-unit vaccine for leprosy is currently in phase Ib clinical testing.

**Working group conclusions:** The working group concludes, that due to paucity of evidence to assess differences in the vaccine efficacy / effectiveness and safety of vaccination at different ages (birth versus age 6 weeks, 6 months or one year), no policy change regarding the age is justified. BCG vaccination at birth together with hepatitis B vaccination is strongly recommended. The group recommends continuing universal BCG vaccination in high incidence TB settings and to expand this recommendation of universal BCG vaccination to high incidence leprosy settings regardless of the TB incidence. Recommendations for selective vaccination of individuals or groups at risk in low endemic countries, switching from universal to selective vaccination, vaccination of HIV-exposed children, immunocompetent HIV-infected individuals on anti-retroviral therapy (ART) and other special risk groups including adolescents and adults are proposed. The group highlighted the urgent need for further research in the development of new vaccines, which should be tested for effectiveness against different pathogenic mycobacterial infections (TB, leprosy and other mycobacterial infections such as Buruli ulcer), and all-cause infant mortality. The group also recommended further detailed molecular characterization of currently available BCG vaccines in terms of strain and product specific aspects, as well as conduct of comparative effectiveness studies to inform vaccination policy makers.

## 2. BCG Working Group Recommendations

### Universal vaccination at birth

In countries or settings with a high incidence of TB and/or leprosy, a single dose of BCG vaccine should be given to neonates at birth, or as soon as possible thereafter, for prevention of TB and leprosy disease. If it cannot be given at birth, it should be given at the earliest opportunity thereafter and should not be delayed. Any delay in vaccination may lead to opportunities for known or unknown exposure to TB or leprosy infected contacts.

As newborns are also recommended to receive their first dose of hepatitis B vaccine as soon as possible after birth, ideally within 24 hours, co-administration of BCG with the hepatitis B birth dose is strongly recommended as it is safe to do so.

If the birth dose was missed, catch-up vaccination of unvaccinated older infants and children is recommended since evidence shows it is beneficial. Catch-up vaccination should be done at the earliest convenient encounter with the health-care system to minimize known or unknown exposure to TB or leprosy infected contacts.

### Selective risk group vaccination at birth

Countries with a low incidence of TB or leprosy may choose to selectively vaccinate neonates in recognized risk groups for developing disease.<sup>1</sup>

High-risk groups to be considered for vaccination include the following:

- Neonates to parents (or other close contacts/relatives) with previous TB or leprosy
- Neonates in immigrant populations from countries with high incidence of TB<sup>2</sup> and/or leprosy.
- Neonates in any other locally identified risk group for TB and/or leprosy.

In a few countries with low TB incidence, BCG vaccination is largely replaced by intensified case detection, contact tracing and supervised early treatment.

### Switching from universal to selective risk group vaccination at birth

Countries with declining rates of TB are encouraged to periodically evaluate the epidemiology of TB and consider if a switch from universal vaccination to selective risk group vaccination would be appropriate.

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<sup>1</sup> Countries with a low-incidence of TB are those with a TB notification rate of <100 TB cases (all forms) per 1 million population per year.

<sup>2</sup> >40per 100,000 population



Before switching to selective BCG vaccination, countries should consider the impact of a switch on prevention of leprosy. Consideration may be given also to other mycobacterial infections, as well as any potential NSE of BCG vaccination on all-cause infant mortality.

When considering switching from universal to selective risk group vaccination, an efficient disease surveillance system capable of showing the current average annual rate of smear-positive pulmonary TB cases is a pre-requisite. Additional data shall be taken into consideration, in particular the average annual rate of tuberculous meningitis in children aged under five years and/or the average annual risk of tuberculous infection in children and should be monitored. Finally the epidemiological situation for leprosy should be assessed through both routine notification data and especially active screening activities. The burden of other mycobacterial infections such as Buruli ulcer disease in the country could be also reviewed.

### **Vaccination of older age groups**

BCG vaccination of unvaccinated/tuberculin skin test (TST)-or interferon gamma release assay (IGRA) negative school-children provides long-term effectiveness (up to 20 years or more). BCG vaccination of older age groups should be considered in:

- Unvaccinated older children, adolescents and adults living in high incidence settings of TB and/or leprosy.
- Unvaccinated older children, adolescents and adults moving from low incidence to high incidence TB/leprosy settings.
- Unvaccinated/TST- or interferon gamma release assay (IGRA) negative persons at risk of occupational exposure in low and high TB incidence areas (e.g. health care workers, laboratory workers, medical students, prison workers)

### **Need for re-vaccination**

There is little additional benefit of repeat BCG vaccination against TB or leprosy. Therefore, revaccination is not recommended even if the TST reaction or result of an IGRA is negative. The absence of a BCG scar after vaccination is not indicative of a lack of protection and is not an indication for revaccination.

### **HIV exposed and other immunocompromised**

BCG vaccination is contraindicated for persons with impaired congenital or acquired immunity (e.g. acquired immune deficiency syndrome (AIDS), known or suspected congenital immunodeficiencies, leukaemia, lymphoma or other malignant disease) and for patients under immunosuppressive treatment (e.g. corticosteroids, alkylating agents, biologic response modifiers, antimetabolites, radiation).

BCG vaccination is contraindicated for HIV infected persons due to their immunosuppression. However, if HIV infected individuals are started on anti-retroviral therapy (ART), are clinically well and immunologically stable

(CD4% > 25% for children under 5 years or CD4 count  $\geq$ 200 if age > 5 years), BCG administration can be considered, especially for those living in high incidence TB settings.

In general, populations with a high prevalence of HIV infection also have the greatest incidence of TB. The following guidance is provided to facilitate national and local decisions on the use of BCG vaccine in infants at risk for HIV infection:

- **Benefits outweigh risks for BCG vaccination.** Neonates born to women of unknown HIV status should be vaccinated.
- **Benefits usually outweigh risks for BCG vaccination.** Neonates born to known HIV-infected women and whose HIV infection status is unknown but who demonstrate no signs or reported symptoms suggestive of HIV infection should be vaccinated particularly if the mother is already on ART.
- **Risks usually outweigh benefits for BCG vaccination.** Neonates who are born to HIV-infected mothers and whose HIV infection status is unknown but who have signs or reported symptoms suggestive of HIV infection should not be vaccinated. However, this recommendation will only be applicable to infants who have not yet received BCG in the first few weeks of life, since clinical manifestations typically occur after the neonatal period. Although evidence is limited, if HIV infection status can be established with early HIV testing, BCG may then be administered once HIV infection has been ruled out *or* the HIV-infected child has become immunologically stable on ART.
- **Risks outweigh benefits for BCG vaccination.** For newborns who are confirmed HIV infected through early virologic testing, although evidence is limited, BCG should not be administered until the infant has been started on ART and confirmed to be immunologically stable (CD4% > 25%).

### Vaccination of special populations, contraindications and precautions

BCG vaccination is contraindicated for individuals known to be allergic to any component of the vaccine.

**Low birth weight** children, although evidence is limited, can receive BCG vaccination at birth. A normal infant dose should be used.

**Preterm infants**, although evidence is limited, can receive BCG vaccination from gestational age 34-36 weeks, and this should be administered at discharge from the neonatal ward.

**Pregnant women**– BCG is contraindicated during pregnancy.

**Lactating women** – There is no contraindication for BCG vaccination of lactating women.

**Travelers** – An individual risk-strategy based on age, duration of travel and the TB incidence in the country to be visited should be considered before vaccination of travelers from non TB endemic countries to TB endemic countries. For young children traveling to TB endemic countries, particularly those under 2 years of age and those likely to have repeated travel during childhood, should be vaccinated.

Asymptomatic neonates born to mothers with confirmed or suspected infectious drug-susceptible TB should receive preventive therapy once TB disease has been excluded and should be regularly followed up to ensure that TB disease does not develop. If an infant remains asymptomatic at the end of preventive therapy, and the baby is HIV-negative, usual practice is that BCG is given.

### **Programmatic considerations for BCG vaccination**

**Choice of vaccine** – Among the many available BCG products there is no preferred product for use, in any age- or risk group.

**Dose of vaccine** – The standard dose of BCG vaccine is 0.05 mL of the reconstituted vaccine given intradermally for children age below one year, and 0.10 mL for recipients aged one year or more. Only one dose of vaccine should be administered.

**Co-administration with other vaccines** - Co-administration at birth with hepatitis B vaccine is recommended. BCG can be co-administered with any other infant routine childhood vaccines.

**Route of administration** - BCG vaccines should be administered strictly intradermally. Some licensed BCG products are available with multi-puncture devices for percutaneous administration. BCG vaccination should be given in a healthy and clean area of skin, and the skin should not be cleaned with antiseptic prior to administration of the vaccine. The vaccine should preferably be given in the lateral aspect of the upper arm. There are no published data on efficacy and safety for other anatomic sites of administration.

### **Recommendations for specific measures including surveillance**

Currently, reporting of childhood TB cases by countries to WHO is broken into two age ranges: 0-4 years and 5-14 years. To better understand the effectiveness of BCG vaccination at various ages, it should be encouraged that national EPI programmes of report TB cases by age in years, (and if possible by months for those less than 1 year) including status of BCG vaccination of cases (preferably with information with used product/batch).

### **Recommendations on research needs**

Development of new vaccines against TB and leprosy is strongly recommended. New vaccines should be assessed for effectiveness against TB, leprosy and Buruli ulcer disease. Their effect on all-cause infant mortality should also be assessed.

More evidence is needed on the influence of BCG vaccine strain on efficacy, effectiveness, and adverse effects. Detailed molecular characterization of BCG products is encouraged. The lack of information on specific strains and their use in different products has significantly hampered interpretation of research studies. Therefore, it is recommended that the strain (including manufacturer and preparation) used for BCG vaccination is specified (i) when recording BCG vaccination in an individual infant's immunization record and (ii) when reporting studies relating to BCG vaccination.

The implementation of BCG vaccination of HIV infected children including those on ART should be monitored and research on effectiveness and safety should be considered

Research for strategies to improve timeliness of BCG vaccination, including limiting wastage of vaccine in multi-dose preparations, should be conducted.

Long-term studies could usefully be conducted to explore BCG vaccine effectiveness, duration of protection particularly in low latitudes. Studies on BCG vaccine efficacy and effectiveness should be carefully assessed when BCG is not given soon after birth or after stringent testing if given in childhood. Other studies could also include the effectiveness of revaccination in different subgroups of the population as well as research on BCG revaccination for TB- and leprosy prevention and on BCG revaccination to contacts of leprosy patients and vaccination after treatment of TB infection in contacts.

Additional studies on the effect of BCG vaccination on all-cause childhood mortality should be undertaken in a greater variety of settings.

Granted that such studies are difficult and expensive, further investigations rigorously designed and implemented may however help clarify outstanding questions.

### **Recommendations to pre-empt BCG vaccine shortages**

Many self-procuring countries have only one registered BCG product and therefore their access to BCG supply is vulnerable. It is recommended that: (i) manufacturers be incentivised to register available BCG products in these countries; (ii) encourage these countries to follow the “WHO Collaborative Procedure for Registration of Prequalified Products<sup>3</sup>”. This pathway would facilitate the registration process in countries where there is a lack of regulatory capacity, and would facilitate the introduction of the vaccine in the country.

The supply base of prequalified BCG vaccine is highly concentrated to a few manufacturers. It is therefore recommended that donors invest to ensure that the current supply base of BCG production is sustained to avoid risk of shortages due to production failure.

There appears to be over-procurement of BCG vaccine in several countries. It is recommended that (i) WHO and UNICEF investigate reasons for possible over-procurement of BCG vaccines; and (ii) to reduce wastage, manufacturers should consider producing smaller number of doses per vial without affecting production capacity.

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<sup>3</sup> WHO Collaborative Procedure for Registration of Prequalified Products. Available at [http://www.who.int/immunization\\_standards/vaccine\\_quality/accelerated\\_review/en/](http://www.who.int/immunization_standards/vaccine_quality/accelerated_review/en/), accessed September 2017.

### 3. Background

Bacillus Calmette-Guérin (BCG) is an attenuated strain of *Mycobacterium bovis* used as a live vaccine against tuberculosis (TB). Since its introduction in 1921, more than 3 billion people have been vaccinated with BCG. BCG is highly effective in preventing the severe forms of tuberculosis that affect infants and young children.

The WHO BCG vaccine position paper<sup>4</sup> was published in 2004. In settings where TB is highly endemic or where there is high risk of exposure to TB, it recommends that a single dose of BCG vaccine should be given to all infants.<sup>5</sup> There is little evidence that revaccination with BCG affords much additional protection<sup>6</sup>, and revaccination is therefore not recommended.

Additional revised BCG vaccination guidelines for infants at risk for HIV infection were published separately in 2007<sup>7</sup>. WHO recommends that, in children who are known to be HIV-infected, BCG vaccine should not be given. In infants with unknown HIV status and who are born to HIV-positive mothers and who lack symptoms suggestive of HIV, BCG vaccine should be given after considering local factors: coverage and success of the prevention of mother to child transmission of HIV (PMTCT) programme; possibility of deferring BCG vaccination in HIV-exposed infants until HIV infection status has been established; availability of early diagnosis of HIV infection in infants; and provision of early ART to HIV-positive infants.

For the use of BCG against leprosy there is no vaccine position paper available. To date the most official recommendation on the use of BCG for leprosy has been provided through the Technical Report Series from the WHO Expert Committee on Leprosy held in 2010 and recommends that ‘Maintaining high levels of BCG immunization in newborns is important in the prevention of leprosy’.

There was a need to perform an updated review of evidence and to determine the need for an updating the recommendations according to current evidence-based standards. Accordingly the WHO Secretariat and the Strategic Advisory Group of Experts (SAGE) on Immunization initiated the process through establishment of a SAGE BCG Working Group in September 2016. The working group reviewed the evidence and requested new modeling data and updated systematic reviews on safety and efficacy and effectiveness.

The Secretariat of the working group is jointly ensured by staff from the 5 following Departments/Programmes: Department of Immunizations, Vaccines and Biologicals (IVB), the Global TB Programme (GTB), the Global Leprosy Programme (GLP), HIV-department and the Department of Essential Medicines and Health Products (EMP).

<sup>4</sup> WER, No. 4, 2004, 79, 25–40, available <http://www.who.int/wer/2004/en/wer7904.pdf?ua=1>, accessed June 2017.

<sup>5</sup> WHO, Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2014, available at: [http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748_eng.pdf), accessed June 2017.

<sup>6</sup> Pereira SM et al. Effectiveness and cost-effectiveness of first BCG vaccination against tuberculosis in school-age children without previous tuberculin test (BCG-REVAC trial): a cluster-randomised trial. *Lancet Infect Dis.* 2012 Apr;12(4):300-6.

<sup>7</sup> WER No. 3, 2007, 82, pp. 18–24. [http://www.who.int/immunization/wer8221bcg\\_May07\\_position\\_paper.pdf?ua=1](http://www.who.int/immunization/wer8221bcg_May07_position_paper.pdf?ua=1), accessed July 2017.

## 4. Tuberculosis

Tuberculosis in humans and animals can be caused by a group of mycobacteria species, the Mycobacterium tuberculosis complex (MTC). The closely related mycobacteria of this complex are: *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium canettii*, *Mycobacterium caprae*, *Mycobacterium microti*, *Mycobacterium mungi*, *Mycobacterium orygis*, *Mycobacterium pinnipedii*, and *Mycobacterium tuberculosis*.

*Mycobacterium tuberculosis* is the most common cause of TB in humans. *M. africanum* and *M. canettii* can also cause human TB. *M. bovis* can affect humans, domestic or wild bovines and goats. Other species of the MTC have been reported to cause TB only in animals.<sup>8,9</sup>

### 4.2. Epidemiology of TB

#### Report by the Global TB Programme

An estimated 2–3 billion people are said to be infected with *M. tuberculosis* globally with about 5–15% ending up developing TB disease during their lifetime.<sup>10</sup> However, the probability or risk of developing TB disease is known to be much higher among people infected with HIV even in the context of ART. With respect to children, the risk of developing active TB following primary infection is greatest in very young children. In the first year of life it is 40% - 60% and 12% - 15% in the second year<sup>11</sup>. The risk declines to 0.5% to 5% in age 2-5 year; <0.5% to 2% in 5-10 year-old children and increases to 10-20% for pulmonary TB (PTB) in children >10 years.

In 2015, an estimated 10.4 million people fell ill with TB (142 per 100,000 population) including 1 million children (10%), 3.5 million women and 5.9 million men. About 1.2 million people (11%) developed HIV-associated TB.<sup>10</sup>

In 2015, an estimated 1.8 million people died from TB among which were 210,000 children, 500,000 women and 1,100,000 men. This includes about 400,000 HIV-associated TB deaths and 190,000 in people with MDR-TB. Although the number of TB deaths fell by 22% between 2000 and 2015, TB remained one of the top 10 causes of death worldwide in 2015 exceeding HIV.

The South East Asian region accounts for 46% of the 10.4 million estimated TB cases (new cases (estimated incidence)) that occurred in 2015; 26% occurred in Africa, 15% in the Western Pacific region; 7% in the Eastern Mediterranean region while Europe and the Americas accounted for 3% each. Six countries accounted for 60% of the new cases namely: India, Indonesia, China, Nigeria, Pakistan and South Africa.

<sup>8</sup> Forrellad et al. Virulence factors of the Mycobacterium tuberculosis complex. *Virulence*. 2013 Jan 1; 4(1): 3–66.

<sup>9</sup> Alexander et al. Novel Mycobacterium tuberculosis Complex Pathogen, *M. mungi*. *Emerg Infect Dis*. 2010 Aug; 16(8): 1296–1299.

<sup>10</sup> WHO Global TB Report 2016. Available at [http://www.who.int/tb/publications/global\\_report/en/](http://www.who.int/tb/publications/global_report/en/), accessed September 2017.

<sup>11</sup> Marais BJ et al. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis*. 2004 Mar;8(3):278-85.

Case notifications are increasing but a large incidence/notification gap remains. In 2015, an estimated 4.3 million cases were not notified to national health authorities. Ten countries represent 77% of that gap out of which the following three countries represent nearly 50% of the notification gap (gap between estimated and notified): India, Indonesia and Nigeria.

HIV is known to be a powerful risk factor for developing TB. Globally, the proportion of TB cases co-infected with HIV was 15% globally with the highest rates in African region at 36% (with co-infection rate in excess of 50% in southern parts of the region). In 2015, Africa accounted for about 71% of the TB/HIV co-infection. Other co-morbidities such as diabetes are emerging in other WHO regions.<sup>12</sup>

TB spreads in poor, crowded and poorly ventilated settings and is linked to HIV infection, malnutrition, alcohol, drug and tobacco use, and diabetes. The most vulnerable populations at risk of TB include, among others, migrants, prisoners, minorities, refugees, and, urban poor.

During the Millennium Development Goals (MDGs), TB treatment saved an estimated 49 million lives between 2000 and 2015. Globally, TB incidence witnessed a decline at a rate of 1.4% per year in 2000–2015, and 1.5% (between 2014 and 2015). Priority actions to end TB in 2017 include: reach missing TB cases; address the MDR-TB crisis; accelerate the response to the TB/HIV co-epidemic; eliminate catastrophic costs; intensify TB research and uptake; and, close financing gaps.

### **4.3. TB control in the era of the UN Sustainable Development Goals**

The UN Sustainable Development Goals (SDGs) 2016-2030 include 17 development goals. Goal 3 is about “good health and well-being” and has 13 targets, of which target 3.3 is to “End the epidemic of AIDS, TB, malaria & neglected tropical diseases and combat hepatitis, water-borne and other communicable diseases. In this new era, the response to TB is moving from halting TB to ending TB by 2030. In May 2014, during the 67<sup>th</sup> World Health Assembly, the WHO Member States adopted the End TB Strategy 2016-2035.<sup>13</sup>

The vision of the End TB Strategy 2016-2035 is “A World Free of TB: zero TB deaths, zero TB disease, and, Zero TB suffering”. The goal is to end the global TB epidemic. The strategy contains milestones and targets. As of 2020, none of the TB affected families should face catastrophic cost due to TB. By 2035, there should be a 95% reduction in the number of TB deaths compared with 2015 and a 90% reduction in TB incidence rate.<sup>13</sup>

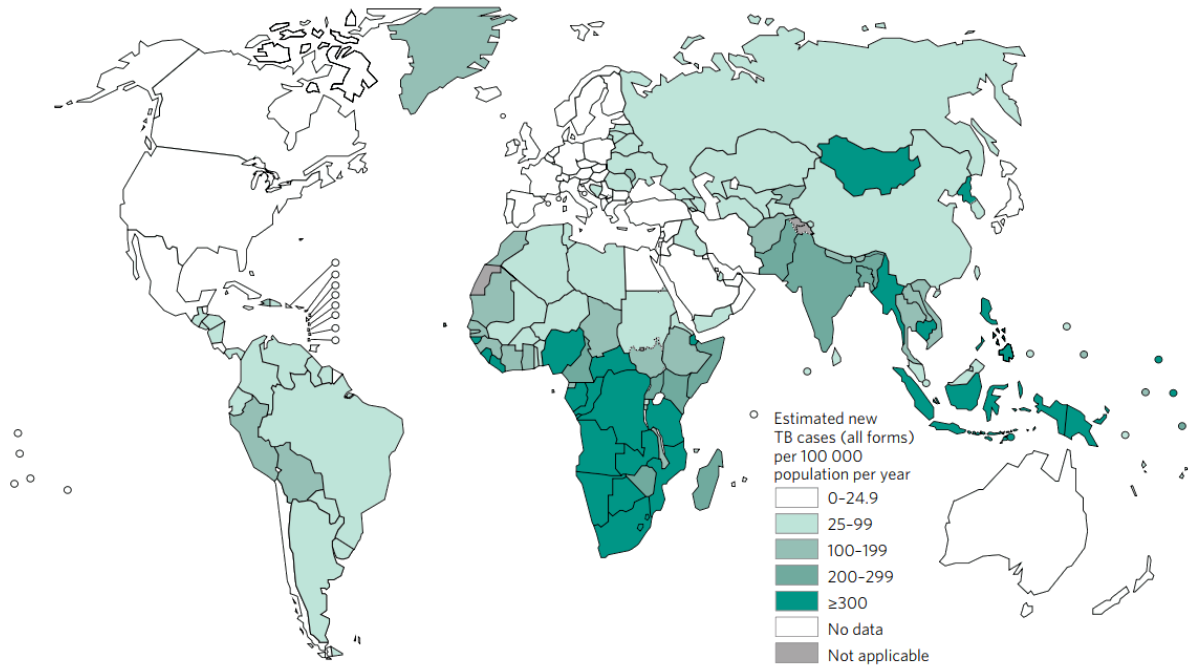
The End TB Strategy has three pillars: Pillar 1 “Integrated, patient-centred TB care and prevention”; Pillar 2 “Bold policies and supportive systems”, and, Pillar 3 “Intensified research and innovation”.<sup>13</sup> The success of the Strategy in driving down TB deaths and illness will depend on countries respecting the following key principles as they implement the interventions outlined in each pillar: Government

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<sup>12</sup> Collaborative framework for care and control of tuberculosis and diabetes, WHO 2011. Available at [http://apps.who.int/iris/bitstream/10665/44698/1/9789241502252\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/44698/1/9789241502252_eng.pdf), accessed August 2017.

<sup>13</sup> WHO. The End TB Strategy. Global strategy and targets for tuberculosis prevention, care and control after 2015. WHO, 2015. Available at [http://www.who.int/tb/strategy/End\\_TB\\_Strategy.pdf?ua=1](http://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1), accessed September 2017.

stewardship and accountability, with monitoring and evaluation; building a strong collation with civil society and communities; protecting and promoting human rights, ethics and equity; and, adaptation of the strategy and targets at country level, with global collaboration.



**Figure 1: Estimated TB incidence rates, 2015. Source: Global TB Report 2016.<sup>10</sup>**

*Role of vaccines among other preventive measures- TB*

Efforts to control the spread of TB will continue to rely on currently available tools, namely: early diagnosis of TB, including universal drug-susceptibility testing, and systematic screening of contacts and high risk groups; treatment of all people with TB including drug-resistant TB, and patient support; collaborative TB/HIV activities, and management of co-morbidities; and, preventive treatment of persons at high risk, and vaccination against TB.

BCG vaccine is highly effective in preventing the severe forms of TB that affect infants and young children. BCG vaccination also may reduce infant mortality by protecting against infections other than TB through beneficial non-specific effects (NSE) on the immune system (see section on NSE).

Ending the TB epidemic by 2030 requires an 80% drop in new TB cases; a 90% drop in people dying from TB; and, 100% of TB-affected families protected from catastrophic cost through better care and prevention; bolder policies and systems; and bigger investments in research and innovation. It is about saving lives, tackling poverty and inequity. Innovations and research are critical to break the trajectory of the TB epidemic. Improved TB vaccines (pre- and post-exposure) are a key element for successful TB control, along with better diagnostics, including new point-of-care tests; as well as safer, easier and shorter treatment regimens for disease and latent TB infection.



#### 4.4. Trends in antibiotic resistance of TB

Multidrug-resistant TB (MDR-TB) has been recognized by WHO as a public health crisis requiring an accelerated response. In 2015, there were an estimated 480,000 new cases of MDR-TB plus an additional 100,000 new cases of rifampicin-resistant TB (580,000 MDR/RR-TB cases).

In 2015, a global average of 3.9% of incident (newly detected) TB cases were estimated to have MDR/RR-TB and 21% among previously treated cases. This pattern has been consistent with the levels reported in previous years. There is however a marked variation in the estimated rates of drug resistance between countries and regions, with the WHO Eastern European region currently having the highest rates of MDR-TB.

WHO has identified 30 countries that contribute about 90% of the global burden of MDR/RR-TB. Furthermore, 45% of the global MDR/RR-TB caseload (absolute numbers) are said to be in three countries namely India; China and the Russian Federation.

By October 2016, extensively drug-resistant TB (XDR-TB) had been reported by 118 WHO Member States. About 51% have resistance to a fluoroquinolone or a second-line injectable agent or both. Overall, 9.5% (95% CI: 7.0–12.1%) of MDR-TB cases have XDR-TB. In some countries the proportion of cases with strains resistant to second-line drugs is much higher than the global average.

Drug susceptibility testing (DST) coverage in 2015 was 24% of new cases; 53% of previously treated cases, 30% overall. In 2015, 132,000 MDR/RR-TB cases among notified TB patients were detected and 125,000 were enrolled on treatment highlighting a large gap between estimated incidence, case detection and treatment enrollment.

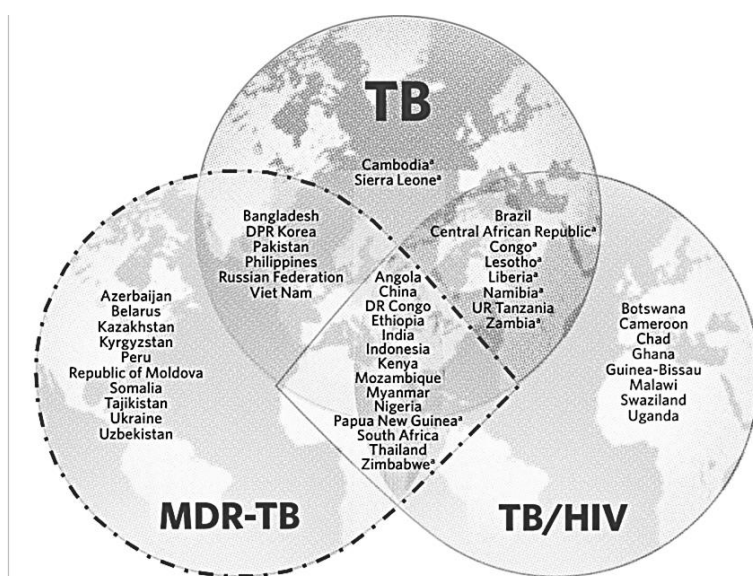


Figure 2: 30 High MDT-TB burden countries. Source: Global TB Report 2016.<sup>10</sup>

Treatment success rate for MDR/RR-TB cases has remained low with only 52% successfully treated among the most recent patient cohort of 2013. Treatment success is even lower among patients with XDR-TB with only 28%

of the 4,086 XDR-TB patients reported by 47 countries in 2015 successfully treated. The biggest numbers reported were in Europe (Russian Federation and Kazakhstan); while South Africa accounted for more than 80% of cases from the African region.

In May 2016, WHO issued updated guidelines for the treatment of drug-resistant TB. WHO now recommends a standardized 9-12 month (shorter) treatment regimen (instead of 24 months-long previously recommended) as the option of first choice in patients with RR or MDR-TB who do not have additional resistance or other factors making them ineligible for that shorter treatment regimen. The recommendation applies to adults, children and people living with HIV. This regimen is being implemented in over 20 countries in Africa and Asia.

WHO recommends rational introduction of new drugs for use in the treatment of MDR-TB. By the end of 2015, at least 70 countries were known to have introduced bedaquiline and 39 countries delamanid (two new drugs for treatment of MDR-TB). However, enrolment of eligible patients remains low, and in big countries namely China, India and Indonesia remains negligible.

In order to effectively address RR- and MDR-TB, five priority actions need to be implemented: (i) prevent the development of drug resistance through high quality treatment of drug-susceptible TB; (ii) expand rapid testing and detection of drug-resistant TB cases; (iii) provide immediate access to effective treatment and proper care; (iv) prevent transmission through infection control; and, (v) increase political commitment with financing.

In summary, although only 3.9% of new and 21% of previously treated TB cases have MDR/RR-TB, globally they amount to 580,000 incident cases each year, posing a serious challenge to goal of ending TB by 2035. Coverage of DST for first and second-line TB medicines is improving but only a fraction of MDR/RR-TB and XDR-TB patients are being detected and placed on adequate treatment. Scaling up the WHO-recommended shorter MDR-TB regimen as well as the use of new drugs is needed to impact on success rates for drug-resistant TB patients globally, but most especially in high burden countries. Surveillance and monitoring continue to improve as digital technologies offer an opportunity to help address some of the weaknesses in data management as well as for patient care (e.g. adherence support). Nevertheless there remains a crisis in the MDR-TB treatment gap that is not only attributable to drug access, but the overall health system capacity to detect and treat these patients. Effective pharmacovigilance for newly introduced drugs, use of trained health care workers and laboratory system capacities must all be considered when addressing MDR-TB.

## 5. Leprosy

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* (*M. leprae*) primarily affecting skin, peripheral nerves, mucosal surfaces of upper respiratory tract and eyes. It is otherwise known as Hansen's disease.

Although the fight against leprosy has gained considerable success with the achievement of elimination of leprosy as public health problem (prevalence <1 per 10 000 at the global level) in 2000 and in most countries at national level in 2005, still more than 200 000 cases were reported in 2016 and the detection rate of the disease (a proxy of incidence rate) is only slightly declining at a rate of about 4% per year.<sup>14</sup> Early diagnosis and complete treatment with multidrug therapy (MDT) remain the key strategies for reducing disease burden in leprosy control. To date guidance in relation to leprosy clinical management including its detection and treatment has been issued through the WHO Technical Report Series 968 and the WHO Expert committee on Leprosy reports, latest being the eighth report on the 2010 executive committee meeting. The previous meeting was held in 1997 (WHO Technical Report Series 874, WHO Expert Committee Meeting Seventh Report 1998). Advances in research in various fields including diagnostics, treatment and more importantly prevention of the disease, have led to countries to issue new policies in the area of prevention of leprosy. Such policies didn't provide guidelines using current WHO methods with defined recommendations in relation to specified level of scientific evidence. Thus, the GLP, planned to develop comprehensive guidelines in regard to all aspects of care including diagnosis, treatment and prophylaxis with the development process to take place within the year 2017. To date the most official recommendation on the use of BCG for leprosy has been provided through the 8<sup>th</sup> Technical Report Series from the WHO Expert Committee on Leprosy recommending 'Maintaining high levels of BCG immunization in newborns is important in for further reducing the burden of leprosy.'<sup>15</sup>

### 5.2. Epidemiology of Leprosy

Though disease usually starts with a skin lesion with loss of sensation, presence of one of the three cardinal signs is considered essential for diagnosis:

- skin lesion with definite loss of sensations
- thickened peripheral nerve trunk
- positive skin smears for acid fast bacilli<sup>16</sup>

Leprosy case definitions have been revised in 2017: paucibacillary (PB) cases have less than five skin lesions whereas, multibacillary (MB) cases have more than five skin lesions and/or involvement of at least one nerve trunk. A proportion of leprosy patients are positive for acid fast bacilli on skin slit smear examination however in leprosy control programmes most of the cases are diagnosed on clinical basis. If a skin slit smear is positive cases are automatically classified as MB. Tertiary care centers do perform histopathological examinations and Polymerase-chain reaction (PCR) as tools to confirm a clinical suspicion. WHO recommended multi-drug therapy

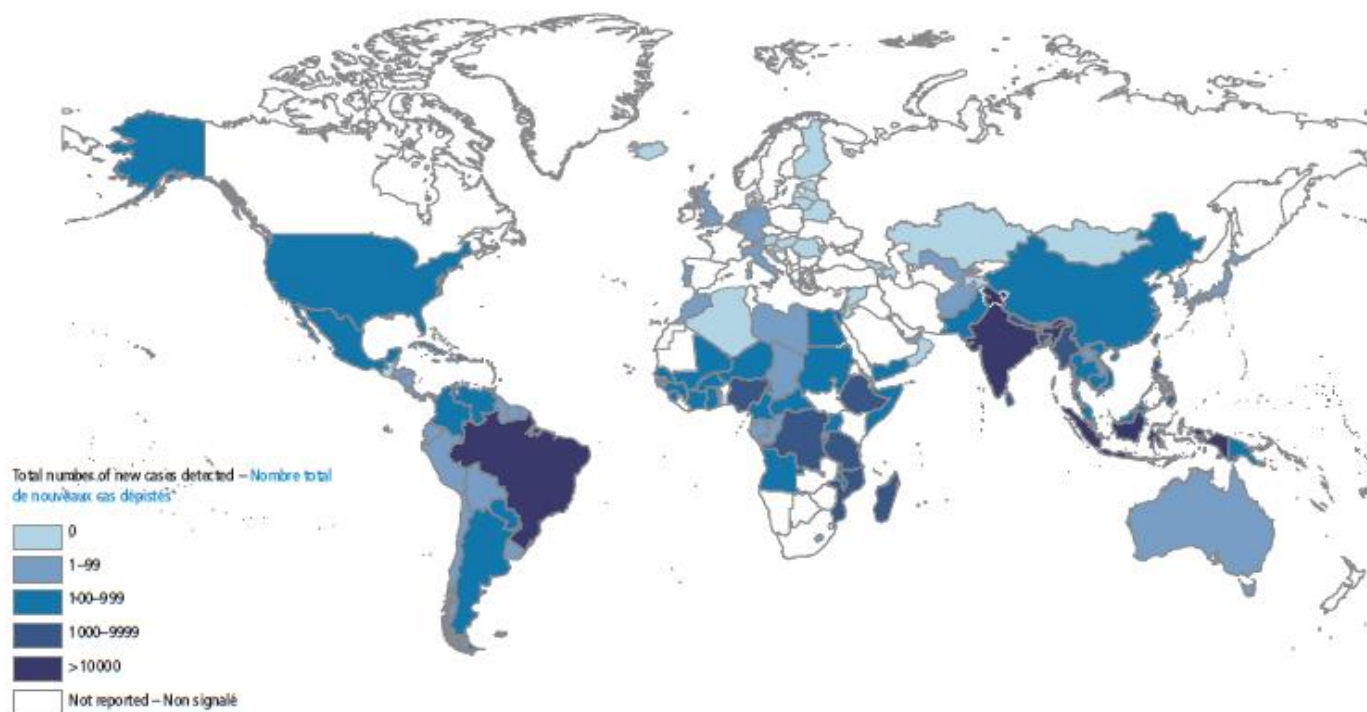
<sup>14</sup>WHO. Global leprosy update, 2016: accelerating reduction of disease burden. Weekly Epidemiological Record No 35, 2017, 92, 501–520.

<sup>15</sup> WHO Expert Committee on Leprosy 8<sup>th</sup> report. Available at

[http://www.searo.who.int/entity/global\\_leprosy\\_programme/publications/8th\\_expert\\_comm\\_2012.pdf](http://www.searo.who.int/entity/global_leprosy_programme/publications/8th_expert_comm_2012.pdf), accessed July 2017.

<sup>16</sup> WHO Technical Report Series 968, Expert committee on Leprosy, eighth report 2010.

(MDT) for treatment of leprosy, six months with two drugs (Rifampicin and dapsone) for PB cases and 12 months with three drugs (Rifampicin, dapsone and clofazimine) for MB cases.



**Figure 3: Geographic distribution of new leprosy cases in 2016.**<sup>17</sup>

In 2016, out of 224 countries globally enlisted by GLP, 143 countries and territories sent their reports on the occurrence of leprosy cases. At the end of the year 2016, 171 948 cases were on MDT with a registered point prevalence rate of 0.23 per 10 000 people globally. The global new case detection rate is at 2.9 per 100 000 people. Trends of new detection of new cases by WHO region from 2006 to 2016 are presented in table 1.

New case detection is not uniform across the world. Out of 143 countries, thirty four reported zero cases; 61 countries reported between one and 99 cases; 36 countries reported between 100 and 999 cases and 12 countries reported more than 1 000 new cases during 2015. These 12 countries accounted for 95% of global new cases in 2015. India alone contributed to 60% of global new case load.

<sup>17</sup> WHO, Global leprosy update, 2016: accelerating reduction of disease burden. Weekly epidemiological record. No 35, 2017, 92, 501–520.

**Table 1: Trends in the detection of new cases of leprosy, by WHO Region, 2006–2016**

WHO REGION	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
<b>AFR</b>	34 468	29 814	28 935	25 345	20 213	20 599	20 911	18 597	20004	19384
<b>AMR</b>	42 135	41 891	40 474	37 740	36 832	36 178	33 084	33 789	28806	27356
<b>EMR</b>	4 091	3 938	4 029	4 080	4 357	4 235	1 680	2 342	2167	2834
<b>SEAR</b>	171 576	167 505	166 115	156 254	160 132	166 445	155 385	154 834	156118	161263
<b>WPR</b>	5 863	5 859	5 243	5 055	5 092	5 400	4 596	4 337	3645	3914
<b>EUR</b>	NA	NA	NA	NA	NA	NA	NA	NA	18	32
<b>Total</b>	<b>258 133</b>	<b>249 007</b>	<b>244 796</b>	<b>228 474</b>	<b>226 626</b>	<b>232 857</b>	<b>215 656</b>	<b>213 899</b>	<b>210740</b>	<b>214783</b>

The number of women detected with leprosy is collected routinely from all countries. Global data shows that 39% of new cases (84,202) reported in 2016 were women. The exact mechanism of transmission remains obscure, with transmission via the respiratory tract suggested by some studies. Proportion of child case or, better, leprosy child rate in a country area indirectly indicates continued transmission of the disease. In 2016, 18,230 new child cases (9%) have been reported. The age at which leprosy among children is seen is usually after five years of age. There are reports available that describe younger children between 2-5 years also have active skin signs of leprosy. The proportion of new cases among children and women is presented in the table. The SEAR has higher proportion of new child cases which is in line with the highest burden of the region compared to the rest of the world. The exact reason why more cases are reported in males is not known with certainty, but it is most likely due to increased exposure to leprosy and/or to sex-related predisposition.

**Table 2: Percentage of Females and children among new cases by WHO Region in 2016**

WHO Region	Percentage of Female	Percentage of Children
<b>AFR</b>	37.3	8.7
<b>AMR</b>	43.7	6.4
<b>EMR</b>	38.2	7.2
<b>EUR</b>	21.9	3.1
<b>SEAR</b>	38.8	8.8
<b>WPR</b>	34.6	9.5
<b>World</b>	39.2	8.5

Proportion of females with leprosy is similar in all regions ranging from 34.6% in WPR to 43.7% in AMR. Globally in 2016 12,819 new grade-2 disabilities (G2D) cases were reported. The numbers of new cases with G2D have reduced noticeably from 14,059 in 2015 to 12,819 in 2016. The lack of a more decisive reduction of the annual new case detection rate is mainly attributed to two reasons: 1. lack of awareness in the community and on early signs of leprosy and 2. A lower level of expertise among health staff as the disease is rarer compared to several decades ago and there has been lack of investments in national leprosy services after the year 2000.

### 5.3. Global Leprosy Strategy 2016-2020

The Global Leprosy Strategy 2016 – 2020 “Accelerating towards a leprosy-free world” was launched in April 2016 with the aim to identify current and potential tools to reduce the leprosy burden at an accelerated rate globally. For addressing leprosy control, the Global Leprosy Strategy 2016–2020 was developed. It aims at accelerating action towards a leprosy-free world. The strategy is structured around three pillars:

- (1) Strengthen government ownership, coordination and partnership
- (2) Stop leprosy and its complications
- (3) Stop discrimination and promote inclusion.

Its targets are:

Number of children diagnosed with leprosy and visible deformities: 0

Rate of newly diagnosed leprosy patients with visible deformities: <1 per million

Number of countries with legislation allowing discrimination on basis of leprosy: 0

Broad core areas of interventions are included under each pillar:

PILLAR I	PILLAR II	PILLAR III
<p>Ensuring political commitment and adequate resources for leprosy programmes.</p> <ul style="list-style-type: none"> <li>• Contributing to universal health coverage with a special focus on children, women and underserved populations including migrants and displaced people.</li> <li>• Promoting partnerships with state and non-state actors and promote intersectoral collaboration and partnerships at the international level and within countries.</li> <li>• Facilitating and conducting basic and operational research in all aspects of leprosy and maximize the evidence base to inform policies, strategies and activities.</li> <li>• Strengthening surveillance and health information systems for programme monitoring and evaluation (including geographical information systems)</li> </ul>	<p>Strengthening patient and community awareness on leprosy.</p> <ul style="list-style-type: none"> <li>• Promoting early case detection through active case-finding (e.g. campaigns) in areas of higher endemicity and contact management.</li> <li>• Ensuring prompt start and adherence to treatment, including working towards improved treatment regimens.</li> <li>• Improving prevention and management of disabilities.</li> <li>• Strengthening surveillance for antimicrobial resistance including laboratory network.</li> <li>• Promoting innovative approaches for training, referrals and sustaining expertise in leprosy such as eHealth.</li> <li>• Promoting interventions for the prevention of infection and disease</li> </ul>	<p>Promoting societal inclusion through addressing all forms of discrimination and stigma.</p> <ul style="list-style-type: none"> <li>• Empowering persons affected by leprosy and strengthen their capacity to participate actively in leprosy services.</li> <li>• Involving communities in actions for improvement of leprosy services.</li> <li>• Promoting coalition-building among persons affected by leprosy and encourage the integration of these coalitions and or their members with other community-based organizations.</li> <li>• Promoting access to social and financial support services, e.g. to facilitate income generation, for persons affected by leprosy and their families.</li> <li>• Supporting community-based rehabilitation for people with leprosy-related disabilities.</li> <li>• Working towards abolishing discriminatory laws and promote policies facilitating inclusion of persons affected by leprosy.</li> </ul>

Given the advances in research in various fields including diagnostics, treatment and more importantly prevention of the disease, this has led to countries issuing new policies especially in the area of prevention of

leprosy. Such policies were not based on current WHO methods for developing guidelines with defined recommendations in relation to specified levels of scientific evidence. Thus, GLP is currently in the process to develop guidelines in regard to all aspects of care, including diagnosis, treatment and prophylaxis with the process to take place within the year 2017. As part of that process the GLP commissioned a literature review on efficacy of BCG and other vaccines to prevent leprosy in the general population and among contacts in the months of March-May 2017 as part of a general review on diagnostics and on preventive and treatment tools for leprosy. As part of the guidelines development process the GLP held an experts' meeting in Delhi on the 30-31 May 2017 named Guidelines Development Group (GDG) meeting. The GDG discussed reviewed the findings of the literature review and developed recommendations through evidence to recommendations tables. For the role of BCG for leprosy control the feedback of the leprosy guideline development group was shared with the BCG working group and to further link the two parallel processes (BCG working group and Guidelines development).

### *The role of the BCG vaccine in the control of leprosy*

Leprosy has important clinical, social, and public health consequence and can only partly be controlled by the antibiotic treatment. Even with the possible introduction of a chemoprophylaxis regimen, due to its partial efficacy the use of vaccine at birth remain an important tool for prevention of the disease; in addition data indicate additional protection for contacts vaccinated at birth who also receive chemoprophylaxis. Evidence on the efficacy of BCG to prevent leprosy is well established<sup>18</sup>, but there have been no WHO guideline recommendations for its use as a leprosy preventive tool. BCG is easily accessible and already part of the vaccination policy of most leprosy endemic countries. As national policy to control TB develops, however, changes in those policies may be made in response to changes in TB epidemiology without consideration of effects on leprosy prevention, which might compromise achievements in leprosy control. The GDG concluded that immune prophylaxis could be important in leprosy and wish to point out the results of the efficacy review to the BCG working group for their consideration, with a focus on efficacy of BCG for preventing leprosy when given at birth/infancy. The evidence on revaccination for adults exposed to a case (contacts) seems too limited at this stage to bring it to the attention of the working group/SAGE; however the use of BCG to prevent leprosy among adults and adults at risk (exposed contacts) cannot be excluded. Other vaccines have been shown to be effective for prevention of leprosy however data are more limited and they don't confer higher protection than BCG. Among those, only one is currently produced namely *mycobacterium indicus pranii* (formerly known as *mycobacterium w*). A current study on its efficacy is planned to be carried out in 4 districts in high burden leprosy states in India.

Therefore while the fundamental efforts to control the spread of leprosy will continue to rely on early diagnosis and multi-drug treatment, leprosy vaccines are a key element for success and the development of efficient, safe and affordable vaccines against leprosy must be a global priority.

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<sup>18</sup> Merle et al. BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. Expert Review of Vaccines. Volume 9, 2010 - Issue 2.

#### 5.4. Antimicrobial resistance in Leprosy

Since the late 80s, due to the raise of drug resistances (mainly dapsone resistance), leprosy monotherapy was replaced by combined treatment. *M. leprae* is a bacterium which cannot be grown in vitro and therefore it is difficult to assess antimicrobial resistance (AMR) with common phenotypic drug susceptibility tests. Nowadays sequencing methods are able to detect mutations in the genome of the bacterium and related resistances. Resistances to rifampicin, dapsone and ofloxacin are linked to drug resistance determining regions (DRDR) of the genes *rpoB*, *folP1* and *gyrA*.

An analysis of data from 18 endemic countries and 1,862 cases revealed that, 127 (6.8%) *M. leprae* strains bear mutations related to resistances (73 rifampicin-resistant, 59 dapsone-resistant and 19 Ofloxacin-resistant strains). Also multi-resistances were detected (20 cases had both rifampicin and dapsone resistance, while 4 cases had both ofloxacin and dapsone resistance, no cases had both rifampicin and Ofloxacin resistance). Resistances to rifampicin were observed in 12 countries. Of those, 3 countries (India, Brazil and Columbia) had more than 5 rifampicin resistant cases during the period of 2009-2015. No increasing trend was observed. Most drug resistant cases were reported in countries where more testing is carried out therefore it is important to expand the surveillance program more widely, to be able to assess trends.<sup>19</sup>

### 6. Non-tuberculous mycobacterial (NTM) infections

Mycobacteria are aerobic Gram positive bacteria with over 100 identified species and most of them are living in the environment e.g. water and soil. The prevalence of environmental mycobacteria is higher in hot than in cold climates. Around 20 mycobacterial species are causing human diseases.

Non-tuberculous mycobacterial (NTM) are also known under the terms atypical mycobacteria and mycobacteria other than tuberculosis (MOTT). Pathogenic NTM can cause pulmonary infections, skin disease and lymphadenitis. The incidence of NTM disease is rising in the past decades. In high-income countries the incidence of NTM lymphadenitis in children is 0.6 to 2.15 cases per 100,000 children per year, and highest rates in the age below 4 years.<sup>20</sup>

The effects of BCG vaccination on NTM infections and especially Buruli ulcer disease (BUD) were recently analyzed in a systematic review.<sup>20</sup> The analysis revealed that BCG is protective against NTM lymphadenitis in children.

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<sup>19</sup> Cambau et al. Results of the global antimicrobial resistance surveillance network for leprosy 2009-2015: a call for vigilance for all communicable diseases. Submitted Article, 2017.

<sup>20</sup> Zimmermann and Curtis et al. Does BCG vaccination protect against non-tuberculous mycobacterial infection? 2017, unpublished (Department of Paediatrics, The University of Melbourne, Parkville, Australia).



The incidence of NTM infection in children in HIC countries is lower in BCG-vaccinated children (RR 0.04 (95%CI 0.01-0.21), concluding that BCG vaccination protects against NTM lymphadenitis.<sup>20</sup> European countries reported an increase in NTM infections when interrupting universal BCG vaccination.<sup>20,21,22</sup>

## 6.2. Buruli ulcer disease

BUD is a chronic debilitating disease caused by *Mycobacterium ulcerans*, which produces the toxin – mycolactone – which causes tissue damage and inhibits the immune response. Often the bacterium affects the skin and sometimes bone, and can lead to permanent disfigurement and long-term disability.

In 2015, 2037 new cases were reported from 13 countries, most patients are children aged less than 15 years. In the last 10 years more than 42,000 BUD cases were reported.<sup>23</sup> BUD was reported in Africa, South America and Western Pacific regions in 34 countries.<sup>23,24</sup> High endemic countries are Benin, Côte d'Ivoire, Ghana, Cameroon and Australia.<sup>23</sup> Three different lineages of *M. ulcerans* are described.<sup>23</sup> In Africa, the incidence of BUD is estimated to be between 21 and 320 cases per 100,000. Children aged below 15 years and adults aged above 49 years are at highest risk of infection.<sup>25</sup> Moreover, children below 5 years of age are less likely to be exposed to *M. ulcerans* than older children.<sup>23,26</sup> Potential risk factors for contracting the disease are contact with water (e.g. presence of wetland, swimming in rivers, contact with stagnant water, and farming activities near rivers), mosquito bites, and BUD history in the family.<sup>23,27</sup> Due to effective national BUD control programs the number of BUD is declining, and leading to hypothesize that humans are causative for the transmission by shedding bacteria into the environment, but the complete mechanism of transmission is not yet understood.<sup>23</sup>

A recent systematic review of randomized controlled trials (RCTs) on effectiveness of BCG against Buruli ulcer have revealed ~50% efficacy (RR 0.5, 95%CI 0.37-0.69) in African settings.<sup>20</sup> In more detail, two RCTs from Uganda report on lower incidence of BUD in BCG vaccinated compared to not vaccinated.<sup>20,28</sup> Higher protection rates were reported in low-incidence areas and only within the first year after vaccination.<sup>20,28</sup> Recent case-control studies in the Democratic Republic of Congo, Ghana and Togo did not observe significant evidence of a protective effect of routine BCG vaccination on the risk of developing either any BUD or severe forms of BUD. (OR 1.34, 95% CI 0.19 to 1.51).<sup>20,29,30</sup> Studies in Benin concluded that BCG vaccination at birth provides significant

<sup>21</sup> Romanus V et al. Atypical mycobacteria in extrapulmonary disease among children. Incidence in Sweden from 1969 to 1990, related to changing BCG-vaccination coverage. *Tubercle and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 1995;76(4):300-310.

<sup>22</sup> Trnka L et al. Six years' experience with the discontinuation of BCG vaccination. 4. Protective effect of BCG vaccination against the *Mycobacterium avium* intracellulare complex. *Tubercle and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 1994;75(5):348-352.

<sup>23</sup> Röltgen K and Pluschke G. Epidemiology and disease burden of Buruli ulcer: a review. *Research and Reports in Tropical Medicine*, November 2015.

<sup>24</sup> WHO. Buruli ulcer (*Mycobacterium ulcerans* infection) Fact sheet: available: <http://www.who.int/mediacentre/factsheets/fs199/en/>, accessed June 2017.

<sup>25</sup> Debacker M et al. Risk factors for Buruli ulcer, Benin. *Emerg Infect Dis*. 2006;12(9):1325–1331.

<sup>26</sup> Röltgen K et al. Late onset of the serological response against the 18 kDa small heat shock protein of *Mycobacterium ulcerans* in children. *PLoS Negl Trop Dis*. 2014;8(5):e2904.

<sup>27</sup> Jacobsen KH and Padgett JJ. Risk factors for *Mycobacterium ulcerans* infection. *Int J Infect Dis*. 2010;14(8):e677–e681.

<sup>28</sup> Bradley DJ et al. BCG vaccination against mycobacterium ulcerans infection (Buruli ulcer). First results of a trial in Uganda. *Lancet*. 1969;1(7586):111-115.

<sup>29</sup> Phillips RO et al., Effectiveness of routine BCG vaccination on buruli ulcer disease: a case-control study in the Democratic Republic of Congo, Ghana and Togo. *PLoS Negl Trop Dis*. 2015 Jan 8;9(1):e3457.

<sup>30</sup> Smith PG et al. The protective effect of BCG against *Mycobacterium ulcerans* disease: a controlled trial in an endemic area of Uganda. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1976;70(5-6):449-457.

protection against the development of *M. ulcerans* osteomyelitis in children under 15 years of age, but does not protect adults aged  $\geq 15$  years<sup>31</sup> and adults.<sup>32,33</sup> Studies in mice, by challenging animals with *M. ulcerans* injection into the footpad, reveal that BCG may lead to a transient protection but depending on host and pathogen.<sup>34,35,36</sup> Characterization of the *M. ulcerans* homologue of the mycobacterial antigen 85 (Ag85A) from BCG which is leading to the protective immune response indicated that cross-reactive protection might be possible, by demonstrating significantly reducing of the bacterial load in *M. ulcerans*-infected mice.<sup>37</sup> The evidence of BCG vaccination therefore suggests some protective effective against Buruli ulcer, but is not completely conclusive.



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2016. All rights reserved

Data Source: World Health Organization  
Map Production: Control of Neglected Tropical Diseases (NTD)  
World Health Organization



**Figure 4: Distribution of Buruli ulcer worldwide, 2015. WHO.**

Source: WHO. [http://gamapserver.who.int/mapLibrary/Files/Maps/Buruli\\_2015.png?ua=1](http://gamapserver.who.int/mapLibrary/Files/Maps/Buruli_2015.png?ua=1)

<sup>31</sup> Portaels, F et al Prophylactic effect of Mycobacterium bovis BCG vaccination against osteomyelitis in children with Mycobacterium ulcerans disease (Buruli ulcer). 2002. Clin. Diagn. Lab. Immunol. 9:1389-1391.

<sup>32</sup> Portaels F et al. Mycobacterium bovis BCG vaccination as prophylaxis against Mycobacterium ulcerans osteomyelitis in Buruli ulcer disease. Infect Immun. 2004 Jan;72(1):62-5.

<sup>33</sup> Nackers F et al. BCG vaccine effectiveness against Buruli ulcer: a case-control study in Benin. Am J Trop Med Hyg. 2006 Oct;75(4):768-74.

<sup>34</sup> Converse PJ et al. BCG-mediated protection against Mycobacterium ulcerans infection in the mouse. PLoS Negl Trop Dis. 2011 Mar 15;5(3):e985.

<sup>35</sup> Fraga AG et al. Cellular immunity confers transient protection in experimental Buruli ulcer following BCG or mycolactone-negative Mycobacterium ulcerans vaccination. PLoS One. 2012;7(3):e33406.

<sup>36</sup> Tanghe A et al. A booster vaccination with Mycobacterium bovis BCG does not increase the protective effect of the vaccine against experimental Mycobacterium ulcerans infection in mice. Infect Immun. 2007 May;75(5):2642-4. Epub 2007 Feb 26.

<sup>37</sup> Tanghe A et al. Protective efficacy of a DNA vaccine encoding antigen 85A from Mycobacterium bovis BCG against Buruli ulcer. Infect Immun. 2001 Sep;69(9):5403-11.

## 7. Current WHO recommendations (2004 and addition of 2007)

The current WHO recommendations for BCG vaccination are:

- 1 BCG vaccine dose to “all infants” (all healthy neonates), as soon as possible after birth, in countries with high TB burden
- No BCG revaccination or boosters
- Low burden TB countries may limit BCG vaccination to infants in high-risk groups (or TST negative older children), and adults who are at high risk for occupational TB exposure and are tuberculin skin test negative

### Low Endemicity Criteria\* to change to selective vaccination

\*International Union Against Tuberculosis & Lung Disease

- Efficient TB notification system in place
- Average annual notification rate of smear-positive pulmonary TB cases <5 per 100,000
- Average annual notification rate of TB meningitis in under 5 years < 1 per 10 million population during previous 5 years
- Average annual risk of TB infection below 0.1%

### WHO Policy Recommendation (2007) Infants at risk of HIV infection

- Children known to be HIV+, even if asymptomatic, should **NOT** be immunized with BCG

### National decision-making on BCG vaccination to be guided by local factors:

- Prevalence of TB in the general population
- Potential for infant exposure to TB
- Prevalence of HIV infection
- Coverage and efficacy of interventions to prevent MTCT of HIV
- Rates of exclusive and mixed breastfeeding
- Capacity to conduct follow-up of immunized children
- Capacity to perform early virological infant diagnosis (in the first months of life)

### WHO Policy Recommendation (2004) Special Risk Groups

#### Adults:

- BCG vaccination NOT recommended (incl. pregnant women)
- Consider for TST negative persons in unavoidable and close contact with cases of multi-drug resistant TB

There is currently no official WHO recommendation for the use of BCG against leprosy or *M. ulcerans*.

## 8. Country policies and implementation

Two different sources of data were used to analyse the policy of countries, the BCG world atlas (updated in 2017)<sup>38</sup> and the WHO/UNICEF Joint Reporting (JRF) (data from 2016)<sup>39</sup>

Based on the data from 180 countries in the BCG World Atlas 157 (87.2%) countries recommended universal BCG vaccination in 2016, while the remaining 23 countries recommended selective vaccination of high-risk groups or had stopped BCG vaccination altogether<sup>38</sup>. Based on the JRF data in 2016 (data of 194 member states) 141 member stated that they recommended universal birth dose, 14 countries within the first week, 21 countries did not have BCG vaccination in the routine schedule and 25 countries recommend selective BCG vaccination or vaccination at a later in childhood (1 during the first month of life, 7 during the first year).

**Table 3: Country practice of BCG vaccination reported in the JRF in 2016<sup>39</sup>**

<b>Total number of countries</b>	<b>194</b>	
• <b>no BCG in the routine schedule</b>	<b>21</b>	<b>10.82%</b>
• <b>BCG vaccination given at birth:</b>	<b>141</b>	<b>72.68%</b>
• <b>BCG vaccination given within the first week</b>	<b>14</b>	<b>7.22%</b>
universal vaccination given at birth and within the first week	143	73.71%
vaccination given at birth and within the first week in high risk groups	12	6.19%
• <b>BCG vaccination given later during life</b>	<b>18</b>	<b>9.28%</b>
universal vaccination	5	2.58%
vaccination in in high risk groups	13	6.7%

Countries which are recommending selective BCG vaccination or no BCG vaccination at all are mostly located in Western Europe. The selective vaccination approach mainly focusses on recommending BCG vaccination in high-risk infants, infants born in high-risk TB settings and individuals involved in high TB risk occupations (e.g. health care workers) or travel. Additional variations in BCG vaccination strategies include 8 countries<sup>38</sup> that recommend tuberculin skin testing post-BCG vaccination. Of note 33 countries had previously recommended multiple BCG vaccinations, but have since ceased revaccination to use a single BCG dose.<sup>38</sup> In the 2016 JRF data, 6 countries still reported practicing BCG revaccination (Bulgaria, Kazakhstan, Russian Federation (the), Tajikistan, Turkmenistan, Ukraine).<sup>39</sup> All countries are high incidence countries and use the Russian BCG strain.

### 8.2. Country policies on the use of BCG against leprosy

Brazil officially recommends BCG (re)vaccination (up to 2 lifetime doses of BCG) for contacts without signs or symptoms of leprosy upon examination, regardless of whether the index case is classified as paucibacillary (PB) or multibacillary (MB). Other countries recommending BCG vaccination as part of national policy to prevent leprosy among contacts of leprosy cases are Colombia (since the year 2000) and Australia (since the year 2008) for children whose parents have leprosy and/or a diagnosis of leprosy, as found in a recent survey conducted by GLP whose results have been recently published.<sup>40</sup>

<sup>38</sup> Zwerling A, et al. The BCG World Atlas: A database of global BCG vaccination policies and practices. PLoS Med. 2011;8(3).

<sup>39</sup> WHO/UNICEF joint reporting process, Data, statistics and graphics 2016. Available at [http://www.who.int/immunization/monitoring\\_surveillance/data/en/](http://www.who.int/immunization/monitoring_surveillance/data/en/), accessed July 2017.

<sup>40</sup> Gillini et al. Global practices in regard to implementation of preventive measures for leprosy. PLoS Negl Trop Dis. 2017 May; 11(5): e0005399.

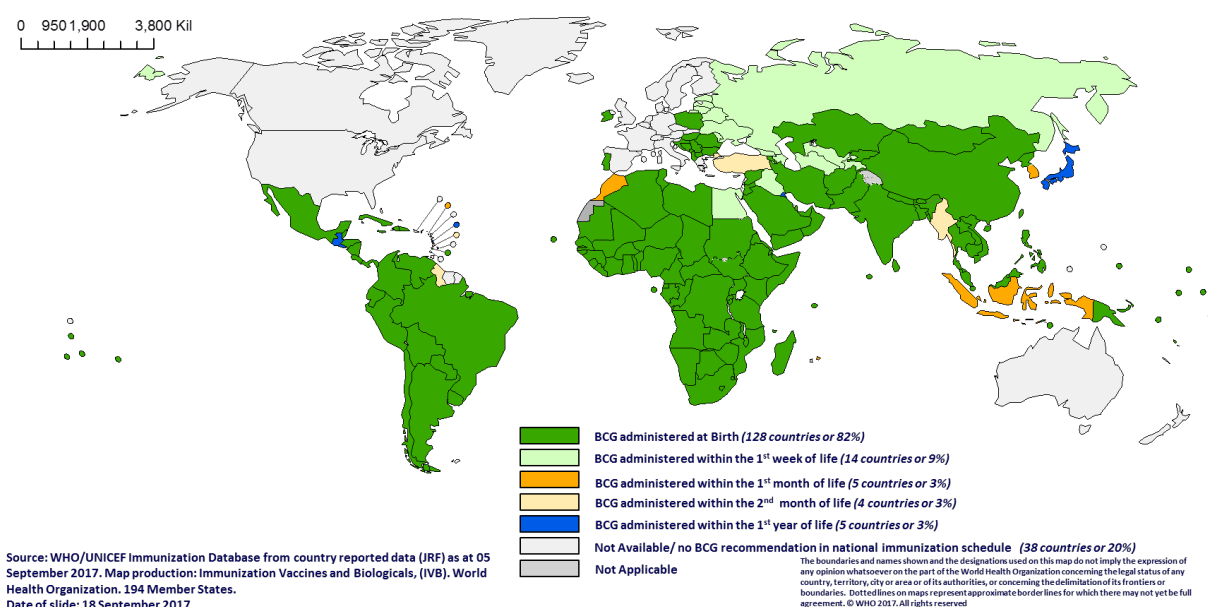


Figure 5: BCG vaccination policies by WHO member states, data from 2016.<sup>39</sup>

Table 4: Summary of global practices in regard with use of immunoprophylaxis for leprosy by region.

Region	Countries using BCG vaccination or revaccination of leprosy contacts as national policy (year)	Countries using BCG/other vaccine for leprosy contacts under research studies (Year)
AFR	None	None
AMR	Brazil (1987), Colombia (2000), Peru (planned)	None
EMR	None	None
SEAR	None	Bangladesh (2016) India ( <i>Mycobacterium indicum pranii</i> vaccine, planned for the beginning of 2017)
WPR	Australia (2008)	None

Source: Gillini et al.<sup>40</sup>

### 8.3. Review of BCG vaccine policies in countries with low TB burden

BCG immunization policies can vary widely in countries with low TB burden, therefore a review of BCG vaccination strategies was conducted through compilation of data from the WHO/UNICEF Joint Reporting Form, national health department websites, Vaccine European New Integrated Collaboration Effort (VENICE) documents, BCG World Atlas database, and literature review using the PubMed database. Review of these data sources showed that there were significant variations in BCG vaccination across 33 low TB incidence countries, defined by the WHO as having an annual TB notification rate of  $\leq 100$  cases of all TB forms per million.

In 2016 (based on the BCG World Atlas) universal vaccination at birth was still recommended in the following 8 countries: Costa Rica, Cuba, the Czech Republic, Ireland, Jamaica, Malta, the United Arab Emirates, and West Bank and Gaza Strip. Jordan and Greece vaccinated children before school age. In Slovakia, neonatal BCG vaccination was optional and free but not mandatory. BCG vaccination of neonates and children less

than 5 years travelling to countries with high TB incidence was recommended in 7 countries: Australia, Canada, Finland, Jordan, New Zealand, Sweden, and Switzerland. Australia offered BCG vaccination for travelling children over 5 years of age as well. Finland, Ireland, Israel, and Sweden selectively vaccinated immigrant children born in high TB incidence countries, while Jordan, New Zealand, Norway, and Slovenia also vaccinated infants living with parents, household members, or caretakers from high incidence countries.

Targeted BCG vaccination in high-risk populations was recommended in several countries. Infants living in a household with persons either with current or past TB were recommended for vaccination in 9 countries: some states of Canada, Cyprus, Finland, Greece, Ireland, Jordan, New Zealand, Sweden, and the USA. Neonates born to parents with current or past leprosy were also recommended for BCG vaccination in Australia and Jordan. Indigenous Australian Aboriginals and Canadian Inuit and first nation’s populations at high risk for TB were also recommended to have neonatal BCG vaccination. Health care workers at high risk of exposure to drug resistant cases were recommended for vaccination in 6 countries: Australia, France, Ireland, Italy, Jordan, and the USA.

#### 8.4. Switching vaccination policy – from universal to selective vaccination

The generated data from the BCG World Atlas are categorizing countries into 3 main policies: (a) current recommendation for universal BCG vaccination at set age (b) previously recommended universal BCG vaccination but currently does not; or (c) BCG recommendation for selected high-risk groups or never recommended at all.

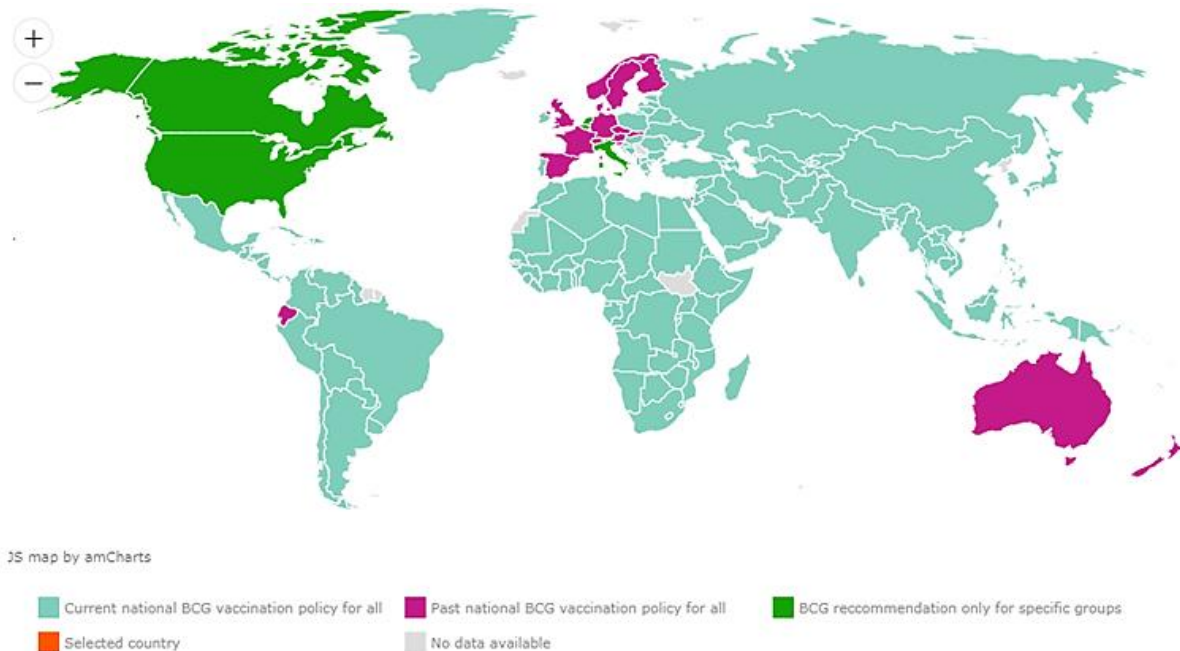


Figure 6: World map displaying BCG vaccination policies by country. Source: BCG World Atlas.



In 2016, WHO/UNICEF Estimates of National Immunization Coverage (WUENIC)<sup>41</sup> did not have routine BCG vaccination data for the following 11 countries: Austria, the Czech Republic, Denmark, Finland, France, Greece, Israel, Italy, Malta, Slovakia, and Slovenia. All 11 countries are located in Europe and 8 (73%) countries did not have routine BCG vaccination for over a decade. Additionally, Canada, Germany, the Isle of Man, Spain, the United Kingdom, and the U.S., had also ceased universal BCG vaccination programmes and therefore not included in the coverage data<sup>38</sup>. The most recent country to discontinue routine BCG vaccination was Slovakia in 2012, followed by the Czech Republic and France in 2009 and 2007 respectively. Although many countries began BCG vaccination programmes in the 1940s-1980s, WUENIC data also shows that several countries have recently adopted BCG vaccination.<sup>38,41</sup>

There are established guidelines for countries shifting away from universal vaccination and towards targeted vaccination of high-risk groups.<sup>42,43</sup> The 2004 WHO position paper<sup>4</sup> on the use of BCG vaccine recommended that “in countries with a high burden of TB, a single dose of BCG vaccine should be given to all infants as soon as possible after birth”. However, in countries with a low burden of TB, countries may choose to “limit BCG vaccination to neonates and infants of recognized high-risk groups for the disease or to skin-test-negative older children”.

### 8.5. BCG vaccine coverage estimate

To determine current BCG policy implementation and vaccine uptake, WHO/UNICEF Estimate of national immunization coverage (WUENIC) was analysed by individual country practices and by WHO region.

The WUENIC vaccine coverage estimates (of countries recommending universal BCG vaccination) is 89.82% across 169 countries in 2016, and all WHO regions have average vaccine coverage greater than 86%. Africa has the lowest average BCG vaccine coverage (86.6%) by WHO region, while the highest average BCG vaccine coverage (94.7%) is in the Americas. The data show an increasing trend in BCG immunization up to 1990, after which vaccine coverage appears to plateau between 80-90% (Figure 7). Since 2000, 5 countries including Japan, Jordan, Kuwait, South Sudan, and Timor-Leste, have increased their BCG vaccine coverage dramatically.

Worldwide, the percentage of countries with BCG coverage <50% has decreased from 16% to less than 5% in the last 25 years (Figure 8). A majority of countries have BCG coverage greater than 80%, with more countries increasing their coverage every year (Figure 8). However, BCG coverage still remains low in some countries, with coverage estimates showing that 11 countries have relatively low BCG coverage (<70%). Within these countries, 4 are in Africa, 3 are in Europe, 3 are in the Eastern Mediterranean, and one is in the Western Pacific region. Although some of these countries are in low TB incidence countries without routine BCG vaccine programmes, such as Sweden, high TB incidence countries such as Equatorial Guinea, Papua New Guinea, and Somalia, also report extremely low vaccine coverage estimates of 48%, 65%, and 39% respectively.

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<sup>41</sup> WHO/UNICEF Estimates of National Immunization Coverage. Available at [http://www.who.int/immunization/monitoring\\_surveillance/data/en/](http://www.who.int/immunization/monitoring_surveillance/data/en/), accessed July 2017.

<sup>42</sup> Dierig A, Tebruegge M, Krivec U, Heining U, Ritz N. Current status of Bacille Calmette Guerin (BCG) immunisation in Europe - A ptbnet survey and review of current guidelines. *Vaccine*. Elsevier Ltd; 2015;33(38):4994–9. Available from: <http://dx.doi.org/10.1016/j.vaccine.2015.06.097>

<sup>43</sup> Altes HK, Dijkstra F, Lugnèr A, Cobelens F, Wallinga J. Targeted BCG Vaccination Against Severe Tuberculosis in Low-prevalence Settings. *Epidemiology*. 2009;20(4):562–8. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00001648-200907000-00015>

The BCG vaccine coverage is  $\geq 99\%$  in 52 countries, with America, Europe, and the Western Pacific region accounting for the majority (73%) of the high coverage countries. Interestingly, Zwerling et al.'s (2011) world map of varying BCG vaccine policies shows that countries that previously recommended universal BCG vaccination but are currently stopping routine immunization, are also in the America, Europe and the Western Pacific region.<sup>38</sup> As countries achieve high BCG vaccine coverage through improved health systems and decrease their TB incidence, policymakers are likely to modify universal vaccination practices to fit the evolving epidemiology of the local population.

### **Vaccine coverage of high-risk groups by selective vaccination**

As the incidence of TB continues to decline in the developed countries, selective vaccination strategies in high-risk populations are increasingly being used as an alternative to universal BCG vaccination.<sup>44,45</sup> However, selective immunization programmes depend heavily on the ability to identify and reach the target population.<sup>46</sup>

Feiring *et al.* (2016) estimated BCG vaccine coverage in selected target groups in Norway and found that children targeted for selective BCG vaccination had a lower coverage of the target vaccine when compared to vaccines in the universal programme<sup>46</sup>. This study emphasizes that improved mechanisms for identifying eligible children and subsequent vaccine delivery are essential for the success of targeted vaccine strategies.<sup>46</sup>

In addition to immigrant populations from countries with high risk of TB, health care workers (HCWs) and travellers to high TB incidence countries are also commonly identified as high-risk groups for targeted BCG vaccination strategies.<sup>47,48</sup> A literature review on European policies for BCG vaccination in HCWs revealed a wide range of policies including immunization of only high-risk sector HCWs, all unvaccinated Mantoux-negative HCWs, or not recommending the BCG vaccine for HCWs at all.<sup>47</sup> Analysis of 3 case studies of children who developed travel-associated TB disease highlighted an absence of information on BCG vaccine efficacy for prevention of travel-associated TB.<sup>48</sup> Due to the paucity of evidence, recommendations on the use of pre-travel BCG immunization were inconsistent and a low threshold for pre-travel immunization in children was advised until more evidence-based guidelines could be produced.<sup>48</sup>

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<sup>44</sup> Tu H-AT, Vu HD, Rozenbaum MH, Woerdenbag HJ, Postma MJ. A review of the literature on the economics of vaccination against TB. *Expert Rev Vaccines*. 2012;11(3):303–17.

<sup>45</sup> Hersh AL, Tala-Heikkilä M, Tala E, Tosteson ANA, Fordham von Reyn C. A cost-effectiveness analysis of universal versus selective immunization with *Mycobacterium bovis* bacille Calmette-Guérin in Finland. *Int J Tuberc Lung Dis*. 2003;7(1):22–9.

<sup>46</sup> Feiring B, Laake I, Molden T, Haberg SE, Nokleby H, Seterelv SS, et al. Do selective immunisation against tuberculosis and hepatitis B reach the targeted populations? A nationwide register-based study evaluating the recommendations in the Norwegian Childhood Immunisation Programme. *Vaccine*. Elsevier Ltd; 2016;34(17):2015–20. Available from: <http://dx.doi.org/10.1016/j.vaccine.2016.02.060>

<sup>47</sup> Bo M, Zotti CM. European policies on tuberculosis prevention in healthcare workers: Which role for BCG? A systematic review. *Hum Vaccines Immunother*. Taylor & Francis; 2016;12(11):2753–64. Available from: <http://dx.doi.org/10.1080/21645515.2016.1200776>

<sup>48</sup> Ritz N, Connell TG, Curtis N. To BCG or not to BCG?. Preventing travel-associated tuberculosis in children. *Vaccine*. 2008;26(47):5905–10.



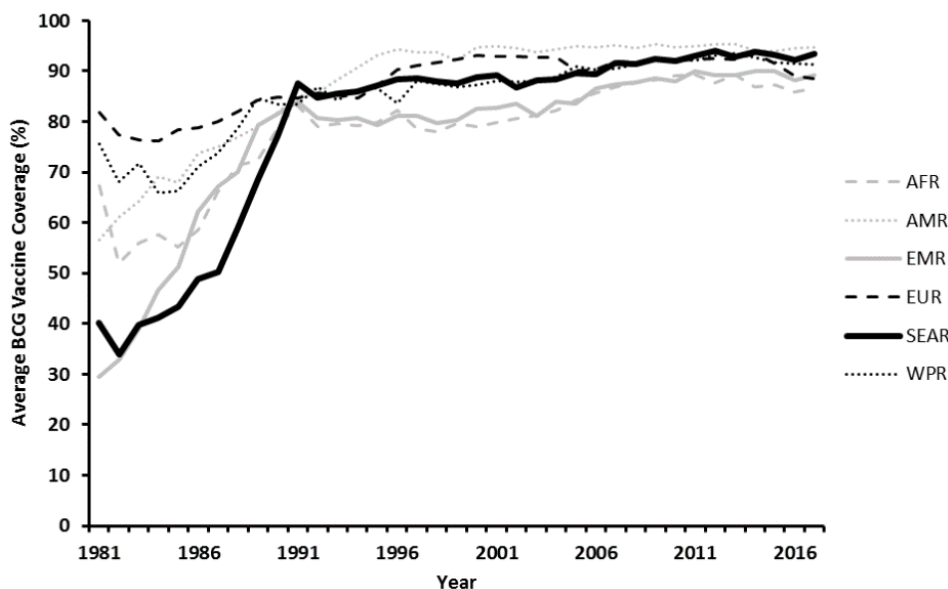


Figure 7: BCG vaccine coverage by WHO Region from 1980-2016.

Source: WUENIC

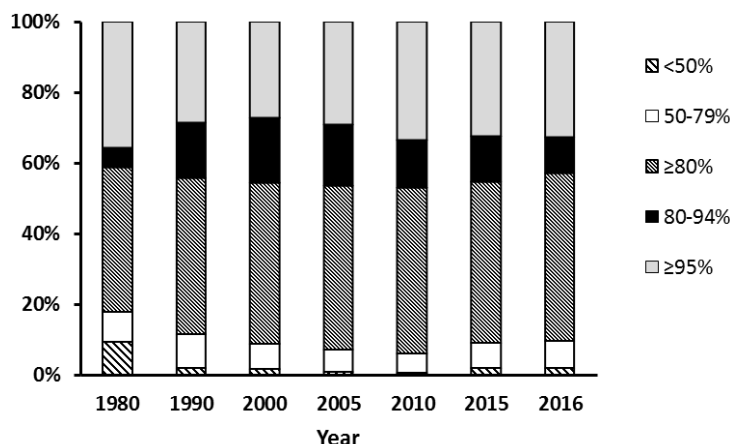


Figure 8: Percentage of countries with BCG coverage <50%, 50-79%, 80-94%, and ≥95%.

Source: WUENIC

### 8.6. Timeliness of BCG vaccination

BCG timeliness findings were obtained from a study examining “Doses of vaccine given out of order or on the same day in the EPI: analysis of survey data” by Colin Sanderson at the London School of Hygiene and Tropical Medicine funded by the World Health Organization Initiative for Vaccine Research. This study used Demographic Health Surveys (DHS) rounds 5 and 6, and Multiple Indicator Cluster Surveys (MICS) round 3 from 71 countries.<sup>49</sup> The median vaccine years covered 2004 to 2007.

<sup>49</sup> Afghanistan; Albania; Armenia; Azerbaijan; Bangladesh; Belize; Benin; Bolivia; Burkina Faso; Burundi; Cambodia; Cameroon; Central African Rep; Chad; Colombia; Comoros; Congo DR; Congo Rep; Costa Rica; Cote d'Ivoire; Djibouti; Dominican Rep; Egypt; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea Bissau; Guyana; Haiti; Honduras; India; Iraq; Jamaica; Jordan; Kenya; Kyrgyz Rep; Lao PDR; Lesotho; Liberia; Madagascar; Malawi; Maldives; Mali; Mauritania; Mongolia; Mozambique; Namibia; Nigeria; Pakistan; Peru; Rwanda; Senegal; Sierra Leone; Sudan; Swaziland; Tajikistan; Tanzania; Thailand; Timor Leste; Togo; Tunisia; Uganda; Ukraine; Uzbekistan; Vanuatu; Vietnam; Yemen; Zambia; Zimbabwe

**Methods**

To allow the same 24-month ‘follow-up’ period for each infant, the analysis was restricted to infants at least 24 months old at the time of the mother’s interview. Only data from infants with dates for all relevant vaccines given could be used. In some surveys, many dates of administration are missing. Therefore, only surveys with at least 40% of vaccine doses dated were included in the analysis. Percentages of infants administered BCG were calculated by week, up to week 130 for each country.

**Findings**

The median BCG coverage among infants across the 71 countries surveyed was 38% by 1 week of age; 75% by 6 weeks of age; 88% by 14 weeks of age and 93% by 52 weeks of age.

**Table 5: BCG coverage among infants by week of administration in 71 countries\***

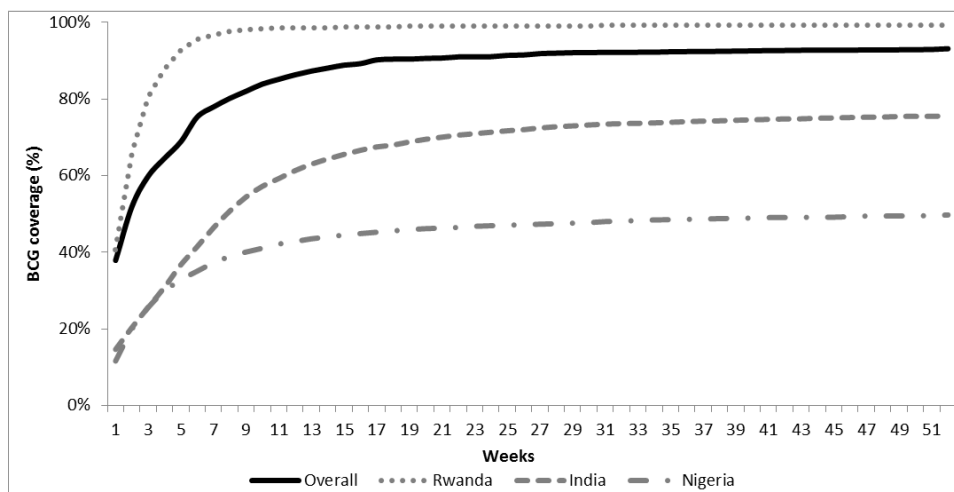
	Number of countries with BCG coverage N (%)		
	<50% N(%)	50-80% N(%)	>80% N(%)
At 1 week	48 (48%)	12 (17%)	11 (15%)
At 6 weeks	13 (18%)	29 (41%)	29 (41%)
At 14 weeks	0 (0%)	8 (11%)	63 (88%)

\*Not weighted for the population

**Data limitations**

Only surveys with at least 40% of vaccine doses administered dated were included in the analysis.

Overall coverage for 71 countries (solid black line); coverage for Rwanda (dashed circular line); coverage for India (solid dashed line) and Nigeria (solid dashed and circular line)



**Figure 9: Median BCG coverage among infants by 1 week up to 1 year of age.**

## 9. Vaccine strains and other factors that are influencing safety and effectiveness of BCG vaccines

BCG vaccine contains a live, attenuated strain of *M. bovis* that was originally isolated from TB infected cattle and cultured for a period of 13 years and a total of 231 passages.<sup>50</sup> Since the BCG vaccine was first used to immunize humans in 1921, over the years, different BCG vaccine seed strains have evolved from the original vaccine strain for production.

BCG vaccine strains that are used worldwide differ in terms of their genetic and phenotypic properties. The original BCG vaccine strain was formerly distributed by the Pasteur Institute of Paris and sub-cultured in different countries using different culture conditions that were not standardised. Over the years, more than 14 sub-strains of BCG have evolved and have been used as BCG vaccine in different parts of the world.

**Table 6: List of manufacturers and vaccine strains (July 2017),**

Manufacturer	Country	Strain	Supplying beyond domestic market	PQ Status	Releasing NRA Functionality	Vial size	Route of administration	Ongoing production
ANLIS	Argentina	Pasteur 1173 P2 strain		N	N	10ds/20ds	unknown	Y
Fundacao Ataulpho de Paiva	Brazil	Moreau, Rio strain	x	N	Y	10ds	unknown	N
BulBio-NCIPD	Bulgaria	Bulgarian substrain (Sofia) SL222	x	Y	Y	10ds/20ds	intradermal	Y
China National Biotec Group (Shanghai)	China	Chinese substrain Shanghai D2PB30 2 (derived from Danish strain 823)	x	N	Y	5ds	intradermal	Y
China National Biotec Group (Chengdu)	China	Chinese substrain Shanghai D2PB30 2 (derived from Danish strain 823)	x	N	Y	5ds	intradermal	Y
Shaanxi Pharmaceutical Holding Group Biological Products	China	Chinese substrain Shanghai D2PB30 2 (derived from Danish strain 823)		N	Y	20ds	unknown	Y
AJBiologics	Denmark	Danish 1331 strain	x	Y	Y	10ds/20ds	intradermal	N
Serum Institute of India	India	Russian (Moscow) - 368	x	Y	Y	10ds/20ds	intradermal	Y
Green Signal Biopharma	India	Danish 1331 strain	x	Y	Y	20ds	intradermal	Y
BCG Vaccine Laboratory, Chennai	India	Danish 1331 strain, Madras Working Seed Lot (MWSL)	x	N	Y	10ds/20ds	intradermal	N
Taj Pharma Ltd	India	Russian (Moscow) - 368		N	Y	20ds	unknown	Y

<sup>50</sup> WHO. State of the art of new vaccine research and development. 2006 (WHO/IVB/06.01; available at [http://whqlibdoc.who.int/hq/2006/WHO\\_IVB\\_06.01\\_eng.pdf](http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.01_eng.pdf), accessed August 2017.

## BCG vaccines – Vaccine strains and other factors

Manu- facturer	Coun- try	Strain	Supplying beyond domestic market	PQ Status	Releasing NRA Functionality	Vial size	Route of ad- ministration	Ongoing pro- duction
BioFarma	Indo- nesia	Pasteur 1173P strain	x	N	Y	5ds/ 10ds	intradermal	Y
Pasteur Instiute of Iran	Iran	Pasteur 1173P2 strain		N	Y	20ds	intradermal	Y
Japan BCG Laboratory (JBL)	Japan	Tokyo 172-1 strain	x	Y	Y	10ds/ 20ds	intradermal/ percoutaneous (multipuncture device)	Y
Biomed Lublin	Poland	Moreau strain	x	N	Y	10ds	intracutaneous	Y
Microgen	Russia	Russian (Moscow) - 368	x	N	Y	10ds/ 20ds	intradermal	Y
Inst. Of Virology, Vaccines and Sera Torlak	Serbia	Pasteur 1173P2 strain	x	N	N	10ds/ 20ds	intradermal	Y
NIIDV	Taiwan	Tokyo 172 strain		N	Y	20ds	intradermal	Y
Queen Saovabha Mem. Inst (Thai Red Cross)	Thai- land	Japanese strain		N	Y	10ds	intradermal	Y
Inst. Pasteur Tunis	Tunisia	Pasteur 1173P2 strain		N	Y	20ds	intradermal	Y
Merck & Co (former Organon)	United States	TICE® strain		N	Y	1ds	percoutaneous (multipuncture device)	Y
IVAC - Institute of Vaccines and Medical Biologicals	Viet- nam	Pasteur 1173P2 strain		N	Y	20ds	unknown	Y

### Data from April 2017

All manufacturers are in condition of serving the domestic market where the product is registered

AJ Biologics acquired the BCG production facility of Statens Serum Institute

Information for Taj Pharma and Shaanxi are derived from public available sources

Filling and finishing companies as well as distributors not included

There may be differences in protection against TB between different strains of BCG, between products made from the same strain by different manufacturers, and between batches made by individual manufacturers (perhaps caused by having more than one genotype in some seed lots).<sup>51</sup> There is currently not a consensus. A systematic review<sup>52</sup> of published trials did not find an association with vaccine strains. However, a large randomized trial in 303,092 neonates in Hong Kong however found that the risk of TB with BCG-Pasteur vaccine was 45% (95% CI 22% - 61%) less than with BCG-Glaxo but was published only in abstract form.<sup>53,54</sup> In

<sup>51</sup> Biering-Sorensen S, Jensen KJ, Aamand SH, Blok B, Andersen A, Monteiro I, et al. Variation of growth in the production of the BCG vaccine and the association with the immune response. An observational study within a randomised trial. *Vaccine*. 2015;33(17):2056-65.

<sup>52</sup> Mangtani P et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clin Infect Dis* 2014; 58: 470–80. Figure 3 and 4.

<sup>53</sup> Comstock GW. Simple, practical ways to assess the protective efficacy of a new tuberculosis vaccine. *Clin Infect Dis*. 2000;30 Suppl 3:S250-3.

<sup>54</sup> Shann F. Editorial Commentary: Different Strains of Bacillus Calmette-Guerin Vaccine Have Very Different Effects on Tuberculosis and on Unrelated Infections. *Clin Infect Dis*. 2015;61(6):960-2.

one observational study<sup>55</sup>, there were large differences in the effectiveness of different BCG vaccine strains in a series of cohort studies in Kazakhstan:

	Effectiveness against	
	Clinical TB notifications	Culture confirmed TB
<b>BCG-Japan</b>	69%	92%
<b>BCG-Serbia</b>	43%	82%
<b>BCG-Russia</b>	22%	51%

The authors noted potential sources of bias in their study, including possible variations in tuberculosis incidence over time, possible changes in diagnostic and notification practices, and possible catch-up vaccination in those unvaccinated. The limitations of current studies make it difficult to draw definitive conclusions. Further research is thus needed.

The effect of differing colony forming units (CFU) concentrations in BCG vaccines is unknown. For example, a dose of BCG-Japan contains approximately 5-fold more CFU than the other WHO prequalified BCG vaccines. The number of CFU claimed by the manufacturers in each 0.05 ml infant intradermal dose is:

Country	Manufacturer	Strain	Dose	CFU
<b>Bulgaria</b>	Intervax	Russia-I	0.05 ml	0.75 - 3 x 10 <sup>5</sup> CFU
<b>Denmark</b>	SSI	Danish 1331	0.05 ml	1 - 4 x 10 <sup>5</sup> CFU
<b>India</b>	Green Signal	Danish 1331	0.05 ml	1 - 4 x 10 <sup>5</sup> CFU
<b>India</b>	SII	Russia-I	0.05 ml	1 - 4 x 10 <sup>5</sup> CFU
<b>Japan</b>	JBL	Tokyo 172	0.05 ml	1.8 - 19.5 x 10 <sup>5</sup> CFU

In addition to determining the CFUs manufacturers are also required to measure the total bacterial concentration which measures both viable and killed bacteria (WHO TRS 979 Annex 3). It is known that there can be a significant quantity of killed bacteria in the finished vaccine depending on manufacturing process<sup>56</sup>, however it is not known whether the quantity of killed bacteria has any impact on the immunogenicity or safety/reactogenicity of the vaccine.

Very little is known about the comparative effectiveness of the WHO prequalified BCG vaccines, and deep genome sequencing has not been done to determine how many different genotypes are in each of the WHO prequalified BCG vaccines. The mixture of genotypes in individual BCG vaccines (at least 2 genotypes in BCG-Denmark and four in BCG-Japan) may contribute to the large inter-batch variation that compromises manufacture. Using a single genotype is likely to lead to more consistent production of BCG and reduce the potential for shortages. Deep genome sequencing should be used routinely for quality control during production of BCG vaccine to monitor variation in the genotypes present in the product.<sup>57</sup>

The formulation of international requirements for freeze-dried BCG vaccine is complicated by the following:

- a) a number of different strains derived from the original strain of BCG are used in vaccine manufacture;

<sup>55</sup> Favorov M, Ali M, Tursunbayeva A, Aitmagambetova I, Kilgore P, Ismailov S, et al. Comparative tuberculosis (TB) prevention effectiveness in children of Bacillus Calmette-Guérin (BCG) vaccines from different sources, Kazakhstan. PLoS One. 2012;7(3):e32567.

<sup>56</sup> Gheorghiu et al. Stabilisation of BCG Vaccines. Dev Biol Stand 87, 251-261. 1996.

<sup>57</sup> Wada T, Maruyama F, Iwamoto T, et al. Deep sequencing analysis of the heterogeneity of seed and commercial lots of the bacillus Calmette-Guérin (BCG) tuberculosis vaccine substrain Tokyo-172. Sci Rep. 2015;5:17827.

- b) many of the strains used in vaccine manufacture contain more than one genotype;
- c) a number of different manufacturing and testing procedures are employed;
- d) it is difficult to determine the relationship between significant differences *in vitro* and *in vivo* between different BCG vaccine strains, in one product over time and differences in protective efficacy against TB in humans;
- e) vaccines are produced with different total bacterial content and numbers of culturable particles; (e.g. BCG Tokyo contains approximately 5-fold more CFU per dose than BCG Russia)
- f) vaccines intended for administration by different routes are prepared. The WHO recommendations<sup>58</sup> focus on ensuring the production of consistent vaccine lots with characteristics similar to those of lots previously shown to be safe and effective. In order to avoid variation, the total number of passages from master seed lot to final product should be monitored and controlled. WHO Reference Reagent substrains (BCG Danish 1331, Tokyo 172-1, Russian BCG-I and BCG Moreau-RJ) are also available as comparators for validity and consistency monitoring in viability assays.

## 10. Market update BCG Vaccines<sup>59</sup>

### Summary

For 2017, BCG vaccine supply is estimated to be 1.5 times greater than forecasted demand. This excess supply is reassuring given the instability of the manufacturing process and is important progress from the restricted supply situation in recent years. However, demand flexibility is limited due to in-country product registration constraints and supply still being concentrated, with a few large suppliers with prequalified products serving most countries. Consequently, shortages may still occur.

**Market highlights-** Over ten years (2005–2015), short-duration stock-outs of BCG (maximum 1.5 months) have been reported across all regions, income groups and procurement methods. The African region, low income countries (LICs) and lower-middle income countries (LMICs) were most affected. In 2014 and 2015, average stock-out duration increased. Stock-outs seem to be caused by several factors: production issues, countries having only one product registered, timely availability of financing (national or external), procurement shortcomings, and inefficient vaccine management.

**Global Demand-** Annual global demand is forecasted at ~350M doses according to a model based on country-reported EPI schedule, UN Population Division (UNPD) population, WHO-UNICEF estimated coverage, 50% wastage, and historical procurement data. Information on past country purchases shows that countries may be over procuring BCG, possibly due to actual wastage >50%, large country stocks, or country target population greater than UNPD estimates. The greatest difference in forecasted demand and historical procurement is seen for self-procuring LMICs.

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<sup>58</sup> WHO. Recommendations to assure the quality, safety and efficacy of BCG vaccines. Annex 3 in WHO TRS No. 979. Available at [http://who.int/biologicals/areas/vaccines/TRS\\_979\\_Annex\\_3.pdf?ua=1](http://who.int/biologicals/areas/vaccines/TRS_979_Annex_3.pdf?ua=1).

<sup>59</sup> The data sources for assessing stock-outs were regional consultations (current) and the WHO/UNICEF Joint Reporting Form (JRF) reported data on stock-outs (past). The demand analysis included sources of historical procurement data (JRF and UNICEF) and global demand forecast (Linksbridge/Gates Foundation Global Vaccine Market Model). Data for the supply analysis were obtained by manufacturer interviews, PAHO Revolving Fund consultations, historical procurement data (JRF and UNICEF), and review of published articles and four policy papers concerning supply. The pricing analysis is based on review of historical data (WHO Vaccine Product, Price and Procurement database (V3P), UNICEF SD, PAHO Revolving Fund)

**Global Supply-** Between 2013 and 2015, manufacturing issues for most WHO prequalified (PQ'd) vaccines led to temporary reduced production or suspension of production. Additionally, some non-PQ'd vaccines exited the market. Nevertheless, supply increased significantly in 2016, as some of the manufacturers' production issues were resolved and the vaccine of a new supplier, GreenSignal, was PQ'd. In 2017, supply is estimated to reach ~500M doses from 19 suppliers. The suppliers can be split into two groups: (1) four suppliers with PQ'd products that can reach 169 countries (86% of WHO member states) that accept UN procurement or have one of the PQ'd products registered and (2) fifteen suppliers with non-PQ'd products that can serve 52 countries where they have product registered. In 2017/2018, three manufacturers are expected to be back on the market and additional capacity could be made available from one other currently active manufacturer.

**Supply/Demand Balance-** For 2017, BCG vaccine supply is estimated to be 1.5 times greater than forecasted demand based on historical procurement data (JRF and UNICEF) and global demand forecast.<sup>60</sup> This excess supply is reassuring given the instability of the manufacturing process and is important progress from the restricted supply situation in recent years. Nevertheless, the BCG market is not risk free. Two main factors contribute to the risk:

- **Supply concentration:** 50% of global vaccine supply is produced by two manufacturers, and, more important, those two manufacturers account for 75% of supply of products PQ'd by WHO. Though the loss of a major supplier would not lead to a supply/demand imbalance, it would certainly create a constrained supply situation. In those circumstances, vaccine requirements for self-procuring countries and countries procuring through the United Nations will need to be coordinated. Of note, these two major suppliers are released by the same National Regulatory Authority (NRA): The Central Drugs Standard Control Organization (CDESCO) of India.
- **Limited demand flexibility:** one-third of countries have only one product registered and, as a result, may be at risk for shortages should a production issue occur. Among those, the most at risk are countries with BCG in the EPI schedule, a large birth cohort, and those that import vaccines, and thus have less control or visibility on production issues and risks.

**Pricing-** Over the past ten years, the price for BCG has remained low – the median reported price in 2015 was US \$0.52 (range \$0.04–\$15.08 for 29 reporting countries, plus UNICEF and PAHO each included as a single price point). Pricing data (2015) for self-procuring countries shows that price per dose varies by income level, with high income countries (HICs) paying significantly more than middle income countries (MICs), albeit for different products/presentations. Disparity by region is also seen; notably, LMICs in the African region (AFR) reported a much higher price per dose than the European region (EUR) or the Western Pacific region (WPR) for the same product. Countries (excluding HIC WPR outlier) are paying up to 32 times more than the UNICEF price. Affordability for countries has not been raised as an issue for the BCG market. Yet, the low price may be leading to under-investment on the production side.

**Areas for Action-** Global immunization stakeholders, countries and manufacturers can work to enhance sustainable access to BCG supply through the following methods:

- Collect and share information on global demand, supply and price of BCG to continue risk identification
- Enhance supply management at country level, reducing procurement volumes when necessary

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<sup>60</sup> Linksbridge SPC. Global Vaccine Market Model (GVMM) Demand Module. 2017.

- Investigate strengthening the production processes of a few key manufacturers for supply security
- Explore opportunities for registration of several BCG products in each country and following the “WHO Collaborative Procedure for Registration of Prequalified Products”

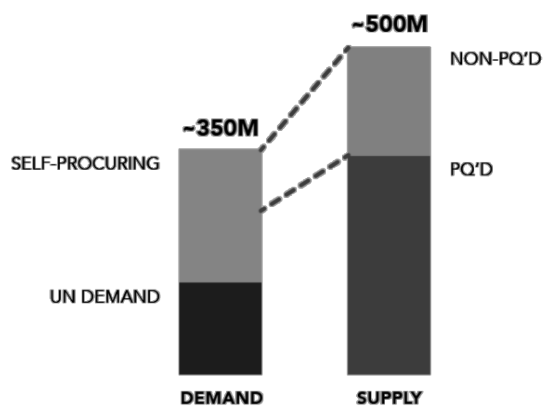


Figure 10: 2017 Estimated Supply/Demand Balance

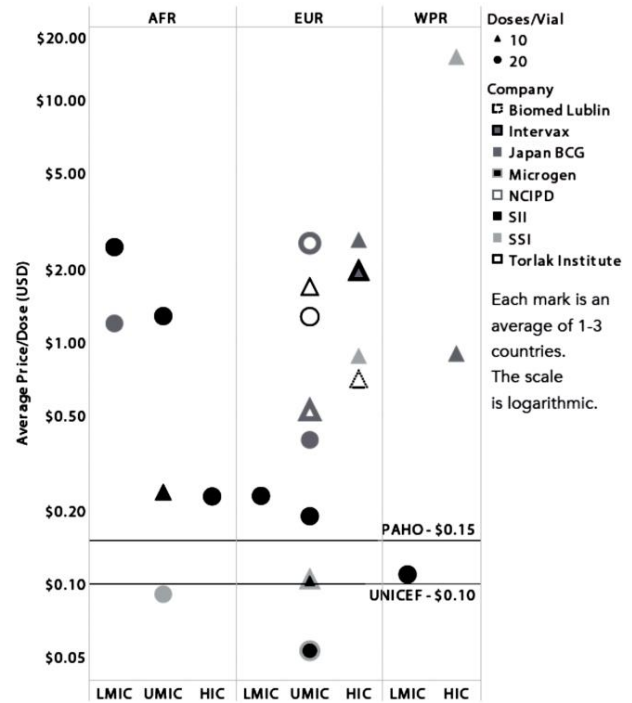


Figure 11: Average self-procuring Price/Dose by manufacturer (2015)

## 10.2. Impact of BCG vaccine shortages

Among countries experiencing BCG vaccine shortages, immunization policy changes included not administering the vaccine, administering the vaccine only when available, cohorting vaccinees on specific days to maximize use of multi-dose vials, and only administering the vaccine in certain populations and regions of the country.<sup>61</sup> Mathematical modeling of pediatric TB deaths during BCG supply shortages estimated that an additional 11,713 additional TB deaths would occur in the first 15 years of life per 10% annual supply shortfall.<sup>62</sup> As BCG supply shortages can result in increased pediatric TB mortality, collaboration between health agencies and vaccine manufacturers is crucial to ensure global BCG supply continuity.<sup>61,62</sup>

<sup>61</sup> Kontturi A et al. The impact of Bacille Calmette-Guerin shortage on immunisation practice and policies in Europe - A Paediatric Tuberculosis Network European Trials Group (ptbnet) survey. *Tuberculosis*. 2016;101:125–9.

<sup>62</sup> Harris RC et al. The potential impact of BCG vaccine supply shortages on global paediatric tuberculosis mortality. *BMC Med*. BMC Medicine; 2016;14(1):138. Available from: <http://bmcmmedicine.biomedcentral.com/articles/10.1186/s12916-016-0685-4>



### 10.3. How to mitigate the impact of BCG shortages

1. In light of the previous global shortage of BCG vaccines, WHO, with UNICEF, prepared a set of priority actions to help cope with the shortage and prioritize distribution of available doses. WHO should work with UNICEF, PAHO Revolving Fund, countries, and manufacturers to understand the cause of the shortage and attempt to resolve it
2. Careful planning of limited supply allocation should occur through collaboration between WHO, UNICEF Supply Division, PAHO Revolving Fund and BCG vaccine manufacturers to provide vaccines to priority countries. Countries/large refugee settings will be prioritized based on their TB and leprosy risk taking into consideration
  - The TB rate per 100,000 population, hence the highest TB transmission and where infants have the highest risk of being infected with TB. This of course will necessitate the updating of the development of a list of countries with the highest TB rate per 100,000 population. In particular, countries with health systems that are not able to track and provide preventive treatment to children should receive priority.
  - The risk of transmission of leprosy is reflected by the leprosy case notification rate and % of children among total notified cases for leprosy.
3. Allocation of vaccine will be deprioritized for any re-vaccination (which is not recommended).

## 11. BCG efficacy and effectiveness against TB

Based on previous available evidence, the efficacy of BCG vaccine was believed to mainly prevent severe forms of tuberculosis (TB) in children. Research evaluating its efficacy to prevent pulmonary TB (PTB) has revealed widely varying results, ranging from little or no protection to relatively high protection. Similarly, previous evidence has suggested that BCG does not prevent TB infection.

Recently, a more extensive evaluation has been carried out towards better understanding the effectiveness of BCG vaccine against various forms of TB and what factors contribute towards its variation in protection. New information is also emerging on BCG vaccine protection against primary TB infection in children exposed to persons with PTB.

### *BCG vaccine efficacy against Pulmonary Tuberculosis - evidence from randomised controlled trials*

Mangtani et al., conducted an extensive systematic review and meta-analysis of randomized controlled trials with the aim of estimating efficacy of BCG against PTB, miliary and meningeal TB, as well as gaining better insight into factors associated with vaccine efficacy.<sup>63</sup> A search of 10 medical databases revealed 18 randomised or quasi-randomised trials published between 1945 and 2004, in which human study subjects were randomised to BCG versus placebo or other control. The participants were followed up to assess incidence of tuberculous disease - PTB (all 18 studies), meningeal or miliary TB (6 studies). The studies involved 309,300 participants and were conducted in various countries: USA (10 trials), Canada (1 trial), India (4 trials) and Haiti (1 trial).

Although an overall rate ratio (RR) of PTB comparing vaccinated with unvaccinated participants of 0.50 (95% CI 0.36 – 0.72) for PTB was noted in the forest plot this was not considered appropriate to use given the

<sup>63</sup> Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PEM, et al. Protection by BCG vaccine against tuberculosis: A systematic review of randomized controlled trials. *Clin Infect Dis.* 2014;58(4):470–80.

considerable heterogeneity noted across the trials. Vaccine protection against PTB varied by a priori defined trial subgroups: study design, age of vaccination, tuberculin skin test (TST) positivity, and distance from the equator. Analysis in the different subgroups showed VE was higher in studies with lower risk of diagnostic detection bias (60%, 95% CI 36 – 75); . Among those vaccinated as neonates, RR for PTB was 0.40 (95% CI 0.28-0.56). Among school age children who were TST negative at time of intervention (mycobacterial naïve), vaccine protection was higher (RR 0.25, 95% CI 0.21 – 0.31), however protection was low among older age groups who were TST negative (RR 0.88, 95% CI 0.58 – 1.31). In studies in which TST status was not stringently determined, therefore may have included TST+ or mycobacterial exposed children, average protection from PTB was lower (school children RR 0.67, 95% CI 0.54 – 0.84, older age groups RR 0.81, 95% CI 0.55 – 1.22).

In this meta-analysis, protection against PTB appeared to be higher in settings further from the equator (latitude > 40° RR 0.32, 95% CI 0.22-0.46 versus latitude 0° - <20° RR 0.78, 95% CI 0.58 – 1.05). However, the 5 studies conducted at latitudes 0° - < 20° were mostly among school age (1 study) or older age groups (3 studies), without stringent TST testing (3 studies). Therefore, findings of lower VE at low latitude settings may be related to inclusion of individuals who were already mycobacteria (TB or non-TB) exposed among other factors such as higher TB endemicity. In contrast, the 8 studies from latitudes beyond 40° were mostly neonatal vaccination (4 studies), or stringently TST negative school age children, with 7 of the 8 studies having low risk of bias (high quality). Findings of higher VE at high latitude settings therefore may be related to inclusion of individuals who were not already mycobacteria exposed among other factors such as lower TB endemicity and general better quality of studies. The 5 studies from latitude 20° – 40° were a mixture of school age or older participants, with mixture of stringent TST testing (3 studies) and non-stringent testing (2 studies), most studies of low bias. Indeed a formal metaregression analysis noted a significant proportion of the effect of latitude on efficacy was attenuated taking into account age at vaccination and tuberculin testing stringency before vaccination. The authors suggested the remaining persistence of a latitudinal effect could be due to the fact that tuberculin testing may not exclude exposure to all environmental mycobacteria.

There is a paucity of BCG vaccine RCTs conducted in low latitudes. This meta-analysis of trials formed part of a larger systematic review that included observational studies.<sup>64</sup> For instance seven of eight case-control studies which were of neonatal BCG against pulmonary TB (with only one above 30% latitude) were pooled indicating a moderate protective effect. Further research and analysis of such studies with low risk of bias and low prior exposure to mycobacteria to provide clarity to this question would be useful.

#### *BCG vaccine efficacy against Meningeal and Miliary Tuberculosis - evidence from randomised controlled trials and Case Control Studies.*

The systematic review by Mangtani *et al*<sup>63</sup>, identified 6 RCTs which reported on BCG protection against meningeal and miliary (disseminated) TB. These studies included 157,264 participants, largely in the USA, Canada or the United Kingdom (5 studies), and one study in Puerto Rico. Vaccination vs placebo was given in neonatal period (2 studies), school age (3 studies), and older age (1 study). Vaccine protection was substantial (RR 0.15, 95% CI 0.08 – 0.31), reducing severe TB in vaccinated individuals by 85%. Protection was highest when vaccination was done in the neonatal period, with 90% reduction of severe TB (RR 0.10, 95% CI 0.01 – 0.77), and among school age children who were TST negative, with 92% reduction of severe disease

<sup>64</sup> Abubakar I et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guérin vaccination against tuberculosis. *Health Technol Assess.* 2013 Sep;17(37):1-372. figure 30 page 66 and figure 34 page 71 page 86 case control studies, and table 12 page 78

(RR 0.08, 95% CI 0.03 – 0.25). Vaccination of school age children or older individuals who were not stringently TST tested revealed little evidence of protection against severe disease, however the numbers of cases of severe TB were small for these age groups (0 – 3 cases) resulting in wide confidence intervals and imprecise estimates.

A systematic review and meta-analysis of 14 case control studies by Trunz *et al.*<sup>65</sup> examined BCG VE against meningitis and against miliary TB. The studies were published between 1980 and 1996, six were conducted in Latin America, predominantly Brazil, and eight in Asian countries, predominantly India. Incidence of TB meningitis was reduced by 73% overall (95% CI 67-87%), with higher protection in the Latin American studies (VE 87%, 95% CI 78-92%) compared to Asian settings (VE 69%, 95% CI 60-76%). Incidence of miliary TB was reduced by 77% (95% CI 58 – 87%) as reported in four of the studies in Asia and Latin America.

These studies support previous evidence that BCG vaccination confers high protection against severe forms of TB, but highlights the paucity of evidence from African high TB endemic settings.

#### *Emerging evidence of BCG vaccine protection against primary infection with tuberculosis*

Recently, the question of whether BCG vaccine provides any protection against primary infection with TB was explored in a systematic review and meta-analysis conducted by Roy *et al.*<sup>66</sup> Previously, it had been believed that the vaccine does not prevent TB infection, however evidence for this has been scarce, largely due to the limitations of TST which cannot distinguish if a positive response is due to *M tuberculosis* infection, or BCG vaccination, or non-tuberculous mycobacterial infection. Recently, T cell based interferon gamma release assays (IGRA) have been developed which are specific for detection of *M tuberculosis* infection, and are not reactive to BCG immune responses or non-tuberculous mycobacterial infection. Therefore, these assays make it possible to identify if an individual is MTB infected or not.

Roy *et al.*<sup>66</sup> examined the question of whether BCG vaccination prevents MTB infection. They searched multiple electronic databases from 1950 to 2013 for studies which satisfied the inclusion criteria. Studies were in community congregated settings and households, and BCG vaccination was determined by one or a combination of BCG scar, medical record documentation, or parental recall of vaccination. Exposure to TB was defined as close contact with person/s with active TB as identified by the treating physicians (in 13 of 14 studies index case had smear positive PTB). TB infection was defined as any positive IGRA result in a child contact, and TB disease was defined as presence of active TB as reported by study authors. Outcomes of both infection and active disease were determined at point of IGRA testing after TB exposure.

Fourteen studies with 3,855 participants were analysed. The settings included European countries (9 studies), Sub-Saharan Africa (3 studies), and Asia (2 studies).

Primary analysis of all 14 studies revealed that BCG vaccinated children exposed to persons with open pulmonary TB had 19% less TB infection than unvaccinated children (95% CI 8 – 29%), and in a subset of 6 studies that followed up exposed children to determine additional incident infection, vaccinees had 27% less TB infection (95% CI 13 – 39%). Protection against infection varied by study quality, with greater protection

<sup>65</sup> Trunz BB *et al.* Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet*. 2006;367(9517):1173–80.

<sup>66</sup> Roy A *et al.* Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis. *BMJ*. 2014;349(aug04\_5):g4643. Available <http://www.bmj.com/content/349/bmj.g4643>, accessed September 2017.

in higher quality studies of low Newcastle-Ottawa score (VE 32%, 95% CI 16 – 45%), and in higher latitudes (latitude 0° - <20°, VE 13%, latitude 20° - < 40°, VE 12%, latitude 40°+, VE 26%).

Restricting analysis to 6 studies which gave follow-up information on progression to active TB (n=1,745), vaccinated children experienced 71% less active TB disease than non-vaccinees (95% CI 42 – 85%).<sup>67,68,69,70,71,72</sup> Among children who were IGRA positive at enrolment (already infected), on follow-up vaccinees had 58% less progression to active TB disease (95% CI 23 – 77%). These findings give us new insight to previously unrecognised protective effects of BCG vaccine – up to 27% prevention of primary TB infection, and 58% prevention of progression to any active TB disease among children age up to 16 years already infected with MTB at time of enrolment into the study.

This new evidence of additional protective effects of BCG vaccination to prevent TB infection albeit modest, as well as to prevent progression to active TB disease, has implications on its overall effect on the control of TB. The infected young child will over the decades become the latent TB “carrier” who may later in life experience reactivation and contribute to TB transmission during their adult life.

The evidence from RCTs showing that BCG prevents PTB by as much as 50%, especially when given in the neonatal period, or in school age children who are TST negative on stringent testing. This evidence should be appreciated as a significant benefit of the BCG vaccine, over and above its well-known protection against severe forms of TB in children.

## 12. BCG efficacy and effectiveness against leprosy

In comparison to the effectiveness of BCG against TB, BCG seems to be more protective against leprosy. The effectiveness of BCG vaccination against leprosy was recently analyzed in a systematic review (5 RCTs, 6 cohort studies, 17 case-control studies).<sup>18,73</sup>

It found BCG to be effective in preventing leprosy, with an overall pooled RR of 0.45 (95% CI 0.34 to 0.56). However, across studies BCG had a variable protective effect, ranging from 20-80% reduction in risk.<sup>74</sup> The variation in the level of protection may be partly related to the strain of BCG studied and variation in study methodology. There was limited data on the effects of age on effects of BCG vaccination efficacy. In the RCTs, BCG had a larger effect in persons vaccinated at <15 years of age compared with those older than 15 years of age. All cohort studies were conducted in persons vaccinated prior to 15 years of age and the case-control studies did not report age of vaccination. Newborns were included in the studies were not analyzed

<sup>67</sup> Eisenhut M et al. BCG vaccination reduces risk of infection with Mycobacterium tuberculosis as detected by gamma interferon release assay. *Vaccine* 2009;27:6116-20.

<sup>68</sup> Eriksen J et al. Protective effect of BCG vaccination in a nursery outbreak in 2009: time to reconsider the vaccination threshold? *Thorax* 2010;65:1067-71.

<sup>69</sup> Soysal A et al. Effect of BCG vaccination on risk of Mycobacterium tuberculosis infection in children with household tuberculosis contact: a prospective community-based study. *Lancet* 2005;366:1443-51.

<sup>70</sup> Dominguez J et al. Comparison of two commercially available gamma interferon blood tests for immunodiagnosis of tuberculosis. *Clin Vaccine Immunol* 2008;15:168-71.

<sup>71</sup> Okada K et al. Performance of an interferon-gamma release assay for diagnosing latent tuberculosis infection in children. *Epidemiol Infect* 2008;136:1179-87.

<sup>72</sup> Tsolia MN et al. Whole blood interferon-gamma release assay is a useful tool for the diagnosis of tuberculosis infection particularly among Bacille Calmette Guerin-vaccinated children. *Pediatr Infect Dis J* 2010;29:1137-40.

<sup>73</sup> Poobalan et al. Systematic review on the effectiveness and efficacy of BCG against leprosy. 2017, unpublished.

<sup>74</sup> Setia et al. The role of BCG in prevention of leprosy: a meta-analysis. *Lancet Infect Dis*. 2006 Mar;6(3):162-70.

separately. The number of BCG doses, and whether the study evaluated a general population or focused on leprosy contacts did not significantly affect results.

For preventing leprosy among contacts of leprosy cases BCG revaccination is used as an approach. The impact of BCG revaccination on reducing disease in contacts of leprosy patients has been investigated with contradictory results. Cunha et al (2008)<sup>75</sup> showed no additive protection of revaccination in a RCT of almost 100,000 Brazilian school children who received their first vaccination at birth. On the other hand an RCT<sup>76</sup>, in Malawian infants and adults showed that, a second BCG vaccination afforded an additional 49% protection compared with no revaccination. A potential explanation for these discrepant results might be that revaccination of adults is only beneficial once the initial immune response from the childhood immunization wanes. The evidence on the effectiveness of revaccination for adults exposed to a case (contacts) seems too limited at this stage, with only 2 RCTs with conflicting results, to consider it for changes in the recommendation of BCG.

Düppre et al (2008)<sup>77</sup> assessed the effectiveness<sup>77</sup> of 1-2 doses of BCG vaccination against leprosy among the contacts of 1161 patients in Brazil over 18 years of follow up. It was noted that of the 122 cases of leprosy detected in this study, 28 (23%) occurred within the first 2-10 months following vaccination. The risk of leprosy during the initial months of exposure was highest among those vaccinated with no previous scar, and assumed not to have received BCG in infancy. However, the number of cases detected declined substantially after the first year, and in the following years the protection rate in this group reached 80%. Over the study period of 18 years, the protection conferred by BCG was 56% and was not substantially affected by previous BCG vaccination. Since 1987 in Brazil, BCG vaccination of all contacts has been considered an effective means of substantially reducing the incidence of leprosy and therefore it is part of the national guidelines on leprosy. As such, Brazil officially recommends BCG (re)vaccination (up to 2 lifetime doses of BCG) for contacts without signs or symptoms of leprosy upon examination, regardless of whether the index case is classified as paucibacillary (PB) or multibacillary (MB).

Schuring et al (2009)<sup>78</sup> evaluated the effects of BCG vaccination status and post-exposure prophylaxis (PEP)<sup>79</sup> in the form of single-dose rifampicin (SDR) on prevention of leprosy in a secondary analysis of a single centre, double blind, cluster randomized, placebo-controlled trial on rifampicin prophylaxis. Individually, BCG vaccination (given at infancy) and PEP (SDR) given to contacts of leprosy patients were each protective against leprosy disease (reduction in risk 57% [95% CI: 24–75%] and 58% [95% CI: 30–74%], respectively). The combined strategies showed a protective effect of 80% at 2 years follow up (for BCG OR: 0.43 (95% CI 0.25 to 0.76), for rifampicin OR: 0.42 (95% CI 0.26 to 0.70) and for combined OR: 0.20 (95% CI 0.08 to 0.50)).

<sup>75</sup> Cunha SS et al. BCG revaccination does not protect against leprosy in the Brazilian Amazon: a cluster randomised trial. *PLoS Negl Trop Dis*. 2008 Feb 13;2(2).

<sup>76</sup> Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. *Lancet*. 1996 Jul 6;348(9019):17-24.

<sup>77</sup> Düppre NC et al. Effectiveness of BCG vaccination among leprosy contacts: a cohort study. *Trans R Soc Trop Med Hyg*. 2008 Jul;102(7):631-8.

<sup>78</sup> Schuring et al, Protective effect of the combination BCG vaccination and rifampicin prophylaxis in leprosy prevention. *Vaccine*. 2009 Nov 23;27(50):7125-8.

<sup>79</sup> PEP in the form of single-dose rifampicin (SDR) has been shown to be effective at reducing the detection of leprosy over 1 to 2 years in contacts (57%) However, PEP was no more effective at reducing incidence of leprosy over a 3 to 4 year period. (Moet et al, Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ*. 2008 Apr 5;336(7647):761-4.)

On the basis of the Schuring data, a large cluster randomized controlled trial (MALTALAP) has begun in Bangladesh to compare the effect of immunization with BCG alone vs BCG plus PEP in in adults and children (>5 years of age) contacts of approximately 1300 new leprosy cases.<sup>80</sup> Recently published observational data from this RCT (after one and half year follow up) indicate that 21 of 5136 contacts developed paucibacillary leprosy within 12 weeks after receiving BCG vaccination.<sup>81</sup> Such cases soon after BCG vaccination could be due to immune reconstitution inflammatory syndrome (IRIS), consistent with the hypothesis that BCG accelerates the natural history of *M. leprae* infection following BCG vaccination. The MALTALAP study will have a follow up over 2 years; however as in the case of the Duppre study, long term follow up (5 to 10 years) will also be needed, due to the long incubation period of the disease, which is assumed to range from around 2 to 20 years. Other whole mycobacteria have been evaluated as vaccines, but there is little evidence that they differ significantly from BCG in protective efficacy, and data are more limited. An Indian study analyzing BCG plus killed *M. leprae* and BCG alone or placebo BCG plus killed *M. leprae* reported that, *M. leprae* significantly reduced the incidence of leprosy compared with saline. The relative risk reduction was 64% (95% CI 50.4% to 73.9%).<sup>82</sup> In contrast a RCT from Malawi reported no significant difference in incidence of leprosy at 5-9 years (0.09% with BCG plus killed *M. leprae* and 0.08% with BCG; RRR 1.06(95% CI 0.62-1.82)).<sup>76</sup>

### 13. Non-specific ('heterologous' or 'non-targeted') effects of BCG

BCG vaccination has been reported to have non-specific ('heterologous') effects (NSE), which, like the specific effects of BCG, may differ between genotypes and manufacturers.<sup>51,83,84,85</sup> The implications of these effects, and the settings and circumstances in which they are clinically important need to be more clearly defined.<sup>86,87,88,89,90</sup> The NSE of BCG should not be confused with the specific and cross-protective effects of BCG vaccination against *M. leprae*, *M. ulcerans* and other non-tuberculous mycobacteria.

In April 2014, SAGE discussed the importance of NSE and stated: *"Regarding the possible non-specific effect of BCG on all-cause mortality, the epidemiological review suggested possible beneficial effects on all-cause mortality. SAGE concluded that the evidence does not support a change in policy for BCG immunization as soon as possible after birth. The available data suggest that the current WHO recommended schedule for BCG vaccine has a beneficial effect on all-cause mortality and this should be emphasized."*<sup>91</sup>

<sup>80</sup> Richardus et al. The combined effect of chemoprophylaxis with single dose rifampicin and immunoprophylaxis with BCG to prevent leprosy in contacts of newly diagnosed leprosy cases: a cluster randomized controlled trial (MALTALAP study). BMC Infect Dis. 2013 Oct 3;13:456.

<sup>81</sup> Richardus et al. Clinical manifestations of leprosy after BCG vaccination: an observational study in Bangladesh. Vaccine. 2015 Mar 24;33(13):1562-7.

<sup>82</sup> Gupte MD, Vallishayee RS, Anantharaman DS, Nagaraju B, Sreevatsa, Balasubramanyam S, et al. Comparative leprosy vaccine trial in south India. Indian J Lepr. 1998;70:369–88.

<sup>83</sup> Anderson EJ et al. The influence of BCG vaccine strain on mycobacteria-specific and non-specific immune responses in a prospective cohort of infants in Uganda. Vaccine. 2012;30(12):2083-9.

<sup>84</sup> Frankel H et al. Different effects of BCG strains - A natural experiment evaluating the impact of the Danish and the Russian BCG strains on morbidity and scar formation in Guinea-Bissau. Vaccine. 2016;34(38):4586-93.

<sup>85</sup> Rentsch CA et al. Bacillus Calmette-Guerin strain differences have an impact on clinical outcome in bladder cancer immunotherapy. Eur Urol. 2014;66(4):677-88.

<sup>86</sup> Shann F. The non-specific effects of vaccines. Arch Dis Child. 2010;95(9):662-7.

<sup>87</sup> Shann F. The heterologous (non-specific) effects of vaccines: implications for policy in high-mortality countries. Trans R Soc Trop Med Hyg. 2015;109(1):5-8.

<sup>88</sup> Flanagan KL et al. Heterologous ("nonspecific") and sex-differential effects of vaccines: epidemiology, clinical trials, and emerging immunologic mechanisms. Clin Infect Dis. 2013;57(2):283-9.

<sup>89</sup> Higgins JP et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. BMJ. 2016;355:i5170.

<sup>90</sup> Pollard et al. Non-specific effects of vaccines: plausible and potentially important, but implications uncertain. Arch Dis Child. 2017 May

<sup>91</sup> WHO. SAGE report April 2014. Weekly epidemiological record No 21, 2014, 89, 221–236.

Subsequently, SAGE has been presented with 2 proposed questions and outlines of RCT protocols to further evaluate the hypotheses relating to NSE of vaccines considered by IVIR-AC most pressing and policy relevant with respect to timing and sequencing of infant vaccines:

[http://www.who.int/immunization/research/implementation/nse\\_protocol\\_comments/en/](http://www.who.int/immunization/research/implementation/nse_protocol_comments/en/). SAGE

reiterated the value of definitive evidence to determine the existence and magnitude of the impact of vaccine NSE on susceptibility to severe childhood infection, particularly all-cause mortality, and the potential implications for national vaccination schedules (including BCG vaccination).

In addition to the WHO initiated protocols for RCTS, two additional RCTs are ongoing:

- (i) The *Calmette trial* in Denmark<sup>92</sup>
- (ii) The *Melbourne Infant Study: BCG for Allergy and Infection Reduction (MIS BAIR)* in Australia.

### Brief overview of the evidence for the NSE of BCG vaccination

A recent systematic review by Higgins *et al*<sup>157</sup> concluded that BCG vaccination was associated with a reduction in all-cause mortality of approximately 50%. Because TB is an infrequent cause of death in infants and young children, this reduction is unlikely to be entirely due to fewer deaths from the disease. It is postulated that, in high mortality settings, BCG's immunomodulatory effects reduce all-cause mortality by also preventing infections other than TB.<sup>93</sup> In addition, BCG-vaccination was associated with increased cellular and antibody responses to unrelated vaccines in studies in The Gambia and Australia<sup>155,94</sup> but not in a recent study in Denmark.<sup>95</sup>

BCG vaccination might also be associated with a reduction in (non-tuberculous) respiratory infections in low mortality settings.<sup>96,97</sup> The results of different studies have sometimes provoked debate.<sup>92,98</sup> Some observational studies suggest BCG-vaccination is also associated with protection against allergies, eczema and asthma, though the findings have been inconsistent.<sup>99,100,101,102,103</sup> One RCT suggests that vaccination with BCG-Denmark of high-risk infants protects against eczema.<sup>104</sup> The *Calmette Study* recently reported that BCG vaccination did not protect against allergy in Denmark.<sup>105</sup> The *MIS BAIR Study* in Australia is ongoing and includes allergy outcomes (allergic (atopic) sensitization, eczema and lower respiratory illness at both 1-year

<sup>92</sup> Stensballe LG et al. BCG vaccination at birth and early childhood hospitalisation: a randomised clinical multicentre trial. *Arch Dis Child*. 2017;102(3):224-31.

<sup>93</sup> Pollard A et al. Non-specific effects of vaccines: plausible and potentially important, but implications uncertain. *Arch Dis Child*. 2017 May 13. pii: archdischild-2015-310282.

<sup>94</sup> Ota MO et al. Influence of Mycobacterium bovis bacillus Calmette-Guerin on antibody and cytokine responses to human neonatal vaccination. *J Immunol*. 2002;168(2):919-25.

<sup>95</sup> Nissen et al. Bacille Calmette-Guérin (BCG) vaccination at birth and antibody responses to childhood vaccines. A randomised clinical trial.

<sup>96</sup> Holm-Delgado MG et al. Acute lower respiratory infection among Bacille Calmette-Guerin (BCG)-vaccinated children. *Pediatrics*. 2014;133(1):e73-81.

<sup>97</sup> de Castro MJ et al. Nonspecific (Heterologous) Protection of Neonatal BCG Vaccination Against Hospitalization Due to Respiratory Infection and Sepsis. *Clin Infect Dis*. 2015;60(11):1611-9.

<sup>98</sup> Benn CS and Sorup S. Commentary: BCG has no beneficial non-specific effects on Greenland. An answer to the wrong question? *Int J Epidemiol*. 2016.

<sup>99</sup> Arnoldussen DL et al. BCG vaccination and allergy: a systematic review and meta-analysis. *J Allergy Clin Immunol*. 2011;127(1):246-53, 53 e1-21.

<sup>100</sup> El-Zein M et al. Does BCG vaccination protect against the development of childhood asthma? A systematic review and meta-analysis of epidemiological studies. *Int J Epidemiol*. 2010;39(2):469-86.

<sup>101</sup> Rousseau MC et al. Potential health effects from non-specific stimulation of the immune function in early age: the example of BCG vaccination. *Pediatr Allergy Immunol*. 2008;19(5):438-48.

<sup>102</sup> Freyne B and Curtis N. Does neonatal BCG vaccination prevent allergic disease in later life? *Arch Dis Child*. 2014;99(2):182-4.

<sup>103</sup> Linehan MF et al. Does BCG vaccination protect against childhood asthma? Final results from the Manchester Community Asthma Study retrospective cohort study and updated systematic review and meta-analysis. *J Allergy Clin Immunol*. 2014;133(3):688-95 e14.

<sup>104</sup> Steenhuis TJ, van Aalderen WM, Bloksma N, Nijkamp FP, van der Laag J, van Loveren H, et al. Bacille-Calmette-Guerin vaccination and the development of allergic disease in children: a randomized, prospective, single-blind study. *Clin Exp Allergy*. 2008;38(1):79-85.

<sup>105</sup> Thøstesen LM et al. Neonatal BCG has no effect on allergic sensitization and suspected food allergy until 13 months. *Pediatr Allergy Immunol*. 2017 Jun 29.

of age and 5-years of age). BCG vaccination may have beneficial effects in type 1 diabetes mellitus<sup>106</sup> and multiple sclerosis.<sup>107</sup> BCG's immunomodulatory properties are routinely exploited in the treatment of bladder cancer.<sup>108</sup> BCG vaccination is associated with protection against melanoma and may play a role in treatment.<sup>109,110,111</sup> A plethora of data from animal studies provide strong evidence for BCG's ability to protect against a wide range of infections other than TB, including bacteria (e.g. *Shigella flexneri*), viruses (e.g. vaccinia virus) and protozoa (e.g. malaria). This literature has recently been reviewed by Freyne *et al.*<sup>112</sup> The immunomodulatory properties of BCG have been explored in *in vitro* experiments for decades (recently reviewed by Freyne *et al.*).<sup>113</sup> A systematic review by Kandasamy *et al.*<sup>114</sup> identified 37 studies which measured non-specific immunological effects (NSIE) of BCG vaccination. The included studies had very heterogeneous study designs, which could not be conventionally meta-analysed, providing a low level of evidence quality. The authors concluded that, while some studies showed evidence suggestive of NSIE, no consistent findings were identified that provide confidence in the nature, magnitude or timing of NSIE in humans following vaccination with BCG nor the clinical importance of the findings. There are several plausible mechanisms for the NSE of BCG and other vaccines (recently reviewed by Goodridge *et al.*<sup>115</sup>). It is likely that the NSE of BCG are mediated partly by heterologous effects on adaptive immunity, but also by potentiating innate immune responses through epigenetic mechanisms, a process termed 'trained immunity'.<sup>116,117</sup>

## 14. Duration of Protection

A systematic review with data up to 2009 analysed the duration of protection. The authors report that there was consistent evidence of a protection for up to 15 years. Longer durations of protection seem to be linked to stringent tuberculin testing or those vaccinating neonates. Protection declines with time at a rate which varies between studies.<sup>118</sup> A few studies included in the review noted protection beyond 15 years after vaccination. One a long term follow-up of a trial reported persistent BCG vaccine efficacy for 50 to 60 years.<sup>119</sup>

<sup>106</sup> Faustman DL *et al.* Proof-of-concept, randomized, controlled clinical trial of Bacillus-Calmette-Guerin for treatment of longterm type 1 diabetes. *PLoS One*. 2012;7(8):e41756.

<sup>107</sup> Ristori G *et al.* Effects of Bacille Calmette-Guerin after the first demyelinating event in the CNS. *Neurology*. 2014;82(1):41-8.

<sup>108</sup> Alexandroff AB *et al.* BCG immunotherapy of bladder cancer: 20 years on. *Lancet*. 1999;353(9165):1689-94.

<sup>109</sup> Rosenthal SR. Cancer precursors and their control by BCG. *Dev Biol Stand*. 1986;58 ( Pt A):401-16.29.

<sup>110</sup> Pfahlberg A *et al.* Inverse association between melanoma and previous vaccinations against tuberculosis and smallpox: results of the FEBIM study. *J Invest Dermatol*. 2002;119(3):570-5.

<sup>111</sup> Krone B *et al.* Protection against melanoma by vaccination with Bacille Calmette-Guerin (BCG) and/or vaccinia: an epidemiology-based hypothesis on the nature of a melanoma risk factor and its immunological control. *Eur J Cancer*. 2005;41(1):104-17.

<sup>112</sup> Freyne B *et al.* BCG-associated heterologous immunity, a historical perspective: intervention studies in animal models of infectious diseases. *Trans R Soc Trop Med Hyg*. 2015;109(1):52-61.

<sup>113</sup> Freyne B *et al.* BCG-associated heterologous immunity, a historical perspective: experimental models and immunological mechanisms. *Trans R Soc Trop Med Hyg*. 2015 Jan;109(1):46-51.

<sup>114</sup> Kandasamy *et al.* Non-specific immunological effects of selected routine childhood immunisations: systematic review. *BMJ* 2016;355:i5225.

<sup>115</sup> Goodridge HS, Ahmed SS, Curtis N, Kollmann TR, Levy O, Netea MG, *et al.* Harnessing the beneficial heterologous effects of vaccination. *Nat Rev Immunol*. 2016;16(6):392-400.

<sup>116</sup> Netea MG, van Crevel R. BCG-induced protection: effects on innate immune memory. *Semin Immunol*. 2014 Dec;26:512-7.

<sup>117</sup> Kleinnijenhuis J, Quintin J, Preijers F, Benn CS, Joosten LA, Jacobs C, *et al.* Long-Lasting Effects of BCG Vaccination on Both Heterologous Th1/Th17 Responses and Innate Trained Immunity. *J Innate Immun*. 2013.

<sup>118</sup> Abubakar *et al.* Protection by Bacillus Calmette-Guérin vaccination against tuberculosis beyond 10 years: Systematic Review and Meta-Analysis, unpublished systematic review. 2017. Unpublished.

<sup>119</sup> Aronson N *et al.* Long-term Efficacy of BCG Vaccine in American Indians and Alaska Natives A 60-Year Follow-up Study. *JAMA*. 2004;291(17):2086-2091.



A cohort study in Brazil suggested that protection lasted for 15–20 years but with no further follow up.<sup>120</sup> A case control study in Saudi Arabia indicated protection in 15 to 24 year olds but not in 25-34 year olds.<sup>121</sup> Since that systematic review data from a Norwegian study has supported findings of a long duration of protection<sup>122</sup> and a recent observational study from the UK reports A 20 year protection was observed in children vaccinated in school age which then declined.<sup>123</sup> Evidence of a protection against TB for at least 10 years from infant vaccination. Considerable missing vaccine record information and the small numbers unvaccinated precluded assessment of longer duration was seen.<sup>123</sup>

## 15. Need for revaccination, vaccination in adolescent and adults

### Summary

Although primary infant BCG vaccination is thought to offer durable protection for more than 10 years and there is more recent evidence it may last for 20 years, there is a potential need for BCG revaccination. BCG revaccination is safe in *Mycobacterium tuberculosis* infected and uninfected populations. The evidence from randomized controlled trials and retrospective cohort and case-control studies demonstrates a limited effectiveness of BCG revaccination in adolescents and adults after primary BCG vaccination in infancy for protection against *M. tuberculosis* infection and TB disease. BCG revaccination is not considered cost-effective.

The data were analysed based on retrieved articles from a systematized literature search in PubMed (see appendix) and were categorized into the following themes: Vaccine Safety efficacy and effectiveness and cost-effectiveness (see section on cost-effectiveness).

### Safety of revaccination

In a study (Moreau strain (Rio de Janeiro substrain)) in 71,000 Brazilian schoolchildren, adverse reactions to BCG revaccination were rare; and no significant difference in the rate of adverse reactions was observed between primary BCG vaccination and BCG revaccination.<sup>124</sup> The incidence of adverse reactions was estimated as 1 per 2,854 vaccinations, with no deaths or BCG disease; RR of adverse reaction to BCG revaccination was reported as 2.3 (95%CI 0.69 – 7.80), compared to primary BCG vaccination. An observational study (BCG-Danish, BCG-British) of BCG revaccination in 2997 Swedish school children also reported that the reactogenicity profile is similar to that of primary BCG vaccination.<sup>125</sup> BCG revaccination of 82 TST positive South African adults (BCG-Danish) showed injection site erythema (68%) and induration (86%) peaked at 1 week; ulceration (76%) peaked at 2 weeks and resolved by 3 months, with diameter of

<sup>120</sup> Barreto ML et al. Neonatal BCG protection against tuberculosis lasts for 20 years in Brazil. *Int J Tuberc Lung Dis* 2005;9:1171–3.

<sup>121</sup> Al Kassimi FA et al. Does the protective effect of neonatal BCG correlate with vaccine-induced tuberculin reaction? *Am J Resp Crit Care Med* 1995;152:1575–8.

<sup>122</sup> Nguidop-Djomo P et al. Duration of BCG protection against tuberculosis and change in effectiveness with time since vaccination in Norway: a retrospective population-based cohort study. *Lancet Infect Dis* 2016;16:219–26.

<sup>123</sup> Mangtani et al. Observational study to estimate the changes in the effectiveness of bacillus Calmette–Guérin (BCG) vaccination with time since vaccination for preventing tuberculosis in the UK. *HEALTH TECHNOLOGY ASSESSMENT VOLUME 21 ISSUE 39 JULY 2017*.

<sup>124</sup> Dourado I et al., Rates of adverse reactions to first and second doses of BCG vaccination: results of a large community trial in Brazilian schoolchildren. *Int J Tuberc Lung Dis*. 2003 Apr;7(4):399–402.

<sup>125</sup> Böttiger M et al., A comparative study of Danish (Statens Serum Institut), Glaxo and Behringwerke vaccines--revaccination of schoolchildren. *J Biol Stand*. 1983 Jan;11(1):1–12.

ulceration >10mm in only 8%, which is a similar reactogenicity profile to that of primary BCG vaccination of TST negative adults in the USA.<sup>126,127</sup>

### Effectiveness of BCG revaccination against TB

**Table 7: Primary papers on BCG revaccination effectiveness**

Author /Year	Study Design	Vaccine Strain	Population	Reference Number
Rodrigues et al., 2005	RCT	BCG- Moreau	Children in Brazil	128
Barreto et al., 2011				129
Barreto et al., 2014				130
Karonga Prevention Trial Group, 1996	RCT	BCG-Glaxo	Individuals in Malawi	76
Leung et al., 2012	Observational study	BCG-Glaxo	Primary school children in Hong Kong	131
Tala-Heikkila et al., 1998	Observational study	BCG-Glaxo	Children 11 to 13 years old in Finland	132
Sepulveda et al., 1992	Observational study	BCG- Pasteur	Young adults in Chile	133

A double-blind, randomised controlled trial of BCG among more than 46,000 people of all ages in Malawi showed no protective benefit of revaccination compared to placebo against confirmed TB disease (IRR 1.43; 95% CI 0.88 – 2.35). However it should be noted that, whilst both primary and BCG revaccination demonstrated added protection against leprosy, neither primary nor BCG revaccination provided protection against TB in this population.<sup>76</sup> The incidence of confirmed pulmonary TB disease was higher in the BCG revaccination group compared to placebo (IRR 1.74; 95% CI 1.00 – 3.03), but was attributed to an excess of HIV-associated TB in the BCG revaccination arm.

Rodrigues and Barreto *et al.*<sup>129,130</sup> conducted the BCG-REVAC RCT, which took place in two Brazilian cities, Salvador and Manaus. Using TB incidence as the primary outcome, the BCG-REVAC study found that among children aged 7-14 years initially vaccinated at birth and then revaccinated with BCG at school age, overall vaccine efficacy was 9% (95% CI: -16 - 29%) after 0-5 years of follow-up and 12% (95% CI: -2 - 24%) after extended follow-up for 9 years.<sup>129</sup> Although no overall benefit of BCG revaccination was observed at either time-point, additional long-term protection against TB disease was observed only at the Salvador site, with a vaccine efficacy (VE) of 19% (95% CI: 3 - 33%), and confined to the subgroup of children less than 11 years of age at revaccination (VE, 33%; 95% CI: 3-54%).<sup>129,130</sup> Although it has been posited that these results are due to climatic and environmental exposures, evidence of differential exposure to non-tuberculous mycobacteria at the two sites is lacking; this may be a chance finding or due to differences in prior sensitization to *M tuberculosis*.

<sup>126</sup> Hatherill M et al. Safety and reactogenicity of BCG revaccination with isoniazid pretreatment in TST positive adults. *Vaccine*. 2014 Jun 30;32(31):3982-8. doi: 10.1016/j.vaccine.2014.04.084. Epub 2014 May 9.

<sup>127</sup> Hoft DF et al. Clinical reactogenicity of intradermal bacille Calmette-Guerin vaccination. *Clin Infect Dis*, 1999. 28(4): p. 785-90.

<sup>128</sup> Rodrigues LC et al., Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet*. 2005 Oct 8;366(9493):1290-5. Epub 2005 Aug 31.

<sup>129</sup> Barreto ML et al. Evidence of an effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: Second report of the BCG-REVAC cluster-randomised trial. *Vaccine*. Elsevier Ltd; 2011;29(31):4875–7. Available from: <http://dx.doi.org/10.1016/j.vaccine.2011.05.023>

<sup>130</sup> Barreto ML et al. Causes of variation in BCG vaccine efficacy: Examining evidence from the BCG REVAC cluster randomized trial to explore the masking and the blocking hypotheses. *Vaccine*. Elsevier Ltd; 2014;32(30):3759–64. Available from: <http://dx.doi.org/10.1016/j.vaccine.2014.05.042>

<sup>131</sup> Leung CC et al. A strong tuberculin reaction in primary school children predicts tuberculosis in adolescence. *Pediatr Infect Dis J*, 2012. 31(2):150-3.

<sup>132</sup> Tala-Heikkila MM et al. Bacillus Calmette-Guerin revaccination questionable with low tuberculosis incidence. *Am J Respir Crit Care Med*, 1998. 157(4 Pt 1): p. 1324-7.

<sup>133</sup> Sepulveda RL et al. Case-control study of the efficacy of BCG immunization against pulmonary tuberculosis in young adults in Santiago, Chile. *Tuber Lung Dis*, 1992. 73(6): p. 372-7.

Suliman *et al.* (2016)<sup>134</sup> reported the immunological effects of BCG revaccination in an RCT, in which participants were randomly allocated to isoniazid (INH) or placebo treatment before BCG revaccination, to determine if INH impacted *M tuberculosis* specific immune response from revaccination. INH treatment and preclearance of bacilli had little effect on lymphocyte responses boosted by BCG revaccination, however, BCG-reactive natural killer (NK) cell responses remained elevated up to one year post-revaccination<sup>134</sup>. The clinical significance of these immunological findings is unclear.

A retrospective cohort study of 303,692 children in Hong Kong who participated in a programme of BCG revaccination of TST negative children at age 6-9 years, showed no protective benefit against TB disease compared to non-participants (RR 1.28; 95% CI 0.92 - 1.77).<sup>131</sup> A retrospective case-control study in Chile also showed no added protection against TB disease from BCG revaccination, measured by number of BCG scars<sup>133</sup>, and similarly, a large retrospective cohort study in Finland that analysed risk of TB disease before and after cessation of programmatic school-age revaccination of TST negative children showed no benefit of BCG revaccination.<sup>132</sup>

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<sup>134</sup> Suliman S et al. Bacillus Calmette-Guérin (BCG) Revaccination of Adults with Latent Mycobacterium tuberculosis Infection Induces Long-Lived BCG-Reactive NK Cell Responses. *J Immunol.*2016;197(4):1100–10.

## 16. Safety of BCG vaccination

Adverse events following immunization (AEFIs) associated with BCG vaccines include local reactions such as injection site abscess or severe ulceration, regional adverse reactions such as ipsilateral regional lymph node enlargement with rare instances of suppuration and fistulae formation and distant disease, in the skin, gut, osteitis (bone) or osteomyelitis (bone marrow). Distal BCG disease may occur more than 12 months after vaccination.

BCG is a live vaccine that has never been cloned and there are now several different seed strains in use that have different phenotypic and genotypic differences. Clusters of AEFIs have been associated with a change in the manufacturing process and/or strain. Between 1971 and 1978 for example, osteitis outbreaks were seen in Finland and Sweden with the highest rates being 72.9 per 100,000 after the manufacture of BCG moved from Sweden to Denmark still based on the Gothenburg strain. The osteitis rates declined when the strain was changed to the Danish (Copenhagen 1331) strain. In the former Czechoslovakia, osteitis rates increased on moving from the Prague to the Moscow strain 2-4 per 100,000). Osteitis as an AEFI is now much rarer.

Rare events, such as disseminated BCG disease, are seen and are more identifiable nowadays with advent of molecular tests. It has a high case fatality rate, requiring urgent medical care and is mostly associated with immunodeficiency both acquired (HIV) and primary immune deficiency syndromes. BCG Immune Reconstitution Inflammatory Syndrome (IRIS)-is also seen with HIV infection. Other BCG syndromes noted have included uveitis and skin lesions such as lupus vulgaris.

WHO commissioned a systematic literature review in early 2017 to review the safety of BCG vaccines so as to obtain sufficient scientific evidence to make public health decisions.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the quality of evidence. Attempts were made to categorise the key findings of the review for all vaccines and for the different products. For PICO questions, the comparator used was no vaccine or another comparator vaccine.

The findings from the systematic review (by Uthman *et al.*<sup>135</sup>) was presented at the GACVS meeting in June 2017, the SAGE BCG Working Group in August 2017 and the WHO secretariat.

The systematic review analysed adverse events following BCG immunization. A total of 287 articles met inclusion criteria. However, only 52 studies reported rates of adverse events, the rest were mainly case reports and case series studies. There was substantial variation in the reported rate of lymphadenitis across countries and across periods, ranging from as low as 0.41 per 1,000 vaccinated children in Saudi Arabia in 2012 to as much as 308 per 1,000 in HIV positive vaccinated children in Haiti in 1994. Evidence was limited on rates of osteomyelitis following BCG immunization.

There was substantial variation in the reported rate of disseminated BCG across countries and across periods, ranging from 1.81 per 1,000 in South Africa to 167 per 1,000 in France. Twelve studies reported not-specified AEFIs between 1979 and 2014 from seven countries. There was variation in the reported rate of not-

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<sup>135</sup>Uthman et al. Adverse events following Bacillus Calmette-Guérin (BCG) immunization: A systematic review, unpublished, 2017.

specified AEFI across the studies, ranging from as low as 0.01 per 1,000 vaccinated children in Brazil in 2013 to as much as 177.82 per 1,000 in France in 2009.

The systematic review analysed the evidence taking into consideration the age of vaccine administration to address the important policy question of differences in AEFI rates for children vaccinated at birth or at the age of 6 weeks. However, no evidence was available.

Moreover, the systematic review also attempted to analyse strain specific adverse reaction rates. However, there is a paucity of evidence on this issue, due to the inadequate reporting of the specific vaccine strains used in the various products.

Uthman *et al.*<sup>135</sup> analysed data on AEFIs related to leprosy. Three different groups were analysed: 1) healthy population, 2) leprosy contacts and 3) leprosy patients. Two studies reported rates of adverse events following antileprosy BCG in healthy population (adenitis: 13.0 per 1,000) and at risk population (recent contacts that developed leprosy after BCG revaccination at 4.0 per 1,000).

The reviewers indicated that, the results of the literature review should be interpreted with caution as many of the studies initially identified were case reports. Those studies were from a variety of surveillance systems or hospital based audits, which are prone to selection and reporting bias.

A short report<sup>136</sup> on adverse events following immunisation with BCG vaccine was made available to the BCG safety subgroup from the Therapeutic Goods Administration Australia for vaccinations between 1 January 2009 – 31 December 2014 in children aged less than 7 years. From this report, the type of AEFI in the descending order of frequency was found to be abscess, injection site reaction, lymphadenopathy, infection, skin reaction, rash, erythema, impaired healing, pyrexia, vaccine error, pain, decreased appetite, hypotonic-hyporesponsive episode, irritability, Kawasaki disease, meningoencephalitis herpetic and osteomyelitis. The BCG vaccine-related AEFI rate per 100,000 doses in children aged less than 7 years are shown in Table 8.<sup>136</sup>

**Table 8: Age at vaccination and BCG vaccine-related AEFI rate per 100,000 doses (includes any passive reports following BCG including reactogenicity seen after most BCG vaccinations)**

Age	BCG AEFI rate	95% CI
0 - <3 m	56	(37-81)
3 - <6 m	204	(132-300)
6 - <9 m	459	(251-769)
9 - <12 m	520	(224-1024)
1-<7 yrs	706	(492-981)
<b>Total</b>	<b>153</b>	<b>(126-184)</b>

<sup>136</sup> Adverse events following immunisation with Bacille Calmette-Guérin vaccination: baseline data to inform monitoring in Australia following introduction of new unregistered BCG vaccine. Alexandra Hendry, Aditi Dey, Frank Beard, Gulam Khandaker, Richard Hill and Kristine Macartney. CDI 2016; 40(4):E470-E474.

## 17. Route of administration

**Summary:** The route of administration is intradermal or percutaneous administration with a multipuncture device or intradermal injection with the Mantoux method. Evidence is not sufficient to favour one of the mentioned methods.

Originally, the BCG vaccine was developed as an oral vaccine by Calmette and Guérin. After the Lübeck disaster in 1930<sup>137</sup>, oral administration has been completely replaced by intradermal administration. Brazil continued oral BCG administration until the 1970s.<sup>138</sup> BCG has been delivered intradermally by multiple methods, including needle injection using the Mantoux technique, multiple puncture devices, scarification, jet injectors, bifurcated needles and multitine devices.<sup>139</sup> WHO recommends intradermal application of the vaccine, preferably on the deltoid region of the arm using syringe and needle, although other application methods such as the multiple puncture technique are practiced in some countries.<sup>4</sup> Today the most conventional administration technique for BCG is the Mantoux method.<sup>139</sup>

The percutaneous administration with the multiple puncture technique is practiced in some countries due to concerns of adverse events by intradermal vaccination.<sup>140,150,151</sup> South Africa could not confirm the concerns of unacceptable high rates of adverse events when reporting on their transition of percutaneous administration to intradermal.<sup>141</sup> The BCG vaccine manufacturers Merck (USA) former Organon, Korea Vaccine and Japan BCG Laboratory produce vaccine for percutaneous BCG administration (see Table 6). In countries where both methods are available, a growing preference of parents for the vaccines by the multipuncture method is noticed.<sup>142</sup>

A literature review compared the intradermal with the percutaneous vaccination. Evidence indicates that the percutaneous is not as precise in administered dose (lower dosages) and accordingly leading to a lower rate of protection especially against the more severe forms of the disease.<sup>148</sup> Comparisons in a RCT between multiple puncture and intradermal methods revealed that intradermal administration led to a tuberculin conversion rate of 93% and administration with the multipuncture instrument to 79% and 86%, depending on the pressure which was required to engage the catch.<sup>150</sup> Nevertheless, the transition from using Tokyo 172 BCG given percutaneously to Danish 1331 BCG given intradermal in South Africa did not prevent more TB cases in children overall but reduced the proportion with disseminated disease. A recently conducted RCT in South African infants vaccinated at birth and followed up for two years showed no significant difference between intradermal BCG vaccine and percutaneous in the incidence of TB for efficacy and safety.<sup>151</sup> The same study reported on higher frequencies of BCG specific IFN $\gamma$  T cells, CD4+ and CD8+ T cell proliferation,

<sup>137</sup> Fox GJ et al. Tuberculosis in Newborns: The Lessons of the "Lübeck Disaster" (1929–1933). *PLoS Pathog.* 2016 Jan 21;12(1):e1005271.

<sup>138</sup> Monteiro-Maia and Teixeira de Pinho, Oral bacillus Calmette-Guérin vaccine against tuberculosis: why not? *Mem Inst Oswaldo Cruz.* 2014 Sep;109(6):838-45.

<sup>139</sup> Plotkin's Vaccines, 7<sup>th</sup> edition, 2017. Chapter 68 New Technologies for Vaccine Administration: Vaccine Macrodelivery Systems at the Points of Care.

<sup>140</sup> Yamamoto S and Yamamoto T. Historical review of BCG vaccine in Japan. *Jpn J Infect Dis.* 2007 Nov;60(6):331-6.

<sup>141</sup> Jeena PM et al., Safety of the intradermal Copenhagen 1331 BCG vaccine in neonates in Durban, South Africa. *Bull World Health Organ.* 2001;79(4):337-43.

<sup>142</sup> Lee H et al., The Current Status of BCG Vaccination in Young Children in South Korea. *Tuberc Respir Dis (Seoul).* 2012 Apr;72(4):374-80. doi: 10.4046/trd.2012.72.4.374.

more secretion of IFN $\gamma$ , TNF $\alpha$  and IL2 and less secretion of IL4 by percutaneous vaccination in comparison with intradermal vaccination.<sup>143,144</sup>

Disposable-syringe jet injectors (DSJI) use needle-free technology, delivering the vaccine through a small nozzle, and is intended to be less dependent on user skill and experience.<sup>145,146</sup> A RCT<sup>149</sup> in South Africa compared administration with DSJI and vaccination with the conventional technique with needle and syringe. The study population consisted of 30 adults and 66 newborns that were randomized to receive the BCG vaccine intradermal through either the standard needle and syringe (NS) method or experimental DSJI method. The majority of adverse events were characteristic BCG-associated lesions at the injection site and there were no differences in adverse event frequencies between DSJI and NS study arms. A literature review<sup>153</sup> on adverse events in Iran identified studies that reported increased risk of adenitis with administration in the right arm compared to the left arm and also when administering in the upper third of the arm.

These studies show that correct vaccine administration technique by a trained health worker is important for the correct dosage and optimal BCG vaccine efficacy and safety.

**Table 9: Primary papers on BCG vaccine administration technique**

Author/Year	Study Design	Vaccination strain	Population	Reference Number
Al Jarad N <i>et al.</i> , 1999	Observational study	No information	Schoolchildren in London	147
Bricks LF, 2004	Literature Review	different	different	148
Geldenhuis <i>et al.</i> , 2015	RCT	Danish strain 1331	Children and adults in South Africa	149
Griffith <i>et al.</i> , 1963	RCT	BCG-Glaxo	schoolchildren in Cardiff	150
Hawkrige A <i>et al.</i> , 2008	RCT	Tokyo 172	South African infants	151
Mahomed H <i>et al.</i> , 2006	Observational study	Tokyo 172 and Danish strain 1331	South African infants	152
Mostaan <i>et al.</i> , 2016	Literature review	French 1173-P2	Infants and children in Iran	153

<sup>143</sup> Davids V *et al.*, Dose-dependent immune response to Mycobacterium bovis BCG vaccination in neonates. *Clin Vaccine Immunol.* 2007 Feb;14(2):198-200.

<sup>144</sup> Davids V *et al.*, The effect of bacille Calmette-Guérin vaccine strain and route of administration on induced immune responses in vaccinated infants. *J Infect Dis.* 2006 Feb 15;193(4):531-6.

<sup>145</sup> Hickling JK *et al.* Intradermal delivery of vaccines: potential benefits and current challenges. *Bulletin of the World Health Organization* 2011;89:221-226. doi: 10.2471/BLT.10.079426. Available at <http://www.who.int/bulletin/volumes/89/3/10-079426/en/>, accessed July 2017.

<sup>146</sup> ten Dam HG *et al.* The use of jet-injectors in BCG vaccination. *Bull World Health Organ.* 43 (5):707-720 1970.

<sup>147</sup> Al Jarad N *et al.* Administration of the BCG vaccination using the multipuncture method in schoolchildren: a comparison with the intradermal method. *Thorax.* 1999 Sep;54(9):762-4.

<sup>148</sup> Bricks LF. Percutaneous or intradermal BCG vaccine? *J Pediatr (Rio J).* 2004 Mar-Apr;80(2):93-8.

<sup>149</sup> Geldenhuis HD, Mearns H, Foster J, Saxon E, Kagina B, Saganic L, *et al.* A randomized clinical trial in adults and newborns in South Africa to compare the safety and immunogenicity of bacille Calmette-Guérin (BCG) vaccine administration via a disposable-syringe jet injector to conventional technique with needle and syringe. *Vaccine.* Elsevier Ltd; 2015;33(37):4719–26. Available from: <http://dx.doi.org/10.1016/j.vaccine.2015.03.074>

<sup>150</sup> Griffith *et al.* A comparison between multiple puncture and intradermal methods of BCG vaccination. *Tubercle.* 1963 Sep;44:372-7.

<sup>151</sup> Hawkrige A Efficacy of percutaneous versus intradermal BCG in the prevention of tuberculosis in South African infants: randomised trial. *Rev Port Pneumol.* 2009 Jul-Aug;15(4):747-9.

<sup>152</sup> Mahomed H *et al.* The impact of a change in bacille Calmette-Guérin vaccine policy on tuberculosis incidence in children in Cape Town, South Africa. *Pediatr Infect Dis J.* 2006 Dec;25(12):1167-72.

<sup>153</sup> Mostaan S, Yazdanpanah B, Moukhah R, Hozouri H, Rostami M, Khorashadizadeh M, *et al.* Adverse effects of BCG vaccine 1173 P2 in Iran: A meta-analysis. *Adv Biomed Res.* 2016;5(1):99. Available from: <http://www.advbiores.net/text.asp?2016/5/1/99/183659>

## 18. Co-administration with other vaccines

### Summary

BCG co-administration with OPV and hepatitis B vaccines is safe. Even when in many settings DPT containing vaccines are administered after 6 weeks of age, a concomitant or a co-administration has proved to be safe. No evidence was retrieved on co-administration with rotavirus, PCV, and bOPV vaccination.

Due to the paucity of primary literature, BCG manufacturers were contacted (Table 10) to collect information of BCG co-administration. Some of the literature on co-administration reports on potential NSE of BCG administered alone or with other administered vaccinations.<sup>154,155</sup> However, there is currently insufficient robust data to draw firm conclusions: for detailed analysis please see WHO draft protocols of clinical trials to assess the non-specific effects of vaccines<sup>156</sup> and Higgins *et al.*<sup>157</sup>

In a study examining antibody response to hepatitis B surface antigen (HBsAg) in 60 infants in Turkey<sup>158</sup>, simultaneous administration of BCG and hepatitis B vaccines did not influence the immune response to HBsAg when compared to administration of hepatitis B vaccine alone. This finding aligns with an older study in Senegal<sup>159</sup>, which also showed that the serological response to HBsAg and poliovirus and cellular response to BCG did not differ between simultaneous administration of hepatitis B, BCG and oral polio vaccine (tOPV) vaccines compared to separate administration groups. One study in India found that BCG vaccine given first followed by hepatitis B vaccination caused less pain, as assessed by the neonatal infant pain scale, than the other order and thus recommends this order of administration.<sup>160</sup> One RCT compared the immunogenicity of a combined intradermal BCG and hepatitis B vaccine with the standard intradermal BCG and intramuscular hepatitis B vaccine in 548 infants in Brazil, and found there to be no difference in the serological response to HBV after the third hepatitis B vaccine dose at 6 months.<sup>161</sup> This cohort was followed up at 7 months, to investigate the BCG specific T-cell proliferation and cytokine production, and there was no difference between the groups.<sup>162</sup>

Table 10 presents the approved co-administration for the various BCG products. Information was collected by from communication with manufacturer and package inserts.

<sup>154</sup> Biai S, Rodrigues A, Nielsen J, Sodemann M, Aaby P. Vaccination status and sequence of vaccinations as risk factors for hospitalisation among outpatients in a high mortality country. *Vaccine*. 2011;29(20):3662-9.

<sup>155</sup> Ritz N, Mui M, Balloch A, Curtis N. Non-specific effect of Bacille Calmette-Guérin vaccine on the immune response to routine immunisations. *Vaccine*. 2013;31(30):3098.

<sup>156</sup> WHO. Call for public comments on draft protocols of clinical trials to assess the non-specific effects of vaccines. Available at [http://www.who.int/immunization/research/implementation/nse\\_protocol\\_comments/en/](http://www.who.int/immunization/research/implementation/nse_protocol_comments/en/), accessed August 2017.

<sup>157</sup> Higgins et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ* 2016;355:i5170

<sup>158</sup> Artan R et al. The effect of concurrent use of hepatitis B and Bacille Calmette-Guérin vaccination on anti-hepatitis B response. *Saudi medical journal*. 2004;25:1939.

<sup>159</sup> Coursaget P et al. Simultaneous injection of hepatitis B vaccine with BCG and killed poliovirus vaccine. *Vaccine*. 1992;10:319-21.

<sup>160</sup> Ravikiran SR et al. Pain Response in Newborns to the Order of Injecting BCG and Hepatitis-B Vaccines: A Randomized Trial. *The Indian Journal of Pediatrics*. 2011;78:693-7.

<sup>161</sup> Carniel EF et al. Immunogenicity and safety of combined intradermal recombinant Hepatitis B with BCG vaccines at birth. *Vaccine*. 2008;26:647-52.

<sup>162</sup> Mazzola TN et al. Robust  $\gamma\delta$  + T cell expansion in infants immunized at birth with BCG vaccine. *Vaccine*. 2007;25:6313-20.



**Table 10: Information of BCG manufacturers regarding co-administration**

\*WHO prequalified vaccines

<p><b>AJBiologics*</b> Product information of the prequalification process.<sup>163</sup> <b>Country of manufacturing:</b> Malaysia; <b>Used Strain:</b> Danish strain <b>Approved co-administration:</b> With DPT, DT, TT, measles, polio vaccines (OPV and IPV), Hepatitis B, Haemophilus</p>	<p><b>China National Biotec Group (Chengdu)</b> Communication with the manufacturer on country practice in China. <b>Country of manufacturing:</b> China; <b>Used Strain:</b> Shanghai D2PB302 strain <b>Approved co-administration:</b> Hepatitis B</p>
<p><b>BCG Vaccine Laboratory</b> Product information of the manufacturer<sup>164</sup> <b>Country of manufacturing:</b> India; <b>Used Strain:</b> Danish strain <b>Approved co-administration:</b> with DPT, DT, TT, measles, polio vaccines (OPV &amp; IPV), Hepatitis-B and Yellow Fever.</p>	<p><b>China National Biotec Group (Shanghai)</b> Communication with the manufacturer on country practice in China. <b>Country of manufacturing:</b> China; <b>Used Strain:</b> Shanghai D2PB302 strain <b>Approved co-administration:</b> Hepatitis B</p>
<p><b>BioFarma</b> Product information of the manufacturer<sup>165</sup> <b>Country of manufacturing:</b> Indonesia; <b>Used Strain:</b> Paris strain <b>Approved co-administration:</b> with DTP, Measles, polio (OPV &amp; IPV) vaccines, Hepatitis B, Haemophilus influenzae type b, yellow fever, and vitamin A supplements.</p>	<p><b>Green Signal Biopharma*</b> Product information of the prequalification process.<sup>168</sup> <b>Country of manufacturing:</b> India; <b>Used Strain:</b> Danish strain <b>Approved co-administration:</b> with DTP, DT, TT, Measles, Polio and Hepatitis B vaccines <b>Inst. Of Virology, Vaccines and Sera Torlak</b> Product information of the manufacturer<sup>169</sup> <b>Country of manufacturing:</b> Serbia; <b>Used Strain:</b> unknown <b>Approved co-administration:</b> -with other inactivated live vaccines -Other vaccines to be given at the same time as BCG vaccine or during the next three months should not be given into the same (left) arm because of the risk of regional lymphadenitis. -BCG vaccine is not recommended to be administered in the period of 4 weeks after the administration of any live vaccine.</p>
<p><b>BioMed Lublin</b> Product information of the manufacturer<sup>166</sup> <b>Country of manufacturing:</b> Poland; <b>Used Strain:</b> Moreau strain <b>Approved co-administration:</b> The interval between BCG and Hepatitis type B vaccinations in newborn infants should not exceed 24 hours. Individuals vaccinated against pertussis, diphtheria, tetanus, typhoid, rabies, influenza, ixodic brain fever or cholera can be vaccinated with BCG vaccine 4 weeks from the previous vaccination. After the BCG vaccination the break interval should be 4 weeks, after that time the individual can be vaccinated against: pertussis, diphtheria, tetanus, typhoid, rabies, influenza, ixodic brain fever and cholera. Vaccines against: poliomyelitis, measles, rubella, mumps - can be administered after a period of 6 weeks from the BCG vaccination. If the vaccine against poliomyelitis is administered simultaneously with the DTP vaccine (diphtheria-tetanus-pertussis) an interval of at least 6 weeks from the BCG vaccination should also be obligatory.</p>	<p><b>Japan BCG Laboratory*</b> Product information of the prequalification process.<sup>170</sup> <b>Country of manufacturing:</b> Japan; <b>Used Strain:</b> Tokyo 172-1 strain <b>Approved co-administration:</b> with DTP, measles, polio (OPV and IPV), hepatitis B, Haemophilus influenzae type b, and yellow fever vaccines and vitamin A supplementation.</p>
<p><b>BulBIO LTD*</b> Product information of the prequalification process.<sup>167</sup> <b>Country of manufacturing:</b> Bulgaria; <b>Used Strain:</b> Moscow or Russian BCG-I <b>Approved co-administration:</b> with DPT, Measles, Polio vaccines (OPV and IPV), Hepatitis B, Haemophilus influenzae type B, and yellow fever vaccine and vitamin D supplementation</p>	<p><b>Pasteur Institute of Iran</b> Communication with the manufacturer on country practice in Iran. <b>Country of manufacturing:</b> Iran; <b>Used Strain:</b> Pasteur 1173P2 strain <b>Approved co-administration:</b> Hepatitis B</p>
	<p><b>Serum Institute of India*</b> Product information of the prequalification process<sup>171</sup> <b>Country of manufacturing:</b> India; <b>Used Strain:</b> Russian BCG-I <b>Approved co-administration:</b> with DTP, DT, TT, Measles, Polio, Hepatitis B, Haemophilus influenzae type b, yellow fever vaccines and vitamin A supplementation</p>
	<p><b>Vaccins et Sérums Institut Pasteur de Tunis</b> Communication with the manufacturer on country practice in Tunis. <b>Country of manufacturing:</b> Tunisia; <b>Used Strain:</b> Pasteur 1173P2 strain <b>Approved co-administration:</b> Hepatitis B</p>

<sup>163</sup> WHO prequalified vaccine AJVaccines. Available at [https://extranet.who.int/gavi/PQ\\_Web/PreviewVaccine.aspx?nav=0&ID=164](https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=164), accessed August 2017.

<sup>164</sup> BCG Vaccine Laboratory, Chennai. BCG VACCINE (10 DOSES) I.P. Available at <http://www.dirbcglab.gov.in/aboutproduct.html>, accessed July 2017.

<sup>165</sup> BioFarma. Available at <http://www.biofarma.co.id/en/produk/vaksin-bcg-beku-kering/>, accessed July 2017.

<sup>166</sup> BioMed Lublin. Antitubercle vaccine BCG 10. Available at [http://www.biomed.lublin.pl/en/index.php?option=com\\_content&view=article&id=102%3Aaszczepionka-przeciwegruclicza-bcg-10&catid=40%3Aleki-na-recepte&Itemid=1](http://www.biomed.lublin.pl/en/index.php?option=com_content&view=article&id=102%3Aaszczepionka-przeciwegruclicza-bcg-10&catid=40%3Aleki-na-recepte&Itemid=1), accessed July 2017.

<sup>167</sup> WHO prequalified vaccine BulBIO LTD. Available at [https://extranet.who.int/gavi/PQ\\_Web/PreviewVaccine.aspx?nav=0&ID=74](https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=74), accessed August 2017.

<sup>168</sup> WHO prequalified vaccine Green Signal Biopharma. Available at [https://extranet.who.int/gavi/PQ\\_Web/PreviewVaccine.aspx?nav=0&ID=294](https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=294), accessed August 2017.

<sup>169</sup> Inst. Of Virology, Vaccines and Sera Torlak Patient information leaflet, BCG vaccine, freeze dried. Available at <http://www.torlakinstitut.com/pdf/BCG-en.pdf>, accessed July 2017.

<sup>170</sup> WHO prequalified vaccine JBL. Available at [https://extranet.who.int/gavi/PQ\\_Web/PreviewVaccine.aspx?nav=0&ID=67](https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=67), accessed August 2017.

<sup>171</sup> WHO prequalified vaccine SSI. Available at [https://extranet.who.int/gavi/PQ\\_Web/PreviewVaccine.aspx?nav=0&ID=117](https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=117), accessed August 2017.

## 19. Update on the status of the pediatric HIV epidemic and implications for BCG administration policies in countries with high burden of HIV

### Summary

- New pediatric infections are decreasing and therefore the probability that a child born to HIV- infected mothers is HIV-infected at the time of BCG vaccination is lower than it used to be (at least in context where PMTCT interventions have been scale up effectively).
- While progress was made in scaling up early infant HIV diagnosis (EID), coverage of diagnosis by 2 months is still low. Therefore, at the programmatic level, waiting for HIV diagnosis to administer BCG would still significantly delay administration in a large proportion of HIV-infected infants
- Innovations such as HIV testing at birth and use of point-of-care (POC) technologies may allow more rapid identification of HIV-infected infants in the near future, but there is currently very limited implementation. Provision of HIV testing with POC at the BCG delivery point has been considered as a potential implementation strategy, but this has not yet been piloted.
- Early ART initiation before immunological and/or clinical progression substantially reduces the risk of BCG-IRIS regional adenitis. As countries move to implement more rapid ART initiation, occurrence of BCGemia and BCG-IRIS is less and less likely.
- The most appropriate timing for BCG vaccination that maximizes both specific and possible NSEs, particularly in HIV-1-exposed children, is thus presently unknown and studies are ongoing.

### What's the likelihood of an HIV-exposed infant to be HIV infected?

Global efforts to stop new HIV infections among children has led to tangible progress. Around 76% of pregnant women living with HIV had access to antiretroviral medicines in 2016, up from 47% in 2010. New HIV infections among children globally have halved, from 300 000 in 2010 to 160 000 in 2016. Five-high burden countries—Botswana, Namibia, South Africa, Swaziland and Uganda—have already met the milestone of diagnosing and providing lifelong antiretroviral therapy to 95% of pregnant and breastfeeding women living with HIV.<sup>173</sup>

Gains have been especially impressive in the 23 “Start Free Stay Free AIDS Free” priority countries<sup>172</sup>, where 88% of pregnant women living with HIV reside. Several of those countries have managed to reduce mother-to-child transmission rates to under 5%, including throughout breastfeeding<sup>173</sup>. A growing number of countries with relatively low HIV prevalence have validated the elimination of mother-to-child transmission of HIV and congenital syphilis. A major milestone on the way to the elimination of mother-to-child transmission of HIV is diagnosing and providing lifelong antiretroviral therapy to at least 95% of pregnant and breastfeeding women living with HIV.

Despite these encouraging figures, one in five women are either not tested for HIV or not started on ART during pregnancy. Moreover, these coverage estimates are based only on ART initiation and do not account

<sup>172</sup> Angola, Botswana, Burundi, Cameroon, Chad, Cote d'Ivoire, DRC, Ethiopia, Ghana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, South Africa, Swaziland, Tanzania, Uganda, Zambia, Zimbabwe, Indonesia and India

<sup>173</sup> UNAIDS. GLOBAL AIDS UPDATE | 2017. [http://www.unaids.org/sites/default/files/media\\_asset/Global\\_AIDS\\_update\\_2017\\_en.pdf](http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf)

for women who are lost to follow-up.<sup>174</sup> Furthermore, the coverage estimates do not capture the proportion of pregnant/breastfeeding women who are virally suppressed.

Transmission rates following incident infection are 2–3 times higher than in women with chronic HIV infection, and the number of children acquiring infection postnatally and in-utero are proportionally increasing.<sup>175</sup> Although policies are in place for partner testing as well as repeat testing of women during pregnancy and breastfeeding, in practice this does not always happen and/or is not systematically documented. As an intervention, partner testing is especially valuable because it can identify HIV-negative women in serodiscordant relationships who should receive HIV prevention interventions. Implementation of maternal HIV screening in immunization clinics is another important strategy for ensuring that women who were HIV-negative at their first antenatal clinic visit have received a repeat HIV test to identify incident HIV infection. National-level programme data are limited in their ability to capture true maternal and infant outcomes due to loss to follow-up or data quality issues. As a result, current global models are likely to underestimate the numbers of new infections in children as well as the true extent of pediatric HIV-related mortality<sup>176</sup>.

According to the most recent estimates, only 43% of infants born to HIV-infected mothers receive virological testing before their 2nd month of age. In several countries, access to early infant diagnosis continues to rise.

Earlier testing<sup>177</sup> and testing at the point of care<sup>178</sup> along with strategies to ensure rapid turnaround of results have shown potential for enabling initiation of ART in the first weeks of life and, maximizing the effect on early morbidity and mortality. Technau *et al.*<sup>177</sup> describes the first experience with point-of-care testing (POCT) to diagnose HIV at birth and provide evidence of good performance for these new technologies around the time of birth. They show that despite the challenges and additional resources needed, combining POCT with birth testing could significantly improve time to treatment initiation and have potential to reduce early mortality and optimize infants' outcomes.

### **Are we able to identify infected infants in a timely manner?**

In settings with a high proportion of attended deliveries, adding virological testing at birth to the existing testing algorithm can enable an earlier and wider provision of HIV testing services to mothers and babies who may not return to the health facility.<sup>173</sup> However, a number of operational issues remain to be resolved, such as the need for additional human resources, active tracking of infants tested and messages that guarantee uptake of repeat testing at six weeks. It is also important to strengthen the overall uptake, retention and linkages in the testing-to-treatment cascade for birth testing to have the expected impact. After South Africa introduced virologic testing at birth and at 10 weeks for all HIV-exposed infants in 2015, the number of HIV-exposed infants receiving virologic testing within seven days of birth increased 15-fold in only three months, while the number of HIV-diagnosed children rose more than six-fold.<sup>173</sup> A number of countries—including Ghana, Kenya, Namibia, Swaziland and Zimbabwe—are in the process of undertaking

<sup>174</sup> Woelk GB *et al.* Retention of mothers and infants in the prevention of mother-to-child transmission of HIV programme is associated with individual and facility-level factors in Rwanda. *J Int AIDS Soc*, 19 (2016), p. 20837

<sup>175</sup> Drake AL *et al.* Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. *PLoS Med*, 11 (2014), p. e1001608

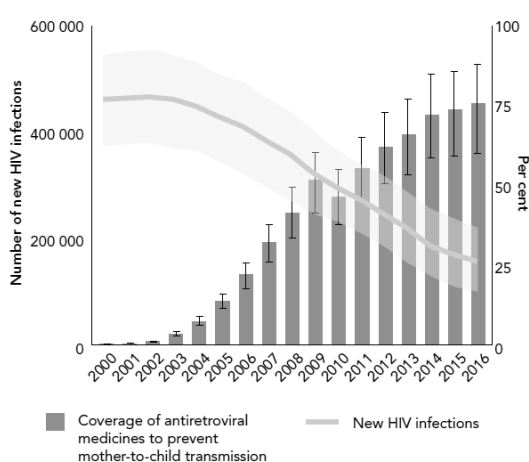
<sup>176</sup> Mahy M *et al.* Improving estimates of children living with HIV from the Spectrum AIDS Impact Model. *AIDS*, 31 (2017), pp. S13-S22.

<sup>177</sup> Technau KG *et al.* HIV-1 point-of-care test for neonatal diagnosis of HIV in the birth testing programme of a maternity hospital: a field evaluation study *Lancet HIV* (2017) published online July 12. [http://dx.doi.org/10.1016/S2352-3018\(17\)30097-8](http://dx.doi.org/10.1016/S2352-3018(17)30097-8)

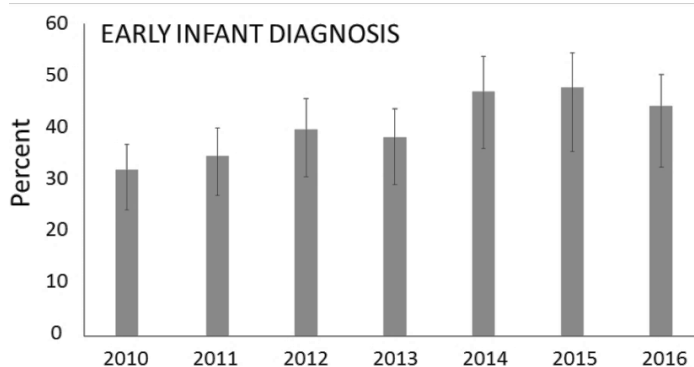
<sup>178</sup> Jani I *et al.* Effect of point-of-care technology on antiretroviral therapy initiation rates in infants. Conference on Retroviruses and Opportunistic Infections. Seattle, WA, USA; Feb 13–16, 2017. Abstract 26.

pilots of virological testing at birth to inform future national scale-up. Provision of HIV testing in conjunction with BCG administration has been considered as a potential implementation strategy to maximize access to HIV testing even for those that don't deliver at facility. However, to our knowledge, no countries have so far piloted this model.

**Figure 12 New HIV infections among children (aged 0–14 years) and coverage of antiretroviral regimens to prevent mother-to-child transmission, global, 2000–2016. Source: UNAIDS 2017 estimates.**



**Figure 13 Percentage of HIV-exposed infants who have been diagnosed within two months of birth, 21 high-burden countries, 2010 and 2016. Source: Global AIDS Monitoring, 2017; UNAIDS 2017 estimates.**



The main benefit of early HIV diagnosis is the potential for rapid initiation of ART to prevent early mortality, particularly in perinatally-infected infants, and future morbidity. However, even when EID is available, linkage to care and treatment initiation occurs only in a small proportion of infected infants. Globally, an estimated 919 000 children were on antiretroviral therapy in 2016, about 43% of all children living with HIV. The rate of increase in the number of children on treatment has slowed in recent years, falling to an annual increase of 6% in 2016 from an annual increase of over 10% in previous years.

#### **In the context of earlier identification and ART initiation, how frequent is BCGemia and BCG-IRIS in HIV infected infants that received BCG?**

In South Africa, all neonates are still vaccinated, regardless of HIV exposure, as the prevalence of TB and HIV is high and HIV diagnosis before 6 weeks of age has not been feasible for long time. Complications occurring soon after initiation of antiretroviral treatment (ART) are usually ascribed to immune reconstitution inflammatory syndrome (IRIS). BCG-related regional adenitis due to IRIS (BCG-IRIS) was described in respectively 6% and 15% of children in two South African cohorts.<sup>179,180</sup> However, these and other reports only included children starting ART following immunological or clinical decline. As immunosuppression is a risk factor for IRIS, early ART initiation in infants should lower the risk of BCG-IRIS. A recently published study

<sup>179</sup> Smith K, Kuhn L, Coovadia A, Meyers T. Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. *AIDS*. 2009; 23:1097–1107. [PubMed: 19417581]

<sup>180</sup> Nuttall JJ, Davies M, Hussey G, et al. Bacillus Calmette-Guérin (BCG) vaccine-induced complications in children treated with highly active antiretroviral therapy. *Int J Infect Dis*. 2008; 12:e99–e105. [PubMed: 18799339]

by Rabie *et al.*<sup>181</sup> showed that early ART initiation before immunological and/or clinical progression substantially reduces the risk of BCG-IRIS regional adenitis. As countries move to implement a more rapid ART initiation occurrence of BCGemia and BCG-IRIS are less and less likely. This appears to be confirmed by observational data from the leDea Southern Africa cohort (Mary Ann Davies personal communication) where lymphadenitis happened in around 0.6% of the 12748 children vaccinated and started on ART with the majority of the cases happening in the 1st year.

### What's the implication for “delaying” or “missing” BCG for HIV infected children?

To overcome the concerns regarding administration of BCG in HIV-infected infants, delaying BCG until these infants are diagnosed as not having HIV-1 infection has been considered. Delaying BCG vaccination could have an unintended consequence of lowering vaccination coverage. There is also some uncertainty regarding whether vaccinating HIV-1-exposed babies with BCG at birth provides protection against serious infections other than TB, i.e., through NSEs, delaying vaccination could result in increased morbidity and even mortality. The most appropriate timing for BCG vaccination that maximizes both specific and possible NSEs, particularly in HIV-1-exposed children, is unknown. A study undergoing in Uganda lead by Nankabirwa *et al.*<sup>182</sup> will address this important question.

## 20. Vaccination of low birth weight and premature infants

Observational cohort studies describe that low birth weight (LBW) infants often receive BCG immunization late compared to normal birth weight infants.<sup>183,184</sup> This policy of not vaccinating low birth weight infants at birth had a negative impact on vaccination coverage for LBW children in Guinea Bissau.<sup>185</sup> An Indian study describes no significant difference in the scar formation in infants studied with varying birth weights after 12 weeks of BCG vaccination.<sup>186</sup> A recent RCT assessed the effects of BCG vaccination on low birth weight infants in Gambia. No effect of early BCG on growth in the first year of life was observed.<sup>187,188</sup> The same study concluded, that early BCG vaccination had no large negative impact on TST and BCG scarring.

Okan *et al.*<sup>189</sup> reported in their study that BCG vaccination in preterm infants at months 2-3 of postnatal life results in a high percentage of BCG scarring and 57% TST conversion. Additionally they reported, that a positive tuberculin response was significantly related to the postnatal weight gain of the preterm infants. Results from other studies suggest also that the preterm infants born at 32-36 weeks of gestation can be

<sup>181</sup> Early antiretroviral treatment reduces risk of bacille Calmette-Guérin immune reconstitution adenitis.

Rabie H, Violari A, Duong T, Madhi SA, Josipovic D, Innes S, Dobbels E, Lazarus E, Panchia R, Babiker AG, Gibb DM, Cotton MF; CHER team. *Int J Tuberc Lung Dis.* 2011 Sep;15(9):1194-200. i. doi: 10.5588/ijtld.10.0721.

<sup>182</sup> Nankabirwa V *et al.* Early versus late BCG vaccination in HIV-1-exposed infants in Uganda: study protocol for a randomized controlled trial. *Trials.* 2017 Mar 31;18(1):152.

<sup>183</sup> Mutua *et al.* Effects of low birth weight on time to BCG vaccination in an urban poor settlement in Nairobi, Kenya: an observational cohort study. *BMC Pediatr.* 2015 Apr 18;15:45. doi: 10.1186/s12887-015-0360-5.

<sup>184</sup> O'Leary *et al.* Neonatal vaccination of low birthweight infants in Ghana. *Arch Dis Child.* 2017 Feb;102(2):145-151.

<sup>185</sup> Roth *et al.* Low birth weight infants and Calmette-Guérin bacillus vaccination at birth: community study from Guinea-Bissau. *Pediatr Infect Dis J.* 2004 Jun;23(6):544-50.

<sup>186</sup> Kaur *et al.* BCG vaccination reaction in low birth weight infants. *Indian J Med Res.* 2002 Aug;116:64-9.

<sup>187</sup> Biering-Sørensen *et al.* Early BCG vaccine to low-birth-weight infants and the effects on growth in the first year of life: a randomised controlled trial. *BMC Pediatr.* 2015 Sep 28;15:137. doi: 10.1186/s12887-015-0452-2.

<sup>188</sup> Biering-Sørensen *et al.* Small randomized trial among low-birth-weight children receiving bacillus Calmette-Guérin vaccination at first health center contact. *Pediatr Infect Dis J.* 2012 Mar;31(3):306-8.

<sup>189</sup> Okan *et al.* Bacillus Calmette-Guérin vaccination in preterm infants. *Int J Tuberc Lung Dis.* 2006 Dec;10(12):1337-41.

effectively immunized with BCG at birth.<sup>190,191,192,193</sup> In a Brazilian study a typical BCG scar was verified in 96.9% of the control group and in 90.0% of the preterm infants.<sup>194</sup> In contrast a study which evaluated the efficacy of BCG vaccine in pre-term infants in UAE concluded that male pre-term infants of lower gestational ages (<33 weeks) are less likely to develop BCG scar and a reactive PPD tuberculin test after BCG vaccination.<sup>195</sup>

## 21. Vaccination of travelers from non TB endemic countries to TB endemic countries

National and international guidelines and recommendations for the use of BCG vaccination for the prevention of travel-associated TB vary widely, reflecting the lack of data on the both the risk of TB and the effectiveness of BCG in this setting. Numerous case reports and case series document the acquisition of TB disease after travel but no studies provide a risk estimate. However, the incidence of TST conversion in adults after prolonged travel to high TB incidence countries has been reported as 0.35% (95% CI 0.2–0.62%) per month of travel.<sup>196</sup> In addition, two studies in children in the US reported an increased prevalence of TST positivity in children who have travelled overseas.<sup>197,198</sup>

The risk of travel-associated TB depends on several factors, including the TB incidence in the country visited, the duration of travel, the degree of contact with the local population and, in particular, the age of the traveler. Those visiting relatives are at higher risk. Infants and young children, especially those under 1 year of age, are at higher risk as they are more likely to develop severe and disseminated forms of TB.<sup>199</sup>

## 22. Cost-effectiveness of BCG vaccination

### Summary

Review of economic analyses of BCG in the literature show that universal BCG vaccination remains cost-effective in LMICs where TB incidence is high. However, in countries where TB incidence is low, selective BCG vaccination of high-risk populations should be considered. There is insufficient data on the effectiveness of BCG revaccination. No studies were found on cost-effectiveness of BCG vaccination for leprosy however considering the double protection against TB and leprosy the BCG vaccination is cost-effective.

<sup>190</sup> Saroha et al. Immunogenicity and safety of early vs delayed BCG vaccination in moderately preterm (31-33 weeks) infants. *Hum Vaccin Immunother.* 2015;11(12):2864-71.

<sup>191</sup> Dawodu et al. Tuberculin conversion following BCG vaccination in preterm infants. *Acta Paediatr Scand.* 1985 Jul;74(4):564-7.

<sup>192</sup> Thayyil-Sudhan S et al. Safety and effectiveness of BCG vaccination in preterm babies. *Arch Dis Child Fetal Neonatal Ed.* 1999 Jul;81(1):F64-6.

<sup>193</sup> Negrete-Esqueda L and Vargas-Origel A. Response to Bacillus Calmette-Guérin vaccine in full-term and preterm infants. *Am J Perinatol.* 2007 Mar;24(3):183-9.

<sup>194</sup> Camargos et al. Tuberculin skin reactivity after neonatal BCG vaccination in preterm infants in Minas Gerais, Brazil, 2001–2002. *Rev Panam Salud Publica.* 2006

<sup>195</sup> Sedaghatian et al. Bacille Calmette Guérin vaccination in pre-term infants. *Int J Tuberc Lung Dis.* 1998 Aug;2(8):679-82.

<sup>196</sup> Cobelens FG, van Deutekom H, Draayer-Jansen IW, Schepp-Beelen AC, van Ger- ven PJ, van Kessel RP, et al. Risk of infection with *Mycobacterium tuberculosis* in travellers to areas of high tuberculosis endemicity. *Lancet* 2000;356(9228):461–5.

<sup>197</sup> Lobato MN, Hopewell PC. *Mycobacterium tuberculosis* infection after travel to or contact with visitors from countries with a high prevalence of tuberculosis. *Am J Respir Crit Care Med* 1998;158(6): 1871–5.

<sup>198</sup> Saiman L, San Gabriel P, Schulte J, Vargas MP, Kenyon T, Onorato I. Risk factors for latent tuberculosis infection among children in New York City. *Pediatrics* 2001;107(5):999–1003.

<sup>199</sup> Ritz N, Connell TG, Curtis N. To BCG or not to BCG? Preventing travel-associated tuberculosis in children. *Vaccine* 2008;26:5904–9.

A literature review of economic analyses of the BCG vaccine for protection against TB was performed. Studies modelling the economic benefits of future TB vaccines or immunotherapeutic effects of BCG vaccine on bladder cancer, arthritis, and non-tuberculous mycobacteria, were excluded. Studies concerning non-human subjects were also excluded. Data on the economic analyses, population of interest and geography, methods, model assumptions, and main conclusions were extracted and summarized.

An initial search was limited to identifying systematic reviews published after January 1st, 2003, to capture information published following the 2004 WHO BCG position paper. A primary literature review was then undertaken to capture all studies published after January 1st, 2008 up to January 20th, 2017.

Using the search strategy described in the Appendix, a total of 89 articles were identified from the initial search and data from two systematic reviews on the economic evaluation and cost-effectiveness of the BCG vaccine were extracted. The primary literature review resulted in identifying 2,624 articles and data from six primary papers relevant to BCG vaccine economics were extracted.

Both systematic reviews by Trunz *et al.*, (2006)<sup>200</sup> and Tu *et al.*, (2012)<sup>201</sup> provided a worldwide perspective on the costs and benefits of the BCG vaccine and concluded that vaccination was cost-effective in high TB incidence settings. Tu *et al.*, (2012) concluded that revaccination of children in developed countries is not considered cost-effective.

From the primary literature review, three studies from low incidence countries in Europe; the Netherlands<sup>202</sup>, Italy<sup>203</sup> and Ireland<sup>204</sup> examined the costs of universal and selective BCG vaccination strategies. Results from these studies found that although universal BCG vaccination in countries with low TB incidence does offer protection in pediatric populations, the additional protection conferred by universal strategies is comparatively small and less cost-effective when compared to targeted vaccination of high-risk groups.

Three studies from high TB incidence settings were reviewed. In South Africa, a study examining the cost-effectiveness of BCG revaccination in adolescents found the incremental cost per year of healthy life recovered ranged from 116-9,237 USD<sup>205</sup>. In Cameroon, a study which didn't directly address BCG vaccine cost-effectiveness found that BCG vaccination in the context of routine EPI services was lower in outreach strategies. In addition, they found that BCG coverage was low (70%), however, BCG accounted for a relatively small amount of vaccine wastage (1.1%) when compared to newer, expensive vaccines such as the pentavalent and yellow fever vaccine. Finally, a study from Brazil<sup>206</sup> explored the cost-effectiveness of BCG vaccination in children 7-14 years of age using a subpopulation of the BCG REVAC cluster-randomized trial.

<sup>200</sup> Trunz BB et al. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet*. 2006 Apr 8;367(9517):1173-80.

<sup>201</sup> Tu H-AT, Vu HD, Rozenbaum MH, Woerdenbag HJ, Postma MJ. A review of the literature on the economics of vaccination against TB. *Expert Rev Vaccines*. 2012;11(3):303-17.

<sup>202</sup> Altes HK, Dijkstra F, Lugnèr A, Cobelens F, Wallinga J. Targeted BCG Vaccination Against Severe Tuberculosis in Low-prevalence Settings. *Epidemiology*. 2009;20(4):562-8. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00001648-200907000-00015>

<sup>203</sup> Bellini I, Nastasi A, Boccalini S. Clinical and economic impact of a specific BCG vaccination program implemented in Prato, central Italy, involving foreign newborns on hospitalizations. *Hum Vaccin Immunother*. Taylor & Francis; 2016;12(9):2383-90. Available from: <https://www.tandfonline.com/doi/full/10.1080/21645515.2016.1182274>

<sup>204</sup> Usher C, Adams R, Schmitz S, Kieran J, O'Flanagan D, O'Donnell J, et al. Evaluating the neonatal BCG vaccination programme in Ireland. *Arch Public Heal*. Archives of Public Health; 2016;74(1):28. Available from: <http://archpublichealth.biomedcentral.com/articles/10.1186/s13690-016-0141-0>

<sup>205</sup> Dye C. Making wider use of the world's most widely used vaccine: Bacille Calmette–Guérin revaccination reconsidered. *J. R. Soc. Interface* 2013 Jul 31;10(87)

<sup>206</sup> Pereira SM, Barreto ML, Pilger D, Cruz AA, Sant'Anna C, Hijjar MA, et al. Effectiveness and cost-effectiveness of first BCG vaccination against tuberculosis in school-age children without previous tuberculin test (BCG-REVAC trial): A cluster-randomised trial. *Lancet Infect Dis*. Elsevier Ltd; 2012;12(4):300-6.

The study found that the average cost of treating one patient with TB was higher than the cost of vaccinating 381 children. This suggested that vaccination of school-age children can be cost-effective in a high TB incidence setting.

The working group concluded that publications related to BCG cost-effectiveness are scarce and of low quality. However, BCG vaccination at infancy is cost-effective in developing countries or settings with TB incidence rates  $>20/100,000$  population or  $>5/100,000$  smear-positive cases per year.<sup>201</sup> Studies show that universal BCG vaccination was no longer cost-effective in countries with low TB incidence and that targeted or selective vaccination strategies are favoured in these settings. Therefore, as the incidence of TB declines in developed countries, discontinuation of universal vaccination or targeted vaccination of high-risk populations will need to be considered. However, it is important to consider how effective implementation of this strategy is dependent on a strong surveillance system to ensure accuracy of data and better defining of high risk group infants and children  $\leq 5$  years with high risk for exposure to individuals with active pulmonary TB.<sup>201</sup> Although studies show potential for revaccination to be cost-effective in specific populations, estimates of BCG vaccine efficacy remain a controversial factor.<sup>201</sup>

The cost-effectiveness of NSE is currently not included in the summary of evidence and is hard to address. It was concluded that this area should be targeted in the research specific section of the recommendation. In the future, novel vaccine candidates should improve cost-effectiveness.

### **23. Innovations and new vaccines under development**

#### **23.2. Innovations and research are critical to break the trajectory of the TB epidemic**

The 10% per year fall in incidence that is needed by 2025 to achieve the goal of the end TB strategy has been previously achieved only within the wider context of universal health coverage (UHC) and broader social and economic development. To lower cases to 10 per 100,000 population by 2035 ("end the global TB epidemic") and achieve a 95% reduction in TB deaths by 2035 will need a technological breakthrough is necessary by 2025 that will allow an unprecedented acceleration in the rate at which TB incidence falls between 2025 and 2035. This will only happen with substantial investment in R&D, so that new tools such as a post-exposure vaccine or a short, efficacious and safe treatment for latent infection, are developed. For this to happen, at least 2 billion \$USD per year are needed for research. In the TAG TB R&D report 2016, TAG (the Treatment Action Group) estimates that 621 million \$USD were available in 2015 for research. This means that in 2015 there was a funding gap of \$USD 1.3 billion. International donor funding has grown for TB, however it is much less than the available funding for HIV and Malaria. To implement the Global Plan to Stop TB 2016-2020, it was estimated that in 8.3 billion \$USD were needed in 2016 alone. Only 6.6 billion \$USD was available in 2016.

#### **23.3. Diagnostic and treatment tools on the horizon**

Nine new diagnostics have been endorsed by WHO since 2007. Several are currently in development including whole genome sequencing on sputum. By 2020, it is expected that a rapid and sensitive point-of-care diagnostic test will be available as well as a triage, predictive latent TB infection (LTBI) test, and rapid drug susceptibility tests (DST). Two new drugs, bedaquiline and delamanid, and a nine-month regimen for MDR-TB were endorsed since 2012. A shorter 12-week regimen for LTBI is now available. In addition, by



2020, we expect a 4 months regimen for Drug Sensitive-TB; 6-9 months regimens for MDR-TB; and, additional new drugs.

### **23.4. What research is required to end the TB epidemic and eliminate TB?**

A radical intensification of efforts is needed across the full spectrum of research: Basic science (immunology, pathogenesis) to prompt discovery of new tools; R&D pipeline for testing and validating new tools; Innovative strategic approaches adapted to specific country needs; Factors influencing health-related practices of patients and health care workers; and, social determinants of health and financial protection.

The Global TB Programme has developed a Global Action Framework on TB research with two main objectives: (i) To promote, enhance and intensify TB research and innovation at country level; and, (ii) To promote, enhance and catalyze TB research at global level. It is fundamental that all countries pursue national research strategies, plans and networks.

To mobilize high-level multisectoral action to accelerate country implementation of the WHO End TB Strategy in order to reach the End TB targets set by the World Health Assembly and the United Nations (UN) SDGs, on 15-16 November 2017 in Moscow, WHO and the Ministry of Health of the Russian Federation are hosting the First Global Ministerial Conference on Ending TB in the Sustainable Development Era: a Multi-sectoral Response. The Ministerial Conference will inform the UN General Assembly High-level Meeting on TB in 2018.<sup>207</sup>

In summary, during the MDG era, the TB response saved 49 million lives. The UN SDGs call to “end the TB epidemic” in an equitable way by 2030. By optimizing and modernizing care and prevention and by enforcing bold policies we can advance and evolve, but up to a certain point only. Discovery, translational research and innovations are crucial to reach the global targets. Intensified efforts and much greater resources in both implementation and research are necessary, and the UN SDGs are an opportunity for all.

### **23.5. New vaccines under development**

#### **23.5.1. Status of TB Vaccine Development - highlights**

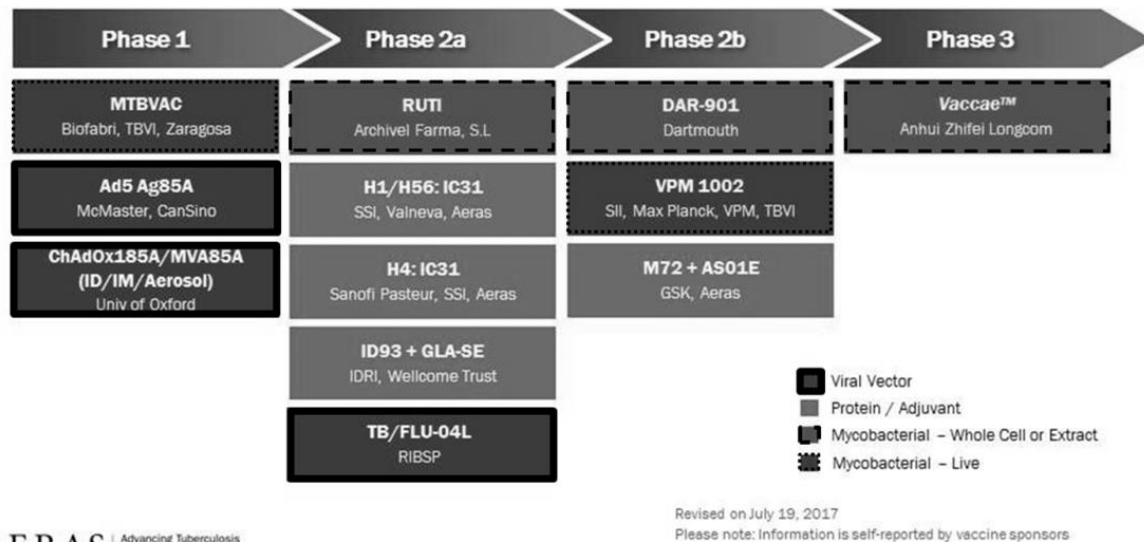
Twelve vaccine candidate approaches are currently in clinical evaluation (see Figure 14). Since a robust cellular response is believed to be required for protection against *M tuberculosis* infection and disease, the majority of candidates are based on components that induce TH1 cytokines such as IFN $\gamma$  or TNF $\alpha$  through induction of CD4<sup>+</sup> or CD8<sup>+</sup> responses.

Prevention of pulmonary TB in adolescents and adults, considering that they are the major source of transmission, is a primary strategic goal in the field of TB vaccine development.

BCG is the only licensed vaccine for TB and is only partially protective in infants. As a live bacterial vaccine, BCG can cause severe disease in immune-compromised individuals, including those who are HIV-infected. Developing safer, more effective (with longer protective duration and more consistent levels of protection) vaccines for BCG replacement is considered an important strategic goal.

<sup>207</sup> Resolution A/RES/71/159 available at [http://www.un.org/en/ga/search/view\\_doc.asp?symbol=A/RES/71/159](http://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/71/159), accessed September 2017.

## Global Clinical Pipeline of TB Vaccine Candidates



**AERAS** Advancing Tuberculosis Vaccines for the World

**Figure 14: Global Clinical TB Vaccine Pipeline**

(According to Aeras: <http://www.aeras.org/pages/global-portfolio>)

Innovative study designs are considered, in absence of established immune correlates of protection, to establish early proof of relevant biological activity. Prevention of infection (POI) studies recruit participants who do not show evidence of past TB infection and monitor conversion to a positive infection diagnostic test. Prevention of recurrence (PoR) studies target patients who have been diagnosed with TB, at various time post diagnosis and treatment. Patients previously treated for TB have a higher incidence of TB disease compared to those with no prior history of the disease, and approximately 90% of these recurrences occur within 12 month of the initial infection. These innovative design aim to reduce the need for large, long and expensive prevention of disease (PoD) trials without evidence of significant biological effect, and thereby reduce investment risks.

Considering the BCG vaccine shortages over the recent years, transfer to liquid culture manufacturing process that is more scalable, reliable and cost effective would be highly desirable. The VPM 1002 vaccine candidate is currently being manufactured in this way. The liquid fermentation for legacy BCG is also being investigated, for what would be a more risk adverse strategy to securing BCG supplies in the mid-term.

The estimated costs of developing a safe and effective TB vaccine are approximately \$1 billion over the next 10-15 years. This cost is small compared to the \$8 billion per year that is required to respond to the TB epidemic with the current tools – and this cost is likely to increase with worsening drug resistance.<sup>208</sup> Hand in hand with vaccine development efforts, WHO will advocate for the need of a TB vaccine in general. The importance is also to be considered in light of the prioritized agenda on antimicrobial resistance (AMR). More candidate vaccines are in early clinical testing.

<sup>208</sup> AERAS. TB Vaccine Research & Development: A Business Case for Investment, [http://www.aeras.org/pdf/TB\\_RD\\_Business\\_Case\\_Draft\\_3.pdf](http://www.aeras.org/pdf/TB_RD_Business_Case_Draft_3.pdf)

### 23.5.2. Status of Leprosy Vaccine Development

As previously described the incidence of leprosy can be reduced due to vaccination with BCG or in combination with killed *M leprae*. Approaches to develop safer, more reproducible BCG based vaccines are under development; referred to as 'BCG improvement strategies'. Several studies, especially from high burden countries, have examined the efficacy of other vaccines and of the combination of post-exposure prophylaxis with BCG at birth and/or with BCG revaccination. Evidence indicates that several other mycobacterial vaccines show similar or slightly lower efficacy compared to BCG vaccination interventions; however, only the M.w (*Mycobacterium indicus pranii*) vaccine remains in production.<sup>209</sup> A new vaccine, the LepVax, is based on a fusion protein and an adjuvant. In animal studies the LepVax appeared to delay and reduce nerve injury. Phase I studies are beginning in America and a phase Ib study is planned to start shortly.<sup>210</sup>

## 24. Additional research needs on BCG

TB control might be improved if a strain of BCG could be identified that provides better protection. This could be done at very low cost with 'ABAB' studies in which all neonates in a defined region would be vaccinated with one strain (A) of BCG for a year and another strain (B) the next year, with the alternation continued for another 2 years (AB). Providing TB were recognised similarly in odd and even years, this design would approach true randomisation but at low cost.<sup>54,55</sup>

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<sup>209</sup> Crains et al. Leprosy. Clinical Evidence 2010;06:915

<sup>210</sup> Smith et al. 19th International Leprosy Congress: the Plenary Sessions. Lepr Rev (2016) 87, 564–569.