World Health Organization

Department of Immunization, Vaccines and Biologicals (IVB)

SAGE

April 2014

Strategic Advisory Group of Experts
1-3 April 2014

CCV, Geneva

World Health Organization

SAGE April 2014

This booklet contains key background documents for the meeting of the Strategic Advisory Group of Experts (SAGE), 1-3 April 2014

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

http://www.who.int/immunization/sage/meetings/2014/april

For password, please send an e-mail to:
sageexecsec@who.int

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World Health Organization

Agenda
Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)
1 – 3 April 2014
CCV/CICG, Geneva

Tuesday, 1 April 2014

Time	Session	Purpose of session, target outcomes and questions for SAGE	
8:30	**Welcome - introduction** J. Abramson, Chair of SAGE		20 min.
8:50	**Report from Director, IVB - Session 1** Global report including key updates and challenges from regions, J.-M. Okwo-Bele, WHO, 30 min. Discussion: 1h 30 min.	**FOR INFORMATION**	2h
10:30	**Coffee/tea break**	**Break**	**30 min.**
11:00	**Report from Director, IVB - Session 1, (Contd.)**		
11:20	**Report from GAVI - Session 2** Report from the GAVI Alliance, S. Berkley, GAVI Alliance, 20 min. Discussion: 20 min.	**FOR INFORMATION**	40 min.
12:00	**Reports from other Advisory Committees on Immunization - Session 3** Report of the Global Advisory Committee on Vaccine Safety (GACVS), M. Wharton, Chair of GACVS, 10 min. Discussion: 20 min.	**FOR INFORMATION**	30 min.
12:30	**Lunch**	**Break**	**1h**

13:30	**Immunization supply chains: strategies for the future of in-country systems strengthening- Session 4** Supply chain challenges continued, P. Colrain, independent consultant, 15 min. Discussion: 15 min. Key innovative solutions for the future, P. Lydon, WHO, 15 min. Discussion: 15 min. Proposed visions and strategies for the next decade 1. WHO-UNICEF Hub and GAVI supply chain strategy, B. Schreiber, UNICEF, 20 min. 2. IPAC "Call to Action", C. Morgan, Chair of IPAC, 10 min. Discussion: 30 min.	**FOR DISCUSSION** This session is a continuation of the one organized for the last SAGE meeting in November 2013. It will provide further evidence into the ongoing constraints faced by country immunization supply chains as uncovered through a deeper analysis of the EVM data. Evidence of innovative systems and technological solutions for the future will be presented. The combination of the evidence on the challenges, and the solution space available has formed the basis of several strategies being developed WHO, UNICEF and GAVI. SAGE is requested to review and provide inputs into the WHO-UNICEF and GAVI strategies and to endorse both the Immunization Practice Advisory Committee's "Call to Action" on in-country immunization supply chain strengthening and the WHO-UNICEF Joint Statement on "Effective Vaccine Management". SAGE is requested to consider whether global policy recommendations could be used to stimulate further efforts and accompany the work to strengthen in country immunization supply systems.	2h
15:30	**Coffee/tea break**	**Break**	**30 min.**
16:00	**Global polio eradication initiative - Session 5** Introduction: Issues for SAGE decisions and discussions. B. Aylward, WHO, 5 min. Detection and interruption of poliovirus transmission. H. Jafari, WHO, 20 min. Discussion: 20 min. Vaccination requirements for the travelers from polio-infected countries: the report from the Polio Working Group. P Figueroa, Chair of SAGE Working Group on polio vaccine, 20 min. Discussion: 80 min. IPV supply, financing and introduction strategy in priority countries. M. Zaffran, WHO, 15 min. Discussion: 20 min.	**FOR DISCUSSION AND DECISION** **For decision:** · Vaccination requirements for the travelers from polio-infected countries · Target date for global readiness for OPV2 withdrawal **For discussion:** · Progress in eliminating wild and vaccine derived poliovirus · Status of the preparation for global OPV2 withdrawal	3h
19:00	**Cocktail**		

Wednesday, 2 April 2014

08:30	**Varicella and herpes zoster vaccines - Session 6** Introduction, J. Abramson, Chair of the SAGE Working Group on varicella and herpes zoster vaccines, 5 min. Varicella: review of evidence (epidemiology, burden and vaccines), J. Seward, Member of the SAGE Working Group on varicella and herpes zoster vaccine, 40 min. Discussion: 25 min. Herpes-Zoster: review of evidence (epidemiology, burden and vaccines), M. Brisson, Member of the SAGE Working Group on varicella and herpes zoster, 25 min. Discussion: 15 min.	**FOR DECISION** Revision of data regarding the global prevalence and burden of disease caused by varicella and herpes zoster according to country development status, as well as revision of safety, effectiveness and duration of protection following varicella and herpes zoster vaccines. Proposed recommendations to SAGE on the use of varicella and herpes zoster vaccines.	2h 30 min.
10:25	**Coffee/tea break**	**Break**	**30 min.**
10:55	**Varicella and herpes zoster vaccines (Contd.) - Session 6** Varicella and herpes zoster vaccines: Review of proposed recommendations, J. Abramson, Chair of the SAGE Working Group on varicella and herpes zoster vaccines, 15 min. Discussion: 50 min.		
12:00	**Lunch**	**Break**	**1h**
13:00	**Alternative vaccination schedules for HPV vaccines - Session 7** Introduction of the topic and objectives of the session , C.-A. Siegrist, SAGE member, 15 min. Summary of the evidence and conclusions from the Ad Hoc Expert Consultation, A. Hall, Chair of Expert Consultation, 30 min. Questions for SAGE- Proposed recommendations/ adjustments to the schedule, C.-A. Siegrist, SAGE member, 15 min. Discussion: 1h	**FOR DECISION** To assess the effect on relevant immunological and clinical outcomes of 2 versus 3 doses of HPV vaccines in adolescent girls 9-13 years of age. To assess the effect immunological and clinical outcomes of various intervals between the first dose and the subsequent doses of HPV vaccines in girls 9-13 years of age (short versus delayed schedules). Expected output: Revised vaccination schedule for HPV vaccines in the above mentioned group.	2h

15:00	**Coffee/tea break**		**30 min.**
15:30	**Pertussis vaccines - Session 8** Introduction of the topic and objectives of the session, C.-A. Siegrist, Chair of SAGE Working Group on pertussis vaccines, 10 min. Summary of the evidence and conclusions from the working group with focus on the potential resurgence of pertussis and comparison of impact of aP and wP, E. Miller, Member of SAGE Working Group on pertussis vaccines, 20 min. Questions: 10 min. Summary of the evidence on strategies to prevent early mortality, E. Miller, Member of SAGE Working Group on pertussis vaccines, 20 min. Questions: 10 min. Review of proposed recommendations, C.-A. Siegrist, Chair of SAGE Working on pertussis vaccines, 15 min. Discussion: 1h 5 min.	**FOR DECISION** Review epidemiological data on pertussis from selected countries using acellular pertussis (aP) and/or whole cell pertussis (wP) vaccines , to evaluate the evidence for resurgence of pertussis, with an emphasis on severe pertussis in very young infants. In countries where the evidence supports resurgence, evaluate the evidence for the hypothesis that this is due to shorter lived protection from aP than wP vaccines. Review the evidence on effectiveness of strategies aimed at reducing severe disease, and deaths in very young infants. Update recommendations on the use of pertussis vaccines.	2h 30 min.
18:00	**End of day**		

Thursday, 3 April 2014

08:30	**Non-specific effects of vaccines on mortality in children under 5 years of age - Session 9** Introduction of the topic - Questions for SAGE T. Nolan, Chair of the SAGE NSE working group, 10 min. Summary of the evidence: Immunology review findings, R. Kandasamy, University of Oxford, 15 min. Out of order and same day vaccinations-update, C. Sanderson, London School of Hygiene and Tropical Medicine, 10 min. Epidemiology review findings, J. Higgins, Bristol University, 45 min. Proposed recommendations from the Working Group T. Nolan, Chair of the SAGE NSE working group, 10 min. Discussion: 1h	**FOR DECISION** Review of the available evidence that addresses the effect of BCG, DTP and measles-containing vaccines on survival/all-cause mortality in children less than five years of age and, the outcomes of the above mentioned reviews and related GRADE tables. Expected output: SAGE recommendation on whether or not the current evidence is sufficient to lead to adjustments in policy recommendations or to warrant further scientific investigation.	2h 30 min.
11:00	**Coffee/tea break**	**Break**	**30 min.**
11:30	**Integration of immunization and child health services - Session 10** Introduction to the session, F. Were, SAGE member, 5 min. Global Context/Landscape: Health Initiatives (MDGs, Every Woman, Every Child, Countdown, etc.) and the imperative for integration and the gaps, Z. Bhutta, SAGE member, 15 min. Overview of WHO's immunization and child health integration efforts, T. Goodman & S. Aboubaker, WHO, 15 min. Ethiopia - Lessons Learned for integrated delivery at the community level, MOH, Ethiopia, 20 min. Discussion: 1h 5 min.	**FOR DISCUSSION** Review current initiatives by WHO/UNICEF, GAVI, and other partners to improve coordination and integration of vaccination with other critical child health services. Assess what additional measures in this context may be needed to strengthen synergies. Discuss how – and to what extent – can immunization be integrated with other child health services at the global, regional, national, district and service delivery levels?	2h
13:30	**Closing**		
13:40	**End of meeting**		

World Health Organization

Meeting of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization
1 – 3 April 2014
Geneva, Switzerland

SAGE members

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Strategic Advisory Group of Experts (SAGE)
Terms of reference

Functions

SAGE is the principal advisory group to WHO for vaccines and immunization. It is charged with advising WHO on overall global policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions. SAGE is concerned not just with childhood vaccines and immunization, but all vaccine-preventable diseases.

SAGE advises the WHO Director-General specifically on the:

1. adequacy of progress towards the achievement of the goals of the Decade of Vaccines (DoV) Collaboration and Global Vaccine Action Plan (GVAP);
2. major issues and challenges to be addressed with respect to achieving the goals of the DoV and GVAP;
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 to achieve the DoV and GVAP goals consistent with its mandate and considering the comparative advantages and the respective roles of partner organizations;
6. cross-departmental activities and initiatives related to vaccine and immunization technologies and strategies and linkages with other health interventions;
7. engagement of WHO in partnerships that will enhance achievement of global immunization goals.

Membership

The SAGE comprises 15 members, who shall serve in their personal capacity and represent a broad range of disciplines encompassing many aspects of immunization and vaccines.

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., influenza control, diarrhoeal diseases, respiratory diseases, research, biologics, immunization safety); and
3. the three major strategic areas of WHO's work relating to immunization (i.e., accelerating innovation, ensuring quality and safety, and maximizing access and links with other health interventions).

SAGE members, including the Chairperson, shall be nominated by the WHO IVB Director in consultation with WHO Regional Offices and other relevant WHO departments 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.

SAGE members are appointed by the WHO Director-General; all nominations for new SAGE members, as well as renewals and discontinuation of appointments to SAGE, must be approved by the WHO Director-General. Consideration will be given to ensuring appropriate geographic representation and gender balance.

Members of SAGE shall be appointed to serve for an initial term of three years. Such three-year terms 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 Chairmanship.

Prior to being appointed as SAGE members and prior to renewal of term, nominees and current SAGE members shall be required to complete a WHO Declaration of Interests as per the attached form (Annex 1).

In addition, prior to confirmation by WHO of their appointment as SAGE members, SAGE nominees shall be required to sign a Confidentiality Undertaking (Annex 2). 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.

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; and
(3) a lack of professionalism involving, for example, a breach of confidentiality.

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 this 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. Focused technical input will be solicited from identified experts and advisory scientific groups.

The Committee has no executive or regulatory function. Its role is solely to provide advice and recommendations to the Director-General of WHO, and includes providing advice and recommendations on urgent matters 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.

Meetings and operational procedures

SAGE will normally meet biannually. The frequency of meetings may, however, be adjusted as necessary. Decisions or recommendations will, as a rule, be taken by consensus.

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 along with the meeting documentation on the SAGE website after the meeting.

UNICEF, the Secretariat of the Global Alliance for Vaccines and Immunization (GAVI), and WHO Regional Offices will participate as observers in SAGE meetings and deliberations.

WHO may also invite other observers to SAGE meetings, including representatives from WHO regional technical advisory groups, non-governmental organizations (NGO), international professional organizations, technical agencies, donor organizations and associations of manufacturers of vaccines and immunization technologies.

Additional experts may be invited to meetings, as appropriate, to further contribute to specific agenda items.

SAGE will work with WHO to develop its priorities of work and meeting agendas.

SAGE will be kept informed by WHO and partner agencies of progress in implementation of strategies and the attainment of objectives at country and regional level. SAGE will also be informed of policies and recommendations set by the WHO regional technical advisory groups. WHO, with advice from SAGE, will determine which policy recommendation issues and information from other WHO technical advisory groups should be brought to the attention of SAGE.

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 the full SAGE in an open public forum. These Working Groups are established on a time-limited basis to help address specific questions identified by SAGE when the issue is particularly complicated and could not be addressed by an existing standing WHO advisory committees. 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.

In addition to attendance of meetings, 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 departmental or cross-departmental meetings.

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 reports to the WHO Director-General (or designee(s)). The SAGE Chairperson will debrief the Director-General (or designee) and the IVB Director following each SAGE meeting. Minutes of SAGE meetings will be taken and circulated among SAGE members. The recommendations/conclusions of SAGE meeting shall be published, with the prior approval of WHO, in the Weekly Epidemiological Record and posted on the IVB Departmental website within two months of each SAGE meeting. In addition, these recommendations and conclusions will be translated into all the WHO headquarters official languages and posted on the IVB Departmental website.

Annex 1

Version: Sept. 2013

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 4 weeks but no later than 2 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.

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. A summary of all declarations and actions taken to manage any declared interests will be **published** in resulting reports and work products. 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 or work concerned, after consulting with you.

Name: Institution: Email:

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

_____

_____

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

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

EMPLOYMENT AND CONSULTING

Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work?

1a Employment — Yes Í No Í

1b Consulting, including service as a technical or other advisor — Yes Í No Í

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 or work?

2a Research support, including grants, collaborations, sponsorships, and other funding — Yes Í No Í

2b Non-monetary support valued at more than US $1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.) — Yes Í No Í

Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting or work?

INVESTMENT INTERESTS
Do you have current investments (valued at more than US $5000 overall) in a commercial entity with an interest related to the subject of the meeting or work? 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 Í No Í

3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company) — Yes Í No Í

INTELLECTUAL PROPERTY
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o you have any intellectual property rights that might be enhanced or diminished by the outcome of the meeting or work?

4a Patents, trademarks, or copyrights (including pending applications) — Yes Í No Í

4b Proprietary know-how in a substance, technology or process — Yes Í No Í

PUBLIC STATEMENTS AND POSITIONS (during the past 3 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 or work, for a commercial entity or other organization? — Yes Í No Í

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 or work? — Yes Í No Í

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 or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage? — Yes Í No Í

6b To your knowledge, would the outcome of the meeting or work 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 Í No Í

6c Excluding WHO, has any person or entity paid or contributed towards your travel costs in connection with this WHO meeting or work? — Yes Í No Í

6d Have your received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this WHO meeting or work? — Yes Í No Í

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 Í No Í

7. **TOBACCO OR TOBACCO PRODUCTS** *(answer without regard to relevance to the subject of the meeting or work)* — Yes Í No Í

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?

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) and 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. 5-6: 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_____

Annex 2

World Health Organization

CONFIDENTIALITY UNDERTAKING

1. Commercial, academic and other research institutions and individual scientists often submit or present for discussion by committees or groups of the WHO Department of Immunization, Vaccines and Biologicals 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.

Date:…….

Signature……...

Name…….
(print or type)

Annex 3

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 the full SAGE in an open public forum.

These Working Groups are 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.

The need for and creation of a Working Group is discussed and agreed during SAGE meetings or SAGE preparatory teleconferences.

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 need to be 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, the Chair of the Working Group, 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 SAGE members (one of whom functions as Chair), WHO staff (one of whom functions as the Working Group technical lead), and additional subject matter experts serving in their own individual capacity and with a view to meet the identified needed expertise for the group. This may include organizations representatives, and members of regional technical consultative groups. 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.

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

A public call for nomination for Working Group members will be posted on the SAGE website together with the relevant TORs of reference of the Working Group and indication of the desirable expertise. SAGE members, regional offices, WHO staff and key partner organizations will also be approached for potential nominations. Nominees will be requested to provide both a Curriculum Vitae and a completed Declaration of Interests prior to being considered for membership on the Working Group. From the pool of nominees, the Working Group Chair, SAGE Executive Secretary and Lead WHO staff will propose a Working Group composition for endorsement by the SAGE Chair and the Director of the Department of Immunization, Vaccines and Biologicals. The proposed list should also identify other names and rationale for proposed selection. In addition to meeting the required expertise, attention will be given to ensure proper diversity in the Group.

Working Group Process
WHO staff 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 research questions developed by the Working Group in order to propose appropriate vaccine policy decisions.

SAGE Working Groups are not allowed to render consensus advice or recommendations directly to the WHO D-G. 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 the SAGE can deliberate and act. Thus, while SAGE Working Groups can and should examine an area in detail and define the issues, including development of options for recommendations, the actual processes of group deliberation resulting in development of the group's consensus and final recommendations must occur in the public forum of SAGE meetings.

Effective communication and a strong working collaboration between the Working Group Chair the 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 shortly after the meetings. Once the minutes are approved by the Working Group, they are circulated to SAGE members. 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 except 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.

In-person meetings of Working Groups may facilitate progress. If possible, they should be anticipated at least two months in advance of the SAGE meeting.

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 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.

Management of Conflict of Interest

The value and impact of SAGE recommendations and WHO policies and recommendations are critically dependent upon public trust in the integrity of the process. Reported interests are assessed and managed according to SAGE procedures. Summarized Declarations of Interest are publicly posted on the SAGE website in conjunction with the Working Group's TORs and composition. Members are expected to inform WHO on any change in relevant interests.

World Health Organization

CURRENT SAGE WORKING GROUPS

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

- Peter Figueroa (Chair of Working Group), University of the West Indies, Jamaica
- Hyam Bashour, changed as of February 2013- retired from Damascus University, Syria (SAGE member until April 2011)
- Zulfiqar Bhutta, The Aga Khan University, Pakistan (Joined the Working Group in March 2012)
- Elizabeth Miller (SAGE member and Chair of the Working Group until February 2014), Health Protection Agency, United Kingdom

Experts

- Walter Dowdle, Task Force for Child Health, USA
- Nick Grassly, Imperial College, UK
- Jacob John, Christian Medical College, India
- Antoine Kabore, retired (formally of WHO/AFRO), Burkina Faso
- Francis Nkrumah, retired (formally of Noguchi Memorial Institute for Medical Research, University of Ghana Medical School, Ghana)
- Walter Orenstein, Emory University, USA
- Kimberley Thompson, Kids Risk Project, Harvard School of Public Health, USA

2. Joint technical expert group (JTEG) on malaria vaccines entering pivotal phase 3 trials & beyond (established April 2009)

JTEG acts as a SAGE (Strategic Advisory Group of Experts on Immunization) Working Group and also as a MPAC (Malaria Policy Advisory Committee) Technical Expert Group. The constitution of JTEG took into account both SAGE and MPAC considerations. The Chair, Peter Smith, is neither a SAGE nor MPAC member. Peter Smith was chosen as an expert in both immunization and malaria policy, having also served as Chair of other immunization and malaria-related WHO advisory committees.

Terms of reference

JTEG provides advice to SAGE and MPAC on activities related to the development of malaria vaccines at or nearing the pivotal phase 3 trial stage. The specific responsibilities of the group are to provide recommendations on:

- The clinical trial data necessary and desirable for evaluation of the public health impact of a malaria vaccine in malaria endemic countries
- The design, conduct, analyses and interpretation of Phase 2, Phase 3 and Phase 4 trials of malaria vaccines.
- The duration and nature of follow-up of participants in planned Phase 3 trials of malaria vaccines.
- The minimum safety and efficacy data to be collected in clinical trials, and data on any impact of malaria vaccines on the immunogenicity of other vaccines, to enable evaluation by WHO for policy recommendations.
- The evaluation of immunogenicity of malaria vaccines in Phase 3 trials and beyond, in particular with regard to possible development of surrogate markers for efficacy.

Composition

SAGE Members

- Zulfiqar Bhutta, Aga Khan University, Pakistan
- Claire-Anne Siegrist, University of Geneva, Switzerland

Experts

- Peter Smith, Chair, London School of Hygiene and Tropical Medicine, UK
- Fred Binka, University of Ghana, Ghana
- Kalifa Bojang, MRC Laboratories, The Gambia
- Blaise Genton, University of Lausanne, Switzerland
- Robert Johnson,National Institutes of Allergy and Infectious Disease, USA
- Kamini Mendis, Independent Consultant, Colombo, Sri Lanka
- Paul Milligan, London School of Hygiene and Tropical Medicine, UK
- Malcolm Molyneux, University of Malawi, Malawi
- Mahamadou Thera, University of Bamako, Mali
- Janet Wittes, Statistics Collaborative Inc., USA

3. SAGE Working Group on influenza vaccines and immunization (established August 2010)

Terms of Reference

Objectives of the Working Group:
1. Prepare for a SAGE evidence-based review and updating of WHO recommendations on the use of seasonal influenza vaccine (e.g. priority target groups) with a particular focus on low and middle-income countries and with a view to update the 2005 WHO influenza vaccine position papers.
2. Prepare for a SAGE discussion on coverage goals for seasonal influenza vaccination to be proposed to the WHA to update the coverage goals contained in the 2003 resolution.
3. Identify essential gaps in evidence that may impede SAGE's ability to update the recommendations on the use of influenza vaccines and propose coverage targets.
4. Provide advice about pandemic vaccine preparedness.

Composition

SAGE Members

- Elizabeth Miller, SAGE member and Chair of the Working Group until February 2014. Health Protection Agency, United Kingdom
- Jon Abramson, Chair, Wake Forest University School of Medicine, United States of America

- Art Reingold, University of California, United States of America. (Joined the Working Group after the SAGE meeting in November 2010)
- Claire-Anne Siegrist, University of Geneva, Switzerland

Experts

- William Kwabena Ampofo, Noguchi Memorial Institute for Medical Research, Ghana
- Joseph Bresee, Centers of Disease Control, USA
- Janet Englund, Seattle Children's Hospital, USA
- Randeep Guleria, All India Institute of Medical Sciences, India
- Yu Hongjie, Chinese Center for Disease Control and Prevention, People's Republic of China
- Michael Pfleiderer, Paul-Ehrlich-Institut, Germany
- David Salisbury, Department of Health, UK (SAGE member until April 2010)
- Barry Schoub, National Institute for Communicable Diseases, South Africa

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

Terms of Reference

- Review progress towards 2015 global measles control targets and regional measles and rubella elimination goals.
- 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 vaccine use (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 SAGE Sub-Committees (i.e., IVIR-AC and IPAC) to address relevant quantitative issues as well as those related to immunization practices.
- Advise SAGE on the appropriate timing for establishing target dates for global eradication of measles and global control or eradication targets for rubella and/or CRS.

Composition

SAGE Members

- Narendra Arora, International Clinical Epidemiology Network, India
- El Tayeb Ahmed El Sayed, Federal Ministry of Health, Sudan (SAGE member until June 2012)
- David Durrheim, Hunter New England Area Health Service and Professor of Public Health, Australia (SAGE member until April 2012)
- Peter Figueroa, Chair of Working Group. University of the West Indies, Jamaica
- Helen Rees, University of Witwatersrand, South Africa (SAGE member until August 2013)

Experts

- Hyam Bashour, Department of Family and Community Medicine, Damascus University, Syria (SAGE member until April 2011)
- Natasha Crowcroft, Surveillance and Epidemiology, Public Health Ontario, Canada
- Heidi Larson, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, UK
- Pier Luigi Lopalco, European Centre for Disease Prevention and Control, Sweden
- William Moss, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
- Susan Reef, Global Immunization Division, Centers for Disease Control and Prevention, USA
- Makoto Takeda, Department of Virology 3, National Institute of Infectious Diseases, Japan

5. SAGE working group dealing with vaccine hesitancy (established March 2012)

Terms of Reference

- Prepare for a SAGE review and advice on how to address vaccine hesitancy and its determinants.
- Define vaccine hesitancy and its scope
- Undertake a review of vaccine hesitancy in different settings including its context-specific causes, its expression and its impact.
- Suggest one or several indicator(s) of vaccine hesitancy that could be used to monitor progress in the context of the Decade of Vaccines Global vaccine Action Plan.
- At global, regional and national levels:

- Perform a landscape analysis of who/what organizations are working on this issue in various settings/countries
- Identify existing activities and strategies that have had or could have a positive impact including looking at successful strategies that have worked and are not specifically related to vaccines or even medicines;
- Identify strategies and activities that did not work well;
- Identify new activities and strategies that could have a positive impact;
- Prioritize existing and new activities/strategies based on an assessment of their potential impact;
- Outline the specific role of WHO in addressing vaccine hesitancy;
- Identify the specific role of regional and country advisory committees.

Composition

SAGE Members

- Xiaofeng Liang, Chair of Working Group, Chinese Center for Disease Control, China
- Juhani Eskola, National Institute of Health and Welfare, Finland

Experts

- Mohuya Chaudhuri, Independent Journalist and Documentary Filmmaker, India
- Eve Dubé, Institut National de Santé Publique du Québec, Canada
- Bruce Gellin, Department of Health and Human Services, USA
- Susan Goldstein, Soul City: Institute for Health and Development Communication, South Africa
- Heidi Larson, School of Hygiene and Tropical Medicine, UK
- Noni MacDonald, Dalhousie University, Canada
- Mahamane Laouali Manzo, Ministry of Health, Niger
- Arthur Reingold, University of California at Berkeley, USA. (SAGE member until November 2011)
- Dilian Francisca Toro Torres, Congress of the Republic of Colombia
- Kinzang Tshering, Jigme Dorji Wangchuck National Referral Hospital, Bhutan
- Yuqing Zhou, Chinese Center for Disease Control, China

6. SAGE Working Group on Varicella and Herpes Zoster Vaccines (established May 2012)

Terms of Reference

The Working Group will be asked to review the evidence, identify the information gaps, and guide the work required to address the information gaps and formulate proposed recommendations in preparation for a SAGE review of the use of varicella and herpes zoster vaccines. This will then lead to an updating the current (1998) varicella vaccine position paper.

The Working Group will specifically be asked to identify and review:

- data regarding the global prevalence and burden of disease caused by varicella and herpes zoster according to country development status
- issues related to varicella and herpes zoster surveillance
- the safety, effectiveness and immunogenicity profile of varicella and herpes zoster vaccines including that of vaccine combinations such as MMRV
- the duration of protection following immunization
- the impact of co-administration of varicella and herpes zoster vaccines with other vaccines
- the impact of varicella vaccination on immunocompromised individuals
- country experiences with introduction and use of varicella vaccines (in countries with information that allows a robust analysis)
- the potential for widespread childhood vaccination to reduce natural boosting through varicella virus circulation in the community and increase the risk of zoster in the adult and elderly population
- evidence on the cost-effectiveness of different approaches, in particular in low and low-middle income countries (as per WHO guidelines)
- additional critical issues that need to be considered in updating the current vaccine position paper.

The review of vaccine safety will consider of a review by the Global Advisory Committee on Vaccine Safety, and that on cost-effectiveness will link with the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC).

Composition

SAGE Members

- Jon Abramson, Chair of Working Group, Department of Paediatrics, Wake Forest University School of Medicine, USA
- Paba Palihawadana, Central Epidemiological Unit, Ministry of Health, Sri Lanka

Experts

- Marc Brisson, Département de Médecine Sociale et Préventive, Laval University, Canada
- Raina MacIntyre, School of Public Health and Community Medicine, University of New South Wales, Australia (was nominated in February 2013 replacing Sin Yun Cheah)
- Philip LaRussa, Division of Pediatric Infectious Diseases, Department of Pediatrics, Columbia University, USA
- Hanne Nøkleby, Division of Infectious Disease Control, Norwegian Institute of Public Health, Norway
- Bolutife Ayokunnu Olusanya, Department of Ophthalmology, University College Hospital, Nigeria
- Jane Seward, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, USA
- Claudia Vujacich, Foundation for Infectious Diseases, FUNCEI, Argentina
- Dapeng Yin, National Immunization Programme, Chinese CDC, China
- Sin Yun Cheah, Health Sciences Authority, Singapore (resigned from the group in February 2013)

7. SAGE Working Group on Pertussis vaccines (established – March 2013)

Terms of Reference

In the light of the recent resurgence of pertussis in some industrialized countries with their toll in terms of infant deaths it was agreed between SAGE and WHO that a new working group (on pertussis would be established to prepare for a SAGE review of the data and to consider updating current pertussis vaccine recommendations as published in the 2010 pertussis vaccine position paper. This is also an opportunity for SAGE to review new data on the effectiveness of various vaccination strategies aimed at reducing infant mortality as well as the pertussis related outcome of the Vaccine schedule optimization project.

Specifically the working group will be asked to:

- Review epidemiological data from countries that have or not experienced a resurgence of pertussis, in particular data that relates to the quality and duration of protection of protection for wP and aP vaccines
- Review, in the context of the above, accumulated data on the usefulness of the following strategies to prevent early mortality
    - Role of vaccination of adolescents and adults
    - “Cocooning”
    - Vaccination of pregnant and lactating mothers
    - Vaccination of newborns

- Update estimates of effectiveness of 1 or 2 dose schedules against mortality
- Create optimal primary vaccination schedule and timing of booster dose(s)
- Propose, based on the above and as necessary, an update of the current recommendations on the use of wP/aP vaccine.

Composition

SAGE Members

- Claire-Anne Siegrist, Chair of Working Group, Department of Pediatrics, University of Geneva, Switzerland
- Elizabeth Miller, (SAGE member and Chair of the Working Group until February 2014) , Public Health England, UK
- Piyanit Tharmaphornpilas, National Immunization Program, Ministry of Public Health, Nonthaburi, Thailand

Experts

- Tom Clark, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, USA
- Kathryn Edwards, Vanderbilt Vaccine Research Program, Vanderbilt University School of Medicine, Nashville, USA
- Nicole Guiso, Institut Pasteur Research Unit, Institut Pasteur, Paris, France
- Scott A. Halperin, Canadian Center for Vaccinology, Dalhousie University, Halifax, Canada

- Teeranart Jivapaisarnpong, Institute of Biological Products, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand
- Daniel Levy-Bruhl, Infectious Diseases Department, Institut de Veille Sanitaire, Saint-Maurice, France
- Peter McIntyre, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, Sydney, Australia
- Gabriela Moreno, Departments of Epidemiology and Immunizations, Ministry of Health, Santiago, Chile
- Carl Heinz Wirsing von König, National reference laboratory for Bordetella infections, Krefeld, Germany

8. SAGE Working Group on non-specific effects of vaccines (established March 2013)

Terms of Reference

WHO's Strategic Advisory Group of Experts (SAGE) has requested the WHO Secretariat to review the evidence concerning the possible non-specific effects of vaccines included in the routine infant immunization schedule.

Preparatory to such a review of the evidence by SAGE in 2013, it is necessary to:

- systematically review all published and grey literature concerning epidemiological studies addressing "non-specific" effects of BCG, measles and, DTP-containing vaccines on survival/all-cause mortality in children under five years of age and,
- critically appraise the evidence using the WHO Strategic Advisory Group of Experts (SAGE) guidelines.

The Working Group will be asked to determine if the current evidence is sufficient to lead to adjustments in policy recommendations or to warrant further scientific investigation, and if so, to define the path towards obtaining unequivocal evidence on these issues that would support future robust, evidence-based adjustments in immunization policies, if warranted.

Guidance for the development of evidence-based vaccine related recommendations.

The Working Group will specifically be asked to:

1. Review and provide guidance on the protocol for two independent systematic reviews (one on epidemiological studies and one on immunological factors) on the evidence of selected vaccines on child survival/ deaths by all causes in children less than 5 years of age.
2. Review the available evidence that addresses the effect of BCG, DTP and measles-containing vaccines on survival/all-cause mortality in children less than five years of age and, the outcomes of the above mentioned reviews and related GRADE tables.
3. Determine if the current evidence on non-specific effects of vaccines is sufficient to lead to adjustments in policy recommendations or to warrant further scientific investigation.

Composition

SAGE Members

- Terry Nolan, Chair of the Working Group, Head, University of Melbourne School of Population and Global Health, Melbourne, Australia
- Zufiqar Bhutta, Department of Paediatrics & Child Health, The Aga Khan University Medical Center, Karachi, Pakistan
- Kate O'Brien, Center for American Indian Health, Johns Hopkins Bloomberg School Public Health, Baltimore, USA

Experts

- Christine Stabell Benn, Research Center for Vitamins and Vaccines, Bandim Health Project, Statens Serum Institut, Denmark
- Mike Brennan, Senior Adviser, Global Affairs. AERAS, Washington D.C., USA
- Stephen Evans, Professor of Pharmacoepidemiology, London School of Hygiene and Tropical Medicine, UK
- Paul Fine, Professor of Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, UK
- Brad Gessner, Scientific Director, Association pour la Medicine Preventive (AMP), Ferney-Voltaire, France
- Diane Griffin, University Distinguished Service Professor Alfred and Jill Sommer Chair W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health; Professor, Medicine and Neurology, Johns Hopkins University School of Medicine, USA
- Jaleela Sayed Jawad, Head of Immunization Group and EPI Manager Ministry of Health, Manama, Bahrain
- Martin Mermikuwu, Professor of Pediatrics, University of Calabar, Nigeria

- Walter A. Orenstein, Professor of Medicine, Infectious Diseases, Emory University, USA
- Dipika Sur, Deputy Director, National Institute of Cholera and Enteric Diseases, Kolkata, India

9. 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:

- 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;
- 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;
- identify successes, challenges and areas where additional efforts or corrective actions by countries, regions, partners, donor agencies or other parties, are needed;
- identify and document best practices;
- 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

- Narendra Arora, Chair of the Working Group, Executive director, International Clinical Epidemiology Network, India
- Yagob Al-Mazrou, Secretary General - Health Services Council of the Kingdom of Saudi Arabia, Saudi Arabia
- Helen Rees, Executive Director - Reproductive Health Research Unit, University of Witwatersrand, South Africa (SAGE member until April 2013)

Experts

- Alejandro Cravioto, Chief Scientific Officer, International Vaccine Institute, Seoul, Republic of Korea
- Fuqiang Cui, Epidemiology Professor, Deputy Director National Immunization Program, China CDC, China
- Elizabeth Ferdinand, Senior Medical Officer of Health and Barbados EPI Manager, Barbados
- Shawn Gilchrist, President, S. Gilchrist Consulting Services Inc., Canada
- Alan Hinman, Senior Public Health Scientist - Task Force for Global Health, USA
- Stephen Inglis, Director, National Institute Biological Standards & Control, Health Protection Agency, UK
- Amani Mahmoud Mustafa, EPI Ministry of Health, Sudan
- Rebecca Martin, Director Global Immunization Division, US CDC, USA
- Rozina Mistry, Lecturer and Course Director, Aga Kahn University, Pakistan
- David Salisbury, Director Immunization, Department of Health, UK

10. SAGE Working Group on Hepatitis E vaccines (established October 2013)

Terms of Reference

The Working Group will be asked to review the evidence with respect to the following questions/issues and to propose recommendations for review by SAGE. This will lead to the publication of a WHO vaccine position paper on the use of hepatitis E. The target date of the publication of the position paper is early 2015.

- Review data regarding the global prevalence and burden of disease caused by hepatitis E virus infection.
- Review issues related to hepatitis E surveillance
- Review existing data on the safety, immunogenicity, efficacy, and cost-effectiveness of the licensed hepatitis E vaccine
- Review the hepatitis E vaccine pipeline.

- Identify potential indications and uses for the hepatitis E vaccine in the context of other hepatitis E preventive, control and treatment strategies/tools
- Provide draft recommendations on the potential use of hepatitis E vaccine.
- To summarize existing evidence on the burden of hepatitis E and on the safety, immunogenicity, efficacy, and cost-effectiveness of the licensed hepatitis E vaccine.
- To provide SAGE with summaries and analyses needed to support its discussion and recommendation process.

Composition

SAGE Members

- Narendra Arora (Chair of the Working Group), Executive director, International Clinical Epidemiology Network, India
- Xiaofeng Liang, Deputy Director General, Chinese Center for Disease Control, China

Experts

- Emily Gurly, Associate Director for Science and Head of Outbreak and Surveillance Research Group, Center for Communicable Diseases, International Centre for Diarrheal Diseases Research, Bangladesh
- Rakesh Aggarwal, Professor Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, India
- David Rein, Principal Research Scientist, NORC at the University of Chicago, Public Health Research Department, USA
- Sally Baylis, Senior scientist and quality assessor, Division of Virology, Paul-Ehrlich-Institut, Germany
- Eyasu Teshale, Centers for Disease Control and Prevention, Division of Viral Hepatitis Epidemiology and Surveillance Branch, USA
- Nilsa de Deus, Head of Research Department National Institute of Health, Minister of Health, Mozambique
- Samreen Ijaz, Clinical Scientist, R&D lead for blood borne infections, Blood Borne Virus Unit, Virus Reference Department, Public Health England, UK
- Rana Jawad Asghar, Resident Advisor, Field Epidemiology and Laboratory Training Programme, Pakistan

11. SAGE Working Group on Japanese encephalitis vaccines (established November 2013)

Terms of Reference

The Working Group will be asked to review the evidence, identify the information gaps, and formulate proposed recommendations on the use of Japanese encephalitis (JE) vaccines for a SAGE review. This will lead to an update of the current (2006) JE vaccine position paper. The target date for publication of the revised vaccine position paper is 2015.

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

- the global prevalence and burden of disease caused by JE, including issues relating to JE surveillance
- the role of inactivated mouse-brain based JE vaccines in the context of other products
- the safety, effectiveness, and immunogenicity profile of inactivated, live attenuated, and chimeric JE vaccines*
- the schedule and age of administration for the first dose of inactivated, live attenuated, and chimeric JE vaccines*
- the duration of protection following immunization with inactivated, live attenuated, and chimeric JE vaccines*
- co-administration of JE vaccines* with other vaccines
- use of JE vaccines* in special populations (e.g. immunosuppressed, pregnancy)
- the disease impact and cost-effectiveness of JE immunization programs
- additional critical issues that need to be considered in updating the current vaccine position paper

*Due to the large number of available JE vaccines with limited global use, the Working Group will focus its in-depth evidence review on products with current or likely international distribution.

Composition

SAGE Members

- Piyanit Tharmaphornpilas, Chair of Working Group, National Immunization Program, Ministry of Public Health, Thailand
- Paba Palihawadana, Central Epidemiological Unit, Ministry of Health, Sri Lanka

Experts

- Alan Barrett, Sealy Center for Vaccine Development, University of Texas Medical Branch, USA
- Susan Hills, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, USA
- Ooi Choo Huck, Sarawak Health Department, Ministry of Health, Malaysia
- Heidi Meyer, Viral Vaccines Section, Paul-Ehrlich-Institut, Germany
- Khin Saw Aye Myint, Eijkman Institute, Indonesia
- Tom Solomon, Institute of Infection and Global Health, University of Liverpool, UK
- Tomohiko Takasaki, Laboratory of Vector-Borne Viruses, National Institute of Infectious Diseases, Japan
- Shyam Upreti, Central Regional Health Directorate, Ministry of Health and Population, Nepal
- Yin Zundong, National Immunization Program, Chinese Center for Disease Control and Prevention, China

World Health Organization

14 March 2014

Strategic Advisory Group of Experts (SAGE) on Immunization
1 - 3 April 2014
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Meeting of the Strategic Advisory Group of Experts on immunization, November 2013 – conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization[1] met on 5–7 November 2013 in Geneva, Switzerland. This report provides a summary of the discussions, conclusions and recommendations.[2]

Report from the WHO Department of Immunization, Vaccines and Biologicals

The report focused on the scale up of immunization services required to reach the Global Vaccine Action Plan (GVAP) goal of 90% national coverage with 3 doses of diphtheria-tetanus-pertussis vaccine (DTP3) in all countries by 2015. This commitment will entail the vaccination of 9.3 million additional infants each year.

Recent successes such as the meningococcal A vaccine project and its impact on the burden of disease and carriage, as well as the delivery of the vaccine using the controlled temperature chain, were noted. Updates were also provided on site-specific results of phase 3 clinical trials of the malaria RTS,S vaccine candidate, the prequalification of the live SA 14-14-2 Japanese encephalitis vaccine as the first WHO prequalified Chinese vaccine, and the life course and integrated approaches to promote the delivery of vaccination with other relevant interventions to children, adolescents, and pregnant women.

[1] See http://www.who.int/immunization/sage/en/index.html

[2] The complete set of presentations and background materials used for the SAGE meeting of 5–7 November 2013 together with summarized declarations of interests provided by SAGE members are available at; http://www.who.int/immunization/sage/meetings/2013/november/en/index.html accessed in November 2013.

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, novembre 2013 – conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination[1] s'est réuni du 5 au 7 novembre 2013 à Genève (Suisse). Le présent rapport donne un résumé des discussions, ainsi que les conclusions et recommandations auxquelles il est parvenu.[2]

Rapport du Département OMS Vaccination, vaccins et produits biologiques

Le rapport s'est concentré sur l'extension des services de vaccination nécessaire pour atteindre l'objectif du Plan d'action mondial pour les vaccins (GVAP) d'une couverture nationale par 3 doses du vaccin antidiphtérique-antitétanique-anticoquelucheux (DTC3) de 90% dans tous les pays d'ici 2015. Cet engagement nécessitera de vacciner 9,3 millions de nourrissons en plus chaque année.

De récents succès, tels que le projet de vaccin contre le méningocoque A et son impact sur la charge de morbidité et le portage, ainsi que l'utilisation du vaccin dans le cadre de la chaîne sous température contrôlée, ont été signalés. Des mises à jour ont également été présentées concernant les résultats d'un essai clinique de phase 3 mené dans différents pays portant sur le vaccin candidat antipaludique RTS,S, la préqualification du vaccin vivant atténué SA 14-14-2 contre l'encéphalite japonaise qui devient ainsi le premier vaccin chinois préqualifié par l'OMS, et les approches intégrées, pour toutes les étapes de la vie, destinées à promouvoir la prestation de services de vaccination en même temps que d'autres interventions pertinentes ciblant les enfants, les adolescents, et les femmes enceintes.

[1] Voir http://www.who.int/imunization/sage/en/index.html

[2] La série complète des communications et des documents de travail de la réunion du SAGE tenue du 5 au 7 novembre 2013, ainsi que les résumés des déclarations d'intérêt fournies par les membres de ce groupe sont disponibles à l'adresse suivante: http://www.who.int/immunization/sage/meetings/2013/November/en/index.html; consultée en novembre 2013.

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Synchronized efforts to roll out the GVAP were being implemented at global, regional and country levels. SAGE reaffirmed the importance of the GVAP and applauded the commitment at regional level.

SAGE commended: the Western Pacific Region (WPR) on the endorsement by the Regional Committee of 2017 as the year for the target to reduce the seroprevalence of hepatitis B surface antigen (HBsAg), to <1% in children <5 years of age; and the South-East Asia Region (SEAR) for the endorsement by its Regional Committee of measles elimination and rubella control targets by 2020.

SAGE acknowledged global progress in scaling up immunization and reiterated the importance of improving the quality of available immunization coverage and disease surveillance data. High quality data, sustained by strong surveillance systems and timely and complete reporting of vaccine administration, should be generated to drive decision-making at all administrative levels, including district level. SAGE emphasized the imperative of country ownership of data collection and recommended that national reporting be streamlined. Guidance should be offered to countries (e.g. on quality or frequency of data collection) to enhance performance and support high data quality.

SAGE expressed grave concern about the current escalation of the political and security situation in Syria and its impact on neighbouring countries. SAGE reemphasized the need for political intervention as well as financial and technical support to countries affected by the current crisis in order to sustain adequate health services. SAGE encouraged donors to provide additional funding to support and strengthen routine immunization and enable the conduct of urgently required interventions such as high quality supplementary immunization activities.

SAGE stressed the importance of improved coordination and integration of immunization initiatives with other critical public health interventions such as clean water and sanitation programmes to ensure universal health coverage. Social determinants of health should be taken into consideration when integrating routine immunization services in primary health care, such as in the newly launched integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD).

SAGE emphasized the importance of enhancing immunization uptake to achieve high levels of coverage and noted that the emerging issue of "vaccine hesitancy" in several countries contributed to the lack of community demand for vaccination. The importance of this problem was stressed by the European Region (EUR), and the Eastern Mediterranean Region (EMR) noted that rumours concerning vaccination were hindering uptake of vaccination in Syria, as well as human papillomavirus (HPV) vaccination in numerous countries.

Des efforts concertés pour mettre en œuvre le GVAP ont été menés en parallèle aux niveaux mondial, régional, et national. Le SAGE a réaffirmé l'importance du GVAP et a salué l'engagement régional à cet égard.

Le SAGE a félicité la Région du Pacifique occidental pour l'approbation par le Comité régional de l'année 2017 comme date butoir pour ramener à <1% la séroprévalence de l'antigène de surface du virus de l'hépatite B (HBs Ag) chez les enfants âgés de <5 ans. Le SAGE a également félicité la Région de l'Asie du Sud-Est pour l'approbation par son Comité régional des cibles d'élimination de la rougeole et de lutte contre la rubéole d'ici 2020.

Le SAGE a reconnu les progrès accomplis à l'échelle mondiale en vue de généraliser la vaccination, et a rappelé l'importance d'améliorer la qualité des données disponibles sur la couverture vaccinale et la surveillance des maladies. Des données de grande qualité, issues de systèmes de surveillance solides et de rapports complets et remis dans les délais sur l'administration des vaccins, doivent être produites pour orienter la prise de décisions à tous les niveaux administratifs, y compris au niveau des districts. Le SAGE a souligné qu'il était impératif pour les pays de s'approprier le système de production de données, et a recommandé de simplifier le processus de notification national. Des orientations devraient être proposées aux pays (par exemple sur la qualité ou la fréquence de production des données) afin d'améliorer les performances et de favoriser un niveau de qualité élevé des données.

Le SAGE s'est vivement inquiété de la dégradation actuelle de la situation politique et de la sécurité en Syrie, et de ses répercussions sur les pays voisins. Le SAGE a insisté à nouveau sur la nécessité d'une intervention politique, ainsi que d'un appui technique et financier aux pays frappés par la crise actuelle afin d'y maintenir des services sanitaires satisfaisants. Le SAGE a invité les donateurs à prévoir un financement supplémentaire pour soutenir et renforcer la vaccination systématique, et pouvoir mener les interventions qui s'imposent d'urgence, comme des activités de vaccination supplémentaire de grande qualité.

Le SAGE a souligné l'importance d'une meilleure coordination et d'une meilleure intégration des initiatives de vaccination avec d'autres interventions de santé publique cruciales telles que les programmes d'accès à l'eau potable et à l'assainissement, afin de garantir la couverture sanitaire universelle. Les déterminants sociaux de la santé font partie des éléments à prendre en compte lorsqu'on cherche à intégrer les services de vaccination systématique dans les soins de santé primaires, comme c'est le cas dans le tout nouveau Plan d'action mondial intégré pour prévenir et combattre la pneumonie et la diarrhée (GAPPD).

Le SAGE a attiré l'attention sur l'importance que revêt l'acceptation de la vaccination pour obtenir des niveaux élevés de couverture, et a constaté que le tout nouveau problème de la réticence face aux vaccins contribue à la faiblesse de la demande communautaire en matière de vaccination. Deux Régions ont souligné l'importance de ce problème. Cette hésitation à l'égard des vaccins a été reconnue comme un problème majeur dans la Région européenne. De plus, la Région de la Méditerranée orientale a constaté que des rumeurs sur la vaccination empêchaient la bonne acceptation de la vaccination en Syrie, de même que la vaccination contre le virus du papillome humain (VPH) dans de nombreux pays.

SAGE noted that in some places the increasing involvement of the private sector in primary health care is not being coordinated with public sector efforts. In particular, differing vaccination schedules in the private and public sectors is a matter of concern.

Report from the GAVI Alliance

The GAVI Alliance report, presented by the CEO, provided a summary on the Alliance's mid-term review, programmatic and policy updates, and outlined the early scoping of GAVI's next vaccine investment strategy and plans for finalizing GAVI's strategy for 2016–2020.

Results at the mid-term indicate that GAVI is on track with its mission indicators including mortality rates in children aged <5 years, the number of deaths averted, and additional children immunized with GAVI support. However GAVI is lagging on progress in health systems support (HSS) and country commitments on co-financing. For HSS the current priority is to determine intermediate indicators and in increasing the HSS disbursement rates to countries.

In November 2013, the Board will consider the next set of proposed vaccine investments including malaria vaccine, pending SAGE recommendations; support for the global cholera vaccine stockpile; funding additional yellow fever vaccination campaigns; and introduction of the inactivated polio vaccine (IPV) in all 73 GAVI-eligible countries.

In June 2014, the Board will be presented with the proposed strategy for 2016–2020. Early indications of the strategy include the need for GAVI to remain focused on immunization, addressing the end-to-end supply chain for all vaccines, increasing equity, sustaining graduating countries, market shaping and sustainability. The need for stronger country ownership was emphasized. In line with the post-2105 development agenda, the Chief executive officer made a plea for revision of the current indicator of a fully immunized child, to specify not only DTP3. SAGE supported this concept.

SAGE noted the importance of having high quality data on key vaccine programme indicators (such as vaccine supply, vaccine coverage, disease surveillance) and asked GAVI to consider rewarding countries which achieve this.

Report from other advisory committees

SAGE was presented with a report of the October 2013 meeting of the Expert Committee on Biological Standardization,[3] the October 2013 meeting of the Immunization Practices Advisory Committee (IPAC)[4] and the

Le SAGE a constaté avec préoccupation que dans certains endroits, l'implication croissante du secteur privé dans les soins de santé primaires n'est pas coordonnée avec les efforts du secteur public. Le SAGE a estimé notamment préoccupant le fait que les calendriers de vaccination employés dans le secteur privé diffèrent de ceux du secteur public.

Rapport de l'Alliance GAVI

Le Directeur exécutif de l'Alliance GAVI a fait le point sur l'évaluation à mi-parcours de l'Alliance, en actualisant les programmes et les politiques, et a présenté le document d'orientation préliminaire concernant la prochaine stratégie de l'Alliance en matière d'investissement dans les vaccins et les plans nécessaires pour finaliser la stratégie de l'Alliance à l'horizon 2016-2020.

Les résultats à mi-parcours indiquent que l'Alliance est en passe d'atteindre les indicateurs de progrès liés à sa mission, qui comprennent le taux de mortalité des enfants de <5 ans, le nombre de décès évités et le nombre d'enfants supplémentaires vaccinés grâce au soutien de l'Alliance. Par contre, l'Alliance est en retard sur ses objectifs de renforcement des systèmes de santé (RSS) et de respect des engagements de cofinancement des pays. Pour le RSS, la priorité actuelle est de mettre en place des indicateurs de performance intermédiaires et d'augmenter les taux de déboursement des fonds accordés aux pays au titre du RSS.

En novembre 2013, le Conseil examinera la prochaine série de projets d'investissements dans les vaccins, notamment le vaccin antipaludique en attendant les recommandations du SAGE; le soutien à la constitution d'un stock mondial de vaccins anticholériques; le financement de campagnes supplémentaires contre la fièvre jaune; et l'introduction du vaccin antipoliomyélitique inactivé (VPI) dans l'ensemble des 73 pays qui remplissent les conditions pour une aide de l'Alliance GAVI.

En juin 2014, le Conseil prendra connaissance de la stratégie proposée pour 2016-2020. Les éléments dont on dispose déjà sur cette stratégie indiquent que l'Alliance GAVI devra rester concentrée avant tout sur la vaccination, en s'intéressant à l'ensemble de la chaîne logistique pour tous les vaccins, en augmentant l'équité, en apportant son soutien aux pays qui se qualifient, et en continuant à structurer et à consolider le marché des vaccins. Le Directeur exécutif a mis l'accent sur la nécessité d'une adhésion plus importante des pays. En ligne avec le programme de développement pour l'après-2015, il a appelé à aller plus loin que l'analyse de l'indicateur actuel, le DTC3, pour prendre la mesure du nombre d'enfants complètement vaccinés. Le SAGE a réservé un accueil favorable à cette idée.

Le SAGE a noté l'importance de disposer de données de grande qualité sur les indicateurs liés aux programmes de vaccination (comme l'approvisionnement en vaccins, la couverture vaccinale, la surveillance des maladies) et a demandé à l'Alliance GAVI d'envisager de récompenser financièrement les pays qui obtiennent de bons résultats en la matière.

Rapport des autres comités consultatifs

Le SAGE a pris connaissance d'un rapport sur la réunion d'octobre 2013 du Comité d'experts de la standardisation biologique,[3] sur la réunion d'octobre 2013 du Comité consultatif sur les Pratiques vaccinales (IPAC)[4], et sur la réunion de

[3] See http://www.who.int/immunization/sage/meetings/2013/november/1_Griffiths_ECBS_REPORT_TO_SAGE_2013.pdf

[4] See http://www.who.int/immunization/sage/meetings/2013/november/4_Deeks_IPAC_Summary_Nov2013_FINAL.pdf

[3] Voir http://www.who.int/immunization/sage/meetings/2013/november/1_Griffiths_ECBS_REPORT_TO_SAGE_2013.pdf

[4] Voir http://www.who.int/immunization/sage/meetings/2013/november/4_Deeks_IPAC_Summary_Nov2013_FINAL.pdf

June 2013 meeting[5] of the Global Advisory Committee on Vaccine Safety (GACVS).

The Chair of the Immunization and Vaccine Related Implementation Research Advisory Committee (IVIR-AC) reported on the June 2013 meeting, highlighting the objectives, process and outcomes of the WHO Implementation Research Priority Setting Exercise which was reviewed by IVIR-AC. The priority setting exercise focused on cross-cutting themes in implementation research, as vaccine-specific priorities are largely covered by other processes including SAGE discussions. Relative to the GVAP, SAGE members emphasized the need to prioritize vaccine implementation research studies in difficult-to-reach populations, e.g. in conflict areas and displaced populations. In order to measure the impact of poverty on immunization programmes, it was stressed that 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 also suggested that studies to examine the integration of immunization with other health interventions should be included in the implementation research agenda, and that implementation research on vaccines should be linked with the WHO Implementation Research Platform.

Vaccination of pregnant and lactating women

In response to a previous request from SAGE, GACVS conducted a comprehensive review of the evidence on safety of vaccination during pregnancy. Reviewing various non-live vaccines (those based on inactivated virus, inactivated bacteria, and the acellular vaccines and toxoids) revealed no safety issues, and GACVS concluded that pregnancy should not preclude women from vaccination with these vaccines if medically indicated. For live vaccines such as measles, mumps and rubella (MMR), GACVS concluded that while there was a theoretical risk to the fetus, no significant adverse outcomes following vaccination have been reported. GACVS noted in its report that the contra-indication for MMR vaccine during pregnancy is purely precautionary.

SAGE acknowledged the importance of this review but expressed concern that its dissemination would not be sufficient to promote maternal immunization as efficiently as necessary, which would require novel approaches to complement the GACVS activities. Given the increasing recognition of the potential of maternal immunization to prevent disease and mortality in pregnant women, fetuses and infants, the absence of safety signals, and failure of immunization advisory bodies

juin 2013[5] du Comité consultatif mondial de la Sécurité vaccinale (GACVS).

Le Président du Comité consultatif sur la recherche pour la mise en œuvre de la vaccination et des vaccins (IVIR-AC) a présenté le compte-rendu de la réunion de juin 2013 de l'IVIR-AC. Il a exposé en particulier les objectifs, le processus et les résultats de l'exercice entrepris par l'OMS dans le but de définir des priorités pour les questions relatives à la recherche sur la mise en œuvre, exercice qui a été suivi par l'IVIR-AC. Cet exercice de détermination des priorités s'est concentré sur des thèmes transversaux essentiels à la recherche sur la mise en œuvre, dans la mesure où les priorités propres à chaque vaccin sont largement étudiées dans le cadre d'autres processus, notamment les discussions au sein du SAGE. Avec le GVAP à l'esprit, les membres du SAGE ont insisté sur la nécessité de donner la priorité aux études de recherche sur la mise en œuvre des vaccins axées sur les populations difficiles à atteindre, par exemple les populations dans les zones de conflit et les populations déplacées. Afin de mesurer l'effet de la pauvreté sur les programmes de vaccination, il a été souligné que le programme de recherche sur la mise en œuvre doit définir ce qu'est l'équité au-delà des indicateurs monétaires économiques traditionnels tels que les gradients socio-économiques, pour inclure d'autres indicateurs d'inégalités tels que l'indice de pauvreté multidimensionnelle ou les répercussions sur les populations marginalisées. Le SAGE a également suggéré d'inclure des études chargées d'examiner l'intégration de la vaccination avec d'autres interventions sanitaires dans le programme de recherche sur la mise en œuvre, et a proposé que la recherche sur la mise en œuvre concernant les vaccins se fasse en lien avec la plateforme de l'OMS pour la recherche sur la mise en œuvre.

Vaccination des femmes enceintes et allaitantes

En réponse à une requête antérieure du SAGE, le GACVS a réalisé un examen approfondi des données factuelles sur l'innocuité de la vaccination des femmes enceintes. Le passage en revue des divers vaccins non vivants (formes inactivées des virus ou bactéries, vaccins acellulaires ou anatoxines) n'a révélé aucun problème de sécurité, et le GACVS a conclu que la grossesse ne doit pas être un obstacle à la vaccination des femmes par ce type de vaccins s'ils sont indiqués sur le plan médical. En ce qui concerne les vaccins vivants tels que le vaccin contre la rougeole, les oreillons et la rubéole (ROR), le GAVCS a conclu que malgré l'existence d'un risque théorique pour le fœtus, aucun effet indésirable post-vaccinal significatif sur l'issue de la grossesse n'a été signalé. Le GACVS a noté dans son rapport que la contre-indication de la vaccination par le ROR pendant la grossesse n'est qu'une pure mesure de précaution.

Tout en mesurant l'importance de cette étude, le SAGE s'est dit préoccupé à l'idée que la publication de ses résultats ne suffise pas à promouvoir la vaccination maternelle aussi efficacement qu'elle le devrait, ce qui exigera de nouvelles approches pour compléter les activités du GAVCS. Devant la reconnaissance grandissante du potentiel de l'immunisation maternelle pour prévenir les maladies et la mortalité aussi bien chez les femmes enceintes que chez les nourrissons et les fœtus, et l'absence de signaux de sécurité, mais devant la réticence ou l'incapacité des

[5] See No. 29, 2013, pp. 301–312 .

[5] Voir Nº 29, 2013, pp. 301–312.

and programmes to recommend and implement maternal immunization, there was discussion on how WHO and SAGE could effectively promote maternal immunization.

Several key issues were identified, including:

i. the traditional risk adverse approach of regulatory authorities which request product-by-product documentation of safety in pregnant women, whereas such data are not generated in clinical trials and thus cannot be included in the label;

ii. the need to encourage data collection, recognizing however the inherently slow process of the product-by-product approach;
iii. the need for increased training of health-care professionals in charge of prenatal and maternal health, for behavioural research on the acceptance of interventions during pregnancy, and for increased promotional activities;
iv. fear of litigation, preventing the vaccine industry from moving forward to serve what is perceived as a small and high risk market.

The discussion also highlighted several positive elements:

i. the interest of a class-specific approach (after appropriate definition of what may or may not be considered alike), allowing integration of biological similarities / biological plausibility into the risk evaluation process;
ii. the complementarity of class-specific and population-specific approaches, which could be associated in matrix analyses;
iii. a quantitative evaluation of the relative risks and benefits could help with modeling the expected impacts of a recommendation in various frameworks;
iv. the importance of quantifying the risk of not vaccinating, bringing an ethical perspective into the evaluation;
v. ethical bodies are more willing than previously to accept the inclusion of pregnant women into clinical trials;
vi. regulatory authorities are increasingly conscious of these issues and are considering how to engage in processes similar as those followed for drugs used during pregnancy or in children, e.g. integrating post-marketing surveillance data into the regulatory process.

With respect to the use of vaccines in lactating women SAGE considered that there is little basis for safety concerns with the currently available vaccines and that the benefits of the vaccines substantially outweigh any potential risk.

SAGE concluded that the recommending bodies, including WHO, need to clearly quantify and communicate the favourable risk–benefit ratio for maternal immunization, and to engage in a dialogue with regulators and

organes consultatifs et des programmes sur la vaccination à recommander et à mettre en place la vaccination maternelle, un débat a été soulevé pour étudier la manière dont l'OMS et le SAGE pourraient promouvoir efficacement la vaccination maternelle.

Plusieurs éléments problématiques importants ont été identifiés, parmi lesquels:

i. l'approche traditionnellement opposée aux risques des autorités règlementaires, qui demandent à chaque produit d'être accompagné d'informations documentées sur son innocuité chez la femme enceinte, alors que ces données ne sont pas obtenues dans des essais cliniques et donc pas incluses dans la notice;
ii. la nécessité d'encourager la collecte de données, sachant toutefois que l'approche produit par produit est un processus intrinsèquement lent;
iii. la nécessité d'une formation accrue des professionnels de santé en charge de la santé prénatale et maternelle, pour favoriser la recherche comportementale sur l'acceptation des interventions pendant la grossesse et intensifier les activités de promotion;
iv. la peur du procès, qui empêche l'industrie des vaccins d'avancer vers ce qui est perçu comme un petit marché à haut risque.

Le débat a également mis en lumière plusieurs éléments positifs:

i. l'intérêt d'une approche adaptée à chaque classe (après avoir défini de manière appropriée ce qui peut, ou non, être considéré comme tel), autorisant l'intégration des similitudes biologiques/de la plausibilité biologique dans le processus d'évaluation des risques;
ii. la complémentarité des approches adaptées aux classes et de celles adaptées aux populations, que l'on pourrait associer dans une analyse matricielle;
iii. le fait qu'une évaluation quantitative des bénéfices et des risques relatifs pourrait faciliter la modélisation des effets attendus d'une recommandation dans plusieurs cadres différents;
iv. l'importance de quantifier le risque de la non-vaccination, en introduisant une perspective éthique dans le tableau analytique;
v. le fait que les organes éthiques semblent plus enclins qu'avant à accepter l'enrôlement des femmes enceintes dans les essais cliniques;
vi. le fait que les autorités règlementaires sont de plus en plus conscientes de ces problématiques et étudient la manière de s'engager dans des processus similaires à ceux qui sont suivis pour les médicaments utilisés pendant la grossesse ou chez les enfants, par exemple l'intégration des données de pharmacovigilance dans le processus règlementaire.

Concernant l'utilisation des vaccins chez les femmes allaitantes, le SAGE a estimé qu'il y avait peu de raisons de s'inquiéter de la sécurité avec les vaccins actuellement disponibles, et que les bénéfices du vaccin l'emportaient encore largement sur les risques potentiels.

Le SAGE a conclu à la nécessité, pour les organes qui émettent des recommandations, notamment l'OMS, de quantifier clairement et de communiquer le rapport bénéfice/risque favorable associé à la vaccination maternelle, et d'entamer un dialogue

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.

Polio eradication

In November 2012, SAGE reaffirmed the importance of removing the type 2 component of the oral polio vaccine (OPV2) from routine immunization programmes globally in the near term, in order to eliminate the most common cause of vaccine-associated polio outbreaks, eliminate the vaccine-associated paralytic poliomyelitis (VAPP) associated with this serotype, secure the serotype-specific gains that have been made to date in global eradication, and enhance the efficacy of OPV to protect against and eliminate the remaining type 1 and 3 wild virus serotypes. SAGE further recommended that prior to the withdrawal of OPV2, by switching from trivalent OPV to bivalent OPV, all countries should add at least one dose IPV to the national routine immunization schedule to (a) reduce the risk of paralytic poliomyelitis if exposure to a type 2 virus occurred after OPV2 withdrawal, (b) improve response to any future use of a monovalent type 2 polio vaccine in the case of an outbreak, (c) reduce transmission of a reintroduced type 2 virus; and (d) boost immunity to the remaining wild poliovirus serotypes 1 and 3.

SAGE reviewed the current status of poliovirus transmission and response activities, then examined the evidence for recommendations on a proposed supply, financing and introduction strategy for IPV, the timing of 1 IPV dose in routine immunization programmes, and the major elements of the proposed strategy for type 2 poliovirus detection and response after OPV2 withdrawal.

While acknowledging the progress made in endemic countries to date in 2013 – including the absence of type 3 wild poliovirus cases since November 2012, the 40% decline in poliomyelitis cases in endemic countries, and the absence of endemic virus in Afghanistan – SAGE echoed the concern of the Independent Monitoring Board that the insecurity and lack of access for vaccinators in large areas of northwest Pakistan and northeastern states in Nigeria now constituted the greatest risk for the completion of eradication. This risk was compounded by the increasing international spread of the virus from those regions in 2013 into the Horn of Africa and the Middle East, which had been polio-free for many years. This reintroduction occurred particularly in highly vulnerable areas such as south/central Somalia and Syria where vaccinator access and security were severely compromised.

avec les responsables de la règlementation et les fabricants pour réexaminer les pratiques règlementaires actuelles à la lumière des données factuelles sur les risques et les bénéfices et la plausibilité biologique concernant l'innocuité des produits.

Le SAGE a demandé au Secrétariat de rédiger une procédure et un plan pour faire avancer ce dossier en vue d'obtenir un meilleur alignement entre les données factuelles relatives à la sécurité vaccinale, les impératifs de santé publique et les processus règlementaires.

Éradication de la poliomyélite

En novembre 2012, le SAGE a réaffirmé l'importance du retrait à court terme du vaccin antipoliomyélitique oral de type 2 (VPO2) des programmes de vaccination systématique du monde entier pour supprimer la cause la plus fréquente des flambées de poliomyélite post-vaccinale, éliminer la poliomyélite paralytique associée au vaccin (PPAV) due à ce sérotype, préserver les bénéfices propres à chaque sérotype qui ont été obtenus jusqu'à présent dans l'éradication mondiale de la poliomyélite, et renforcer l'efficacité du VPO afin d'assurer une protection contre les poliovirus sauvages des types 1 et 3 et les éliminer. Le SAGE a recommandé en outre que préalablement au retrait du VPO2, lors du passage du VPO trivalent au VPO divalent, tous les pays ajoutent au moins une dose du VPI dans leurs programmes de vaccination systématique afin de a) réduire le risque de poliomyélite paralytique en cas d'exposition au type 2 après le retrait du VPO2, b) améliorer la réaction immunitaire à un VPO monovalent type 2 si jamais celui-ci devait être utilisé dans le futur en cas de flambée, c) réduire la transmission d'un poliovirus de type 2 réintroduit, et d) renforcer l'immunité contre les poliovirus sauvages des types 1 et 3.

Le SAGE a fait le point sur la transmission du poliovirus et les activités d'intervention, puis a examiné les données factuelles lui permettant d'émettre des recommandations sur un projet de stratégie d'approvisionnement, de financement et d'introduction concernant le VPI, le calendrier choisi pour l'introduction de 1 dose du VPI dans les programmes de vaccination systématique, et les principaux éléments de la stratégie proposée pour la détection du poliovirus de type 2 et la riposte contre ce virus après le retrait du VPO2.

Tout en reconnaissant les progrès accomplis jusqu'à présent, en 2013, dans les pays d'endémie, notamment l'absence de cas de poliovirus sauvage de type 3 depuis novembre 2012, la baisse de 40% des cas de poliomyélite dans les pays d'endémie, et l'absence de virus endémique en Afghanistan, le SAGE s'est associé aux inquiétudes du Comité de suivi indépendant pour lequel l'insécurité et la très grande difficulté d'accès, pour le personnel vaccinateur, aux grands territoires du nord-ouest du Pakistan et aux états du nord-est du Nigeria représentent désormais la plus grande menace pour l'éradication complète de la maladie. Ce risque a été rehaussé par la propagation internationale croissante du virus, depuis ces régions jusqu'à la corne de l'Afrique et le Moyen-Orient en 2013, qui étaient pourtant exempts de poliomyélite depuis de nombreuses années. Cette réintroduction s'est notamment faite dans des zones hautement vulnérables telles que le sud et le centre de la Somalie et la Syrie, où l'accès et la sécurité du personnel vaccinateur étaient gravement compromis.

SAGE called for a step-change in the combination of high-level political, community engagement, communications, and innovative operational approaches (e.g. use of military medical corps) needed to ensure vaccinator access into these areas. SAGE reiterated its recommendation that an Expert Review Committee under the auspices of the International Health Regulations review the value of vaccinating all travellers to and from polio-affected areas. Also recommended were more systematic programme action to reduce vulnerability to polio by means of mass campaigns, strengthening of routine immunization, early IPV introduction, addressing the specific issue of nomadic populations, and enhanced surveillance, including the targeted expansion of environmental sampling.

Le SAGE a appelé à passer à la vitesse supérieure et à créer de meilleures synergies entre un engagement politique à haut niveau, la participation des communautés, les actions de communication, et les approches opérationnelles novatrices (par exemple le recours à un corps médical militaire), nécessaires pour garantir l'accessibilité de ces zones au personnel vaccinateur. Le SAGE a renouvelé sa recommandation de voir un comité d'examen, constitué d'experts, dans le cadre du Règlement sanitaire international examiner l'utilité de vacciner tous les voyageurs à destination ou en provenance des zones où sévit la poliomyélite, et a recommandé des mesures programmatiques plus systématiques pour réduire la vulnérabilité au virus de la poliomyélite via des campagnes de masse, un renforcement de la vaccination systématique, une introduction précoce du VPI, le traitement du problème spécifique des populations nomades, et une surveillance accrue, notamment l'augmentation ciblée de la fréquence du prélèvement d'échantillons dans l'environnement.

SAGE reviewed evidence on IPV immunogenicity by age, and recommended that countries introducing 1 dose of IPV into the routine immunization schedule should administer that dose ≥14 weeks of age, in addition to the 3 to 4 doses of OPV in the primary series. As IPV immunogenicity is highest after 14 weeks of age due to reduction in maternal antibodies that otherwise interfere with immunogenicity, IPV administration at 14 weeks maximizes the benefit of IPV in protecting children against type 2 poliovirus after OPV2 cessation, while helping to close immunity gaps to types 1 and 3 virus. In countries with primary immunization contacts at 6, 10 and 14 weeks of age or 2, 3, and 4 months of age, the IPV dose should be added at the DPT3-OPV3 contact; for countries with a 2, 4, and 6 months schedule, the IPV dose could be added at the DPT3-OPV3 contact, though DPT2-OPV2 can also be considered. For children vaccinated with bivalent OPV but who did not receive IPV at 14 weeks of age, the IPV doses can be given at any subsequent immunization contact. Those starting the routine immunization schedule late (age >3 months) should receive IPV at the first immunization contact. SAGE recommended that countries should have flexibility to consider alternative schedules (e.g. IPV administration earlier than 14 weeks) based on local conditions (e.g. documented risk of VAPP prior to 4 months of age). The Global Polio Eradication Initiative (GPEI) should develop clear communication strategies on the rationale for the introduction of 1 dose of IPV and address operational issues at country level.

Le SAGE a analysé les données scientifiques sur l'immunogénicité du VPI en fonction de l'âge, et a recommandé aux pays qui introduisent 1 dose de VPI dans leur calendrier de vaccination systématique d'administrer cette dose à un âge ≥14 semaines, en plus des 3-4 doses de VPO de la série de primovaccination. L'immunogénicité du VPI étant maximale après l'âge de 14 semaines en raison de la disparition progressive des anticorps maternels qui interfèrent par ailleurs avec l'immunogénicité chez l'enfant, l'administration du VPI à un âge ≥14 semaines maximise le bénéfice du VPI pour protéger les enfants contre le poliovirus de type 2 après l'arrêt du VPO2, tout en aidant à combler les lacunes immunitaires à l'égard des types 1 et 3. Dans les pays où les contacts pour la primovaccination ont lieu à l'âge de 6, 10 et 14 semaines ou à 2, 3 et 4 mois, la dose de VPI doit être ajoutée au contact pour le DTC3-VPO3; pour les pays dont le schéma vaccinal est à 2, 4, et 6 mois, la dose de VPI pourrait être ajoutée au contact pour le DTC3-VPO3, mais le DTC2-VPO2 peut également être envisagé. En ce qui concerne les enfants vaccinés par le VPOb mais qui n'ont pas pu recevoir le VPI à l'âge de 14 semaines, les doses de VPI peuvent être administrées à n'importe quelle séance de vaccination suivante. Ceux qui démarrent tardivement le calendrier de vaccination systématique (après l'âge de 3 mois) devront recevoir le VPI lors de leur premier contact pour une vaccination. Le SAGE recommande que les pays aient une certaine marge de manœuvre pour envisager d'autres calendriers de vaccination (par exemple administration du VPI avant l'âge de 14 semaines), selon la situation locale (par exemple risque documenté de PPAV avant l'âge de 4 mois). L'Initiative mondiale pour l'éradication de la poliomyélite (IMEP) doit élaborer des stratégies de communication claires permettant de justifier l'introduction de 1 dose de VPI, et régler les problèmes opérationnels au niveau de chaque pays.

SAGE commended the remarkable progress in developing an introduction strategy for IPV supply, and financing by the Immunization Systems Management Group (IMG) as well as the broader work to prepare for OPV2 withdrawal and IPV introduction, through the collaborative efforts of WHO, UNICEF, GAVI, United States Centers for Disease Control and Prevention (CDC), and other partners. SAGE endorsed the proposed strategy, including the tiering of countries based on the risk of circulating vaccine-derived poliovirus (cVDPV) emer-

Le SAGE a salué les progrès remarquables réalisés par le Groupe de gestion des systèmes de vaccination (IMG) dans la mise en place d'une stratégie d'introduction, de financement et d'approvisionnement en VPI, ainsi que les travaux plus vastes destinés à préparer le retrait du VPO2 et l'introduction du VPI, grâce aux efforts collaboratifs de l'OMS, de l'UNICEF, de l'Alliance GAVI, des *Centers for Disease Control and Prevention* (CDC) des États-Unis et d'autres partenaires. Le SAGE a approuvé la stratégie proposée, notamment la hiérarchisation des pays en fonction du risque d'émergence et de propagation du poliovirus

gence and spread. SAGE emphasized that while tiering should help focus technical support, accelerated IPV introduction must be pursued in all 4 tiers of countries. SAGE recommended early IPV introduction into routine immunization systems of all polio-endemic and high-risk countries to help accelerate eradication and reduce vulnerability. All such countries (Tier 1 and 2) should by mid-2014 have established a plan for IPV introduction; all countries should have a plan by end-2014.

To facilitate prioritization, planning and implementation of IPV introduction at country level, SAGE recommended that consideration be given to developing a resolution on accelerated IPV introduction for submission to the World Health Assembly (WHA) in 2014. Such a resolution should call for all countries to have completed planning for IPV introduction by end-2014, with IPV introduction implemented in all countries by end-2015.

SAGE noted the IMG analysis showing that existing IPV suppliers have sufficient capacity to meet global demand under the current endgame strategy. SAGE recognized the extensive work with IPV suppliers to ensure the lowest possible price for low- and low-middle income countries. At the same time, SAGE noted that there is still a significant gap between the GPEI long-term target price (US$ 0.50–US$ 0.60 per dose) and the likely IPV price for 2014–2018, even though the latter is expected to be approximately US$ 1.0 per dose for GAVI-supported countries. SAGE encouraged continued work to achieve lower cost IPV options and products, and agreed that GPEI should continue to develop intradermal IPV delivery systems in particular, as such administration could be needed to deliver IPV rapidly on a mass scale in response to type 2 outbreaks following OPV2 withdrawal.

SAGE endorsed the 5 major components of the proposed strategy for type 2 virus detection and response after OPV2 cessation, in the areas of virus notification, surveillance, vaccine stockpiles, response and management of travellers. SAGE requested that the Polio working group draft the necessary protocols for these components for presentation to the SAGE in 2014.

Decade of Vaccines (DoV) Global Vaccine Action Plan (GVAP) implementation monitoring: progress report 2013

Following the endorsement of the DoV GVAP by the WHA in May 2012,[6] Member States requested that WHO monitor progress and report annually, using an accountability framework, to guide immunization discussions and future actions. In response to this request, a Monitoring & Evaluation/Accountability Framework was developed and a process for an annual independent

[6] See WHA resolution 65.17

circulant dérivé d'une souche vaccinale (PVDVc). Le SAGE a souligné que même si la hiérarchisation devrait aider à concentrer l'appui technique là où il est le plus nécessaire, il importe de poursuivre l'introduction accélérée du VPI dans chacun des 4 niveaux de pays. Le SAGE recommande l'introduction précoce du VPI dans les systèmes de vaccination systématique de tous les pays d'endémie et à haut risque pour la poliomyélite afin d'accélérer l'éradication et réduire la vulnérabilité. Tous ces pays-là (niveau 1 et niveau 2) doivent avoir établi d'ici le milieu de l'année 2014 un plan pour l'introduction du VPI; tous les pays doivent avoir un plan d'ici fin 2014.

Pour faciliter l'établissement des priorités ainsi que la planification et la mise en œuvre de l'introduction du VPI au niveau des pays, le SAGE recommande que l'on envisage l'élaboration d'une résolution sur l'introduction accélérée du VPI qui serait présentée pour examen à la prochaine Assemblée mondiale de la santé en 2014. Une telle résolution devrait appeler tous les pays à terminer la planification de l'introduction du VPI d'ici fin 2014, l'introduction du VPI étant mise en œuvre dans tous les pays d'ici fin 2015.

Le SAGE a pris note de l'analyse du Groupe de gestion des systèmes de vaccination montrant que les fournisseurs actuels du VPI disposent d'une capacité suffisante pour faire face à la demande mondiale dans le cadre de la stratégie en cours pour la phase finale. Le SAGE a pris la mesure du travail considérable accompli avec les fournisseurs du VPI pour garantir le prix le plus bas possible pour les pays à faible revenu et à revenu intermédiaire (tranche inférieure). Parallèlement, le SAGE a noté qu'il subsiste un écart important entre le prix à long terme ciblé par l'IMEP (US$ 0,50-0,60 par dose) et le prix probable du VPI pour 2014-2018, même si ce dernier devrait être de l'ordre de US$ 1,0 par dose pour les pays de l'Alliance GAVI. Le SAGE a encouragé la poursuite des travaux visant à obtenir des produits et des options de vaccination par le VPI à moindre coût, et s'est entendu sur le fait que l'IMEP devait continuer à mettre au point des formules d'administration du VPI intradermiques en particulier, car une telle administration pourrait s'avérer nécessaire s'il fallait un jour administrer rapidement le VPI à grande échelle en réponse à une flambée de type 2 survenant après le retrait du VPO2.

Le SAGE a approuvé les 5 principales composantes de la stratégie proposée pour la détection du virus de type 2 et la riposte contre ce virus après l'arrêt du VPO2, qui couvrent les domaines suivants: notification des cas, surveillance, stocks de vaccins, riposte, et prise en charge des voyageurs. Le SAGE a demandé à ce que le groupe de travail sur la poliomyélite rédige une première version des protocoles nécessaires dans ces 5 domaines pour les lui présenter en 2014.

Décennie de la vaccination (DoV) – Suivi de la mise en œuvre du Plan d'action mondial pour les vaccins (GVAP): rapport de situation 2013

Suite à l'approbation du GVAP dans le cadre de la DoV lors de la 65e Assemblée mondiale de la Santé en mai 2012,[6] les États membres ont prié le Directeur général de l'OMS de suivre les progrès accomplis par les États et de faire rapport chaque année, au moyen d'un cadre de responsabilisation, dans le but de guider les débats sur la vaccination et les futures interventions. En réponse à cette requête, un cadre de suivi et d'évalua-

[6] Voir résolution 65.17 de l'Assemblée mondiale de la Santé.

review of progress defined. The monitoring framework was noted by the 66th WHA in May 2013.[7]

In accordance with the defined process, a detailed report was prepared by WHO and, along with independent submissions by 6 stakeholders[8], reviewed by the SAGE DoV working group. The report was based on information provided by Member States through the WHO and UNICEF Joint Reporting Form and surveillance reports as well as numerous other sources of information.

The assessment of progress by the SAGE DoV working group was presented to SAGE for review, discussion and inputs.

SAGE recognised that although several of the issues are already well known, having them all compiled in one document is an important achievement, allowing a more comprehensive overview of issues and challenges faced by countries.

SAGE welcomed the decision to highlight data quality improvement as the main theme for this first report. Availability of high quality data on each of the key vaccine programme determinants, including but not limited to vaccine coverage is fundamental for improving immunization programme performance at all levels and for accountability. SAGE recommended that every country should have district level coverage data within 2 years and a process for independent monitoring and data validation, and noted that this was also selected as a critical issue to be tackled by Regional Committees. All available sources of data, including non-immunization sources (e.g. nutrition programmes) should be explored to obtain a comprehensive view of programme performance, new information and communication technologies should be used to improve the recording, reporting and analysis of data at all administrative levels.

SAGE recommended development of a "dashboard" for all the countries to be able to monitor progress towards the GVAP targets which should address the need for more accountability from countries and partners.

SAGE recommended that countries and partners increase their effort to ensure that every country has a functional National Immunization Technical Advisory Group (NITAG), in view of the need for NITAGs to play a role in improving data quality, especially on vaccine coverage and disease impact and to ensure that decisions are based on strong evidence.

tion/responsabilisation a été élaboré, et un processus permettant chaque année l'examen indépendant des progrès a été défini. La 66e Assemblée mondiale de la Santé qui s'est réunie en mai 2013 a pris note de ce cadre de suivi.[7]

Conformément au processus défini, un rapport détaillé a été rédigé par le Secrétariat et, en même temps que des rapports indépendants présentés par 6 parties prenantes,[8] examiné par le groupe de travail du SAGE sur la Décennie de la vaccination. Le rapport du Secrétariat s'est appuyé sur les informations fournies par les États membres par le biais du formulaire de notification conjoint de l'OMS/UNICEF et des rapports de surveillance, ainsi que sur de nombreuses autres sources de données.

L'évaluation des progrès conduite par le groupe de travail du SAGE sur la DoV a été présentée au SAGE pour examen, discussion et commentaires.

Le SAGE a reconnu que même si plusieurs problèmes sont déjà bien connus, le fait de les avoir tous réunis dans un seul document est une réalisation importante, qui permettra d'avoir une vue plus complète des problèmes et des enjeux auxquels sont confrontés les pays.

Le SAGE a salué la décision de mettre en exergue «l'amélioration de la qualité des données» comme thème principal de ce premier rapport. Il est en effet fondamental de disposer de données de grande qualité sur chacun des déterminants essentiels des programmes de vaccination, notamment mais sans limitation, la couverture vaccinale, si l'on veut améliorer l'efficacité des programmes de vaccination à tous les niveaux, car il s'agit de la pierre angulaire de la responsabilisation. Le SAGE recommande que chaque pays dispose de données sur la couverture au niveau des districts d'ici à 2 ans, et d'un processus 1) de validation des données et 2) de suivi indépendant. Il a été noté que cette question a également retenu l'attention des comités régionaux, qui l'ont considérée comme une question essentielle à traiter. Le SAGE a signalé que toutes les sources disponibles de données, y compris les sources non liées à la vaccination (par exemple les programmes de nutrition) devaient être explorées pour obtenir un aperçu complet de l'efficacité des programmes et que les nouvelles technologies de l'information et de la communication devaient être utilisées pour améliorer l'enregistrement, la notification et l'analyse des données à tous les niveaux administratifs.

Le SAGE a recommandé la mise en place d'un tableau de bord pour que tous les pays soient en mesure de suivre les progrès accomplis vers la réalisation des objectifs du GVAP, ce qui répondrait au besoin d'une plus grande responsabilisation de la part des pays et des partenaires.

Le SAGE a recommandé que les pays et les partenaires redoublent d'efforts pour faire en sorte que chaque pays possède un Groupe technique consultatif national sur la vaccination (GTCV), étant donné que les GTCV ont leur rôle à jouer dans l'amélioration de la qualité des données, notamment celles relatives à la couverture vaccinale et à l'impact des maladies, et pour que les décisions se fondent sur une base factuelle solide.

[7] See WHA report A66.19.

[8] Agence de Médecine Préventive, Barcelona Institute for Global Health, Johns Hopkins Bloomberg School of Public Health, PATH, Sabin Vaccine Institute, and Save the Children.

[7] Voir rapport A66.19 de l'Assemblée mondiale de la Santé.

[8] Agence de Médecine Préventive, Barcelona Institute for Global Health, Johns Hopkins Bloomberg School of Public Health, PATH, Sabin Vaccine Institute, et Save the Children.

While SAGE recognized the need to monitor indicators and to have recommendations related to each GVAP Goal and Strategic Objective, but the large number of recommendations may create difficulties for countries in prioritizing their critical actions. SAGE therefore proposed a reduction in the number of recommendations that should be taken forward in the reports to the WHO governing bodies, focusing on the most urgent and high priority actions to be taken by Member States.

SAGE endorsed the following objectives as the major areas of necessary focus: (i) improving data quality; (ii) increasing immunization coverage; (iii) accelerating progress towards measles and rubella/ congenital rubella syndrome (CSR) elimination; and (iv) enhancing country ownership of national programmes. This should allow the WG to prioritize the specific issues on which to focus during the next few years. The revised SAGE assessment report is the basis for the first annual report to the WHO governing bodies and is available at: http://www.who.int/immunization/global_vaccine_action_plan/sage_dov_gvap_progress_report_2013.pdf.

Pandemic and interpandemic influenza vaccines

In 2007, SAGE recommended policies for the establishment and use of influenza A(H5N1) vaccine stockpiles during a pandemic and in 2009, guidelines for the use of A(H5N1) vaccines during the inter-pandemic period.[9] Since then, WHO developed the Pandemic Influenza Preparedness Framework (PIP Framework) for sharing influenza viruses and access to vaccines and other related benefits. The PIP Framework provides a model for legally binding contracts with individual vaccine manufacturers, so-called "Standard Material Transfer Agreements type-2 (SMTA2)" through which WHO will secure access, on a real-time basis, to pandemic vaccine at the time of a pandemic. As a result, WHO requested that previous recommendations regarding the constitution of a A(H5N1) vaccine stockpile and use of A(H5N1) vaccines be re-examined.

Based on the recognition that (a) the PIP Framework secures immediate access to pandemic vaccine production, (b) there is no significant change in A(H5N1) epidemiology, (c) there is a substantial risk of poor antigenic/strain match between the actual pandemic virus and stockpiled A(H5N1) vaccine and (d) the value of a stockpiled vaccine for containment of a nascent pandemic remains doubtful, SAGE agreed that WHO should not create a stockpile of A(H5N1) vaccine, but should ensure immediate access to pandemic vaccines under the PIP Framework. SAGE also highlighted the need for WHO (a) to ensure equitable access by low- and middle-income countries and (b) to put in place a strategy for timely communication of any delays in vaccine availability in case of a pandemic.

[9] See No. 24, 2009, pp. 244–248.

Bien que le SAGE ait reconnu la nécessité de suivre des indicateurs et de disposer de recommandations pour chaque objectif stratégique et but du GVAP, un trop grand nombre de recommandations risque de créer des difficultés pour les pays au moment où ils devront prioriser toutes leurs interventions essentielles. C'est pourquoi le SAGE a proposé de diminuer le nombre de recommandations présentées dans les rapports à l'intention des organes directeurs de l'OMS, en se concentrant sur les mesures les plus urgentes à prendre prioritairement par les États membres.

Le SAGE a confirmé les recommandations suivantes comme étant les principaux domaines dans lesquels il est essentiel d'agir: 1) améliorer la qualité des données; 2) augmenter la couverture vaccinale; 3) progresser plus rapidement vers l'élimination de la rougeole et de la rubéole/syndrome de rubéole congénitale (SRC); et 4) renforcer l'appropriation des programmes nationaux par les pays. Cela devrait permettre au groupe de travail de hiérarchiser les questions spécifiques à traiter au cours des prochaines années. Le rapport d'évaluation révisé du SAGE sert de base au premier rapport annuel présenté aux organes directeurs de l'OMS, et est consultable à l'adresse: http://www.who.int/immunization/global_vaccine_action_plan/sage_dov_gvap_progress_report_2013.pdf.

Vaccins antigrippaux en phase pandémique et interpandémique

En 2007, le SAGE a recommandé certains principes pour l'établissement et l'utilisation de stocks de vaccins antigrippaux A(H5N1) pendant une pandémie, et en 2009, des lignes directrices concernant l'utilisation des vaccins antigrippaux A(H5N1) au cours de la période interpandémique.[9] Depuis, l'OMS a élaboré le «Cadre de préparation en cas de grippe pandémique pour l'échange des virus grippaux et l'accès aux vaccins et autres avantages» (Cadre PIP). Le Cadre PIP propose un mécanisme permettant de conclure des accords juridiquement contraignants avec des fabricants de vaccins individuels, que l'on appelle «Accords types sur le transfert de matériels 2 (SMTA 2)», et grâce auxquels l'OMS assurera l'accès en temps réel au vaccin pandémique au moment d'une pandémie. De ce fait, l'OMS a demandé à ce que les recommandations antérieures concernant la constitution d'un stock de vaccins antigrippaux A(H5N1) et l'utilisation des vaccins antigrippaux A(H5N1) soient réexaminées.

Puisque (a) le Cadre PIP garantit l'accès à la production des vaccins pandémiques en temps réel, (b) il n'y a eu aucun changement significatif dans l'épidémiologie du H5N1, (c) il existe un risque substantiel de mauvaise correspondance antigène/souche entre le véritable virus de la pandémie et le vaccin anti-H5N1 mis en réserve et (d) l'utilité d'un vaccin mis en réserve pour juguler une pandémie naissante reste incertaine, le SAGE a convenu que l'OMS n'a pas à créer de stocks de vaccins anti-H5N1, mais doit garantir l'accès en temps réel aux vaccins pandémiques en vertu du Cadre PIP. Le SAGE a également souligné la nécessité pour l'OMS de (a) assurer un accès équitable à ces vaccins par les pays à revenu faible ou intermédiaire, et (b) mettre en place une stratégie pour la communication dans les meilleurs délais de tout élément susceptible de retarder la disponibilité des vaccins en cas de pandémie.

[9] Voir N° 24, 2009, pp. 244–248.

Regarding the question of inter-pandemic use of A(H5N1) vaccines (if and when available), SAGE agreed that (a) no clear change in the low level of risk to exposed populations has been observed, (b) no changes in populations at risk for highly pathogenic avian influenza (HPAI) H5N1 virus infection have been observed and (c) while risk remains low, even in exposed populations, certain high-risk groups may benefit from vaccination given the severity of the disease. Therefore, SAGE concluded that its previous recommendations on the use of A(H5N1) vaccine during inter-pandemic periods, mainly focusing vaccination of persons at high risk of A(H5N1) disease through occupational exposure, should remain unchanged.[9]

Finally, SAGE received a presentation on the epidemiologic situation regarding avian A(H7N9) virus and related vaccine development. As of 5 November 2013, 139 confirmed human cases of A(H7N9) influenza and 45 deaths (case-fatality rate 32.4%) were reported from China, mostly following exposure at live poultry markets. There is currently no evidence showing sustained human-to-human transmission of A(H7N9) virus though continued sporadic human cases and small clusters can be expected. WHO has not issued any recommendations with regard to special screening procedures at entry points or any travel and trade restrictions. Currently, 6 vaccine viruses have been developed using reverse genetics, while efforts using classical reassortant vaccines have so far been unsuccessful. There are 5 clinical trials ongoing for A(H7N9) influenza vaccines.

Measles and rubella elimination

SAGE reviewed the status report prepared by the measles and rubella WG and commended countries and regions for the significant reduction in measles incidence and for reducing measles mortality by 75% since 2000. AMR has maintained elimination of both measles and rubella and WPR is approaching interruption of endemic measles transmission. However, based on current trends and programme performance, the 2015 global targets as well as regional elimination targets in EUR (2015), EMR (2015) and AFR (2020) will not be achieved on time.

SAGE noted that among the WHO Regions, only the AMR and EUR have rubella elimination targets. In keeping with the GVAP target of measles and rubella elimination in 5 WHO Regions by 2020, SAGE urged AFR, EMR, SEAR and WPR to work towards establishing regional rubella elimination goals.

SAGE emphasized that in order to achieve measles elimination, vaccination coverage needs to be >95% for 2 doses of MCV administered through routine immunization or supplementary immunization activities

Concernant la question de l'utilisation interpandémique des vaccins anti-A(H5N1) (si et quand ils sont disponibles), le SAGE s'est entendu sur le fait que (a) aucun changement évident ne semble être intervenu dans le faible niveau de risque que courent les populations exposées, (b) aucun changement ne semble être intervenu dans le type de population menacée d'infection par le virus H5N1 de la grippe aviaire hautement pathogène (IAHP), et (c) bien que le risque reste faible, même dans les populations exposées, il se peut que la vaccination soit bénéfique à certains groupes à haut risque au vu de la gravité de la maladie en cas d'infection. Par conséquent, le SAGE a conclu que ses recommandations précédentes sur l'utilisation du vaccin anti-H5N1 pendant la période interpandémique, essentiellement centrées sur la vaccination des personnes à haut risque d'infection par le virus A(H5N1) suite à une exposition en milieu professionnel, doivent demeurer inchangées.[9]

Enfin, dans le cadre de ses compétences en matière de surveillance de la situation, le SAGE a assisté à un exposé sur la situation épidémiologique concernant le virus aviaire A(H7N9) et la mise au point de vaccins correspondants. Au 5 novembre 2013, 139 cas humains confirmés de grippe A(H7N9) et 45 décès (taux de létalité 32,4%) ont été déclarés par la Chine, principalement à la suite d'une exposition sur les marchés de volaille vivante. À l'heure actuelle, aucun élément de preuve ne permet d'envisager une transmission interhumaine durable du virus A(H7N9) mais il devrait y avoir persistance de cas humains sporadiques, isolés ou en petits groupes. L'OMS n'a pas émis de recommandations sur des procédures de dépistage particulières aux points d'entrée, ni imposé de restrictions en matière de voyages ou d'échanges commerciaux. Actuellement, 6 virus vaccinaux ont été mis au point par génétique inverse, tandis que les efforts pour utiliser les vaccins réassortis classiques se sont soldés jusqu'ici par un échec. Il y a 5 essais cliniques en cours sur des vaccins contre le virus grippal H7N9.

Élimination de la rougeole et de la rubéole

Le SAGE a examiné le rapport de situation préparé par le groupe de travail sur la rougeole et la rubéole et a félicité les pays et les Régions pour la diminution importante de l'incidence de la rougeole et pour la diminution de la mortalité due à la rougeole de trois quarts depuis 2000. La Région des Amériques est parvenue à éliminer durablement à la fois la rougeole et la rubéole et le Pacifique occidental s'approche de l'interruption de la transmission endémique de la rougeole. Pourtant, sur la base des tendances actuelles et des performances des programmes, les cibles mondiales d'ici 2015, de même que les cibles régionales pour l'élimination dans les Régions de l'Europe (2015), de la Méditerranée orientale (2015) et de l'Afrique (2020), ne seront pas atteintes à temps.

Le SAGE a pris acte que seules la Région des Amériques et la Région européenne ont fixé des cibles en vue de l'élimination de la rubéole. Conformément à la cible du GVAP d'éliminer la rougeole et la rubéole dans 5 Régions de l'OMS d'ici 2020, le SAGE a demandé instamment aux Régions de l'Afrique, de la Méditerranée orientale, de l'Asie du Sud-Est et du Pacifique occidental de travailler à l'établissement de buts régionaux pour l'élimination de la rubéole.

Le SAGE a tenu à préciser que pour parvenir à éliminer la rougeole, la couverture vaccinale doit être >95% pour 2 doses du vaccin à valence rougeole administrées dans le cadre de la vaccination systématique ou à l'occasion d'activités de vaccina-

(SIAs). To prevent measles outbreaks this high level of coverage needs to be maintained uniformly across all districts. For many countries now at <90% coverage nationally, reaching >95% coverage will require substantial additional investments over a sustained period of time. SAGE urged countries and partners to raise the visibility of measles and rubella elimination activities and make the necessary investments of financial and human resources required to strengthen health systems and achieve more equitable access to immunization services. SAGE stressed the importance of building on the work of the polio programme and integration of measles and rubella with other critical services in a way that helps to strengthen the health system and achieve universal health care.

WHO currently recommends 1 dose of rubella[10] vaccine but 2 doses of measles[11] and mumps[12] vaccines in order to protect children against the corresponding diseases. In view of the burden due to CRS, SAGE urged countries achieving ≥80% measles coverage through routine or SIAs, or both, to take the opportunity offered by measles elimination activities to introduce rubella-containing vaccines (RCVs). Countries introducing RCV for the first time should carry out a catch-up campaign using measles and rubella vaccine (MR) or measles, mumps and rubella vaccine (MMR) targeting children aged 9 months to <15 years, and use MR or MMR in routine immunization with the first dose of measles-containing vaccine (MCV).

SAGE recommended that those countries which currently give the first dose of RCV with the 2nd routine dose of measles vaccine should change the schedule to give the first dose of RCV with the first dose of MCV as MR or MMR, because coverage with the first dose of MCV is usually higher than for the second dose and immunogenicity is equally high.

Countries using different MCVs (i.e. measles (M), MR or MMR) for the 1st and 2nd doses should use the same vaccine (either MR or MMR) for both routine doses to simplify vaccine procurement, logistics, recording, reporting, and to increase coverage and decrease vaccine wastage. These programmatic advantages likely outweigh the marginal increase in vaccine cost (e.g. US$ 0.30 per dose difference between M and MR).

Whenever the number of pre-school children susceptible to measles approaches the equivalent of one birth

tion supplémentaire (AVS). Pour prévenir les flambées de rougeole, il faut que ce niveau élevé de couverture soit atteint uniformément au sein de tous les districts. Pour bon nombre de pays ayant à ce jour une couverture <90% au niveau national, atteindre une couverture au moins égale à 95% exigera des investissements supplémentaires importants sur une durée prolongée. Le SAGE prie instamment les pays et les partenaires d'accroître la visibilité des activités d'élimination de la rougeole et de la rubéole et de faire les investissements nécessaires en moyens financiers et humains, qui sont indispensables pour renforcer les systèmes de santé et permettre un accès plus équitable aux services de vaccination. Le SAGE a souligné l'importance de s'appuyer sur les travaux du programme sur la poliomyélite et d'intégrer la rougeole et la rubéole à d'autres services essentiels, d'une façon permettant de renforcer le système de santé et d'offrir l'accès universel aux soins.

L'OMS recommande actuellement l'administration de 1 dose du vaccin contre la rubéole[10] mais de 2 doses du vaccin contre la rougeole[11] et du vaccin contre les oreillons[12] afin de protéger les enfants contre ces maladies. Compte tenu de la charge de morbidité du SRC, le SAGE prie instamment les pays atteignant une couverture antirougeoleuse ≥80% par la vaccination systématique ou les activités de vaccination supplémentaire, ou les deux, de saisir l'occasion offerte par les activités d'élimination de la rougeole pour introduire les vaccins à valence rubéole. Les pays qui introduisent pour la première fois un vaccin à valence rubéole devront réaliser une campagne de rattrapage au moyen du vaccin antirougeoleux-antirubéoleux (RR) ou du vaccin antirougeoleux-antiourlien-antirubéoleux (ROR) ciblant les enfants âgés de 9 mois à <15 ans, et devront impérativement utiliser le RR ou le ROR dans leur vaccination systématique avec la première dose du vaccin à valence rougeole.

Le SAGE a recommandé que les pays qui délivrent leur première dose de vaccin à valence rubéole avec la 2e dose du vaccin antirougeoleux administrée de façon systématique délivrent désormais leur première dose de vaccin à valence rubéole avec la première dose du vaccin à valence rougeole (RR ou ROR), parce que la couverture par la première dose du vaccin à valence rougeole est habituellement plus élevée que celle obtenue par la deuxième dose et l'immunogénicité est tout aussi élevée.

Les pays utilisant différents vaccins à valence rougeole (à savoir, antirougeoleux, antirougeoleux-antirubéoleux, ou antirougeoleux-antiourlien-antirubéoleux) lors des contacts pour la 1re et la 2e dose doivent utiliser le même vaccin (RR ou ROR) pour les 2 doses administrées de façon systématique, afin de simplifier les achats de vaccins, la logistique, l'enregistrement, la notification, et afin d'augmenter la couverture et de diminuer le gaspillage de vaccins. Ces avantages programmatiques contrebalanceront probablement l'augmentation marginale du coût du vaccin (par exemple, une différence de US$ 0,30 par dose entre le vaccin antirougeoleux et le vaccin antirougeoleux-antirubéoleux).

Chaque fois que le nombre d'enfants d'âge préscolaire sensibles à la rougeole s'approche de l'équivalent d'une cohorte de nais-

[10] See No. 29, 2011, pp. 301–316.

[11] See No. 84, 2009, pp. 349–360.

[12] See No. 82, 2007, pp. 51–60.

[10] Voir Nº 29, 2011, pp. 301–316.

[11] Voir Nº 84, 2009, pp. 349–360.

[12] Voir N° 82, 2007, pp. 51–60.

cohort, the country needs to conduct a national follow-up SIA using MCV to prevent an outbreak of measles.

SAGE reviewed several country examples with different vaccine delivery strategies to determine criteria for when countries should expand the target age range for SIAs beyond the currently recommended 5 years (for follow-up measles SIAs) and 15 years (for introductory MR SIAs).

Based on country experience, both in the AMR and other regions, SAGE reaffirmed the need to achieve and maintain ≥95% coverage in routine services and SIAs. As there is no single criterion for identification of the target age range for measles or MR SIAs, SAGE recommended that countries integrate their surveillance, demographic, survey and (if available) seroprevalence data together with vaccination coverage information, history of MCV and RCV use, and local knowledge to determine the age distribution of susceptibility and hence the target age range of measles and MR SIAs. Additional information to consider in relation to MR SIAs is rubella immunity among women of child-bearing age, the epidemiology of rubella and CRS, age-specific fertility rates, and the age of mothers of CRS-affected infants.

For countries aiming to accelerate progress towards a rubella elimination goal by addressing immunity gaps in adults, SAGE recommended that any SIAs targeting immunity gaps in adults should include both males and females.

Vaccination coverage should be verified for all measles and MR SIAs through statistically valid and generally accepted methodology and that, where possible, all doses given during SIAs should be documented in the child's vaccination record and the number of zero-dose children vaccinated recorded by age group.

SAGE reviewed existing global and regional recommendations on vaccination of health workers and the scientific literature on nosocomial measles and rubella outbreaks. Because of the known risk of spreading disease from health workers to patients or from patients to health workers, SAGE recommended that all health workers[13] should be immune[14] to measles and rubella

sance, le pays doit conduire une AVS de suivi nationale au moyen du vaccin à valence rougeole afin de prévenir une flambée de la maladie.

Le SAGE a passé en revue l'exemple de plusieurs pays ayant des stratégies d'administration de vaccins différentes, afin de déterminer les critères qui président au choix du moment où les pays doivent étendre la tranche d'âge cible pour les AVS au-delà de l'âge de 5 ans (pour les AVS de suivi contre la rougeole) ou de 15 ans (pour les AVS liées à l'introduction du vaccin anti-rougeoleux-antirubéoleux) actuellement recommandé.

Sur la base de l'expérience des pays, aussi bien dans la Région des Amériques que dans d'autres Régions, le SAGE a réaffirmé la nécessité d'obtenir et de maintenir une couverture d'au moins 95% dans les services de vaccination systématique et les AVS. Aucune règle ni aucun critère ne permet à lui seul de déterminer la tranche d'âge cible pour les activités de vaccination supplémentaire contre la rougeole, seule ou en association avec la rubéole. Le SAGE a donc recommandé que les pays intègrent leurs données de surveillance, démographiques, d'enquêtes et (si disponibles) de séroprévalence aux informations sur la couverture vaccinale, à l'historique de l'utilisation du vaccin à valence rougeole et du vaccin à valence rubéole, et aux connaissances locales, pour déterminer la répartition de la sensibilité selon l'âge, et à partir de là, la tranche d'âge cible pour les activités de vaccination supplémentaire contre la rougeole, seule ou en association avec la rubéole. D'autres informations dont il faut tenir compte pour les activités de vaccination supplémentaire contre la rougeole et la rubéole sont l'immunité vis-à-vis de la rubéole chez les femmes en âge de procréer, l'épidémiologie de la rubéole et du SRC, les taux de fécondité propres à chaque âge, et l'âge des mères de nourrissons atteints de SRC.

À l'intention des pays qui souhaitent accélérer leur progression en vue de la réalisation des objectifs d'élimination de la rubéole en cherchant la manière de traiter les lacunes de l'immunité chez les adultes, le SAGE a recommandé d'inclure à la fois les hommes et les femmes dans toutes les AVS ciblant les lacunes de l'immunité chez les adultes.

La couverture vaccinale doit être vérifiée à l'issue de toutes les activités de vaccination supplémentaire contre la rougeole, seule ou en association avec la rubéole, par des méthodes statistiquement valides et généralement acceptées, et dans la mesure du possible, toutes les doses administrées pendant les AVS doivent être consignées dans le carnet de vaccination de l'enfant et le nombre d'enfants vaccinés qui n'avaient jamais reçu aucune dose auparavant doit être enregistré par groupe d'âge.

Le SAGE a revu les recommandations mondiales et régionales en vigueur sur la vaccination des agents de santé et la littérature consacrée aux flambées d'infections nosocomiales rougeoleuses et rubéoleuses. À cause du risque connu de propagation de la maladie des agents de santé aux patients ou vice-versa, le SAGE a recommandé que tous les agents de santé[13] soient immunisés[14] contre la rougeole et la rubéole (dès lors que la rubéole a été

[13] All persons involved in patient care such as health care professionals, residents, students, laboratory staff, as well as persons in public health such as field workers, epidemiologists, laboratory staff and community health workers.

[14] Either written documentation of receipt of 2 doses of MCV and at least 1 dose of RCV or positive serologic (IgG) test results from a proficient laboratory.

[13] Toutes les personnes impliquées dans les soins aux patients, tels que les professionnels de santé, les internes, les étudiants, le personnel de laboratoire, ainsi que les personnes qui travaillent dans le domaine de la santé publique, telles que les agents de terrain, les épidémiologistes, le personnel de laboratoire et les agents de santé communautaire.

[14] Soit un document écrit attestant que la personne a bien reçu 2 doses de vaccin à valence rougeole et au moins 1 dose de vaccin à valence rubéole, soit des résultats de test sérologique (IgG) positifs délivrés par un laboratoire compétent dans ce domaine.

(once rubella has been introduced into the national programme). Verification of vaccination and/or immunity should be integrated into standard infection control guidelines or other health-worker standards of care. For health workers who have contact with patients, documentation of immunity should be required before signing a contract or entering into a training programme. SAGE recommended that standard infection control measures should be enforced to prevent or reduce the spread of measles and rubella and that regions and countries should develop plans to operationalize these recommendations.

SAGE endorsed the findings from the survey to identify gaps in essential evidence and programme barriers to achieving measles and rubella elimination targets; 12 topics/areas were prioritized for operational or basic science research. SAGE encouraged the WG to disseminate the findings and to promote implementation of the research agenda.

Smallpox vaccines

The last case of smallpox occurred in 1977. In 1980 the World Health Assembly declared the global eradication of this disease. A global stockpile of vaccines, held in Switzerland, was created with donations from Member States. In 2004, the Ad Hoc Committee on orthopoxvirus infections recommended that the stockpile should consist of 200 million doses. The current physical stockpile kept by WHO in Switzerland is approximately 2.4 million doses and the WHO stockpile kept within donating countries is 32 million doses.

Given the different set of vaccines available (1st generation vaccines used during the eradication campaign and made from the lymph or skin of inoculated animals, 2nd generation vaccines produced in tissue cells and further attenuated, and 3rd generation vaccines based on replicating or non-replicating virus) WHO plans to make an informed decision on which vaccines to include in the stockpile for use in case of a re-emergence of smallpox. Therefore, SAGE was asked to respond to the following questions: Which vaccine should be recommended for use during an outbreak of smallpox and how many doses should be stockpiled? What groups should be targeted for vaccination if an outbreak occurs? Which groups should be vaccinated for preventive use and with which vaccine?

SAGE was presented with the status of vaccine production and composition of the current stockpiles, a systematic review of safety, immunogenicity and effectiveness of available vaccines and grading of the evidence, and the conclusions and recommendations of an expert consultation.

Regarding which vaccines should be used for outbreak control, target populations and composition of the WHO stockpile, SAGE provided the following recommendations:

i. Vaccines recommended for use in case of smallpox outbreaks should be lyophilized (to maximize

introduite dans le programme national). La vérification de la vaccination et/ou de l'immunité doit être intégrée dans des lignes directrices standard sur la lutte contre les infections, ou dans d'autres normes en matière de soins concernant les agents de santé. Pour les agents de santé qui travaillent au contact des patients, la preuve de l'immunité doit être exigée avant toute signature de contrat ou participation à un programme de formation. Le SAGE a recommandé l'application de mesures standard de lutte contre les infections pour prévenir ou réduire la propagation de la rougeole et de la rubéole, et l'élaboration de plans par les Régions et les pays pour traduire dans les faits ces recommandations.

Le SAGE a approuvé les conclusions de l'enquête visant à identifier les lacunes dans les données essentielles et les obstacles programmatiques qui empêchent d'atteindre les cibles d'élimination de la rougeole et de la rubéole. Douze sujets/domaines ont été sélectionnés en priorité pour la recherche opérationnelle ou la recherche en sciences fondamentales. Le SAGE a encouragé le groupe de travail à diffuser ces conclusions et à favoriser la mise en place du programme de recherche.

Vaccins antivarioliques

Le dernier cas de variole a été signalé en 1977. En 1980, l'Assemblée mondiale de la Santé a déclaré la maladie officiellement éradiquée. Un stock mondial de vaccins, détenu en Suisse, a été créé à l'aide de contributions versées par les États membres. En 2004, le Comité ad hoc sur les orthopoxviroses a recommandé que les stocks comprennent au total 200 millions de doses. Le stock actuellement physiquement conservé par l'OMS est d'environ 2,4 millions de doses et le stock de l'OMS conservé dans les pays donateurs est de 32 millions de doses.

Compte tenu des différents types de vaccins disponibles (vaccins de 1re génération utilisés pendant l'éradication et préparés à partir de lymphe ou de peau d'animaux inoculés, vaccins de 2e génération produits dans des cellules de tissus, et vaccins réplicatifs ou non réplicatifs de 3e génération ou encore plus atténués), l'OMS a souhaité prendre une décision éclairée sur le type de vaccins à inclure dans les stocks et à utiliser en cas de réémergence de la variole. Le SAGE a donc été invité à répondre aux questions suivantes: quel vaccin doit-on recommander pendant une flambée de variole et combien de doses doit-on mettre en réserve? Quels groupes doit-on vacciner en priorité si une flambée survient? Et qui doit se faire vacciner à titre préventif et avec quel vaccin?

Le SAGE a été informé de la situation en matière de production de vaccins et de la composition des stocks actuels, s'est penché sur une revue systématique de la sécurité, de l'immunogénicité et de l'efficacité des vaccins disponibles accompagnée d'une évaluation de la qualité des données selon l'approche GRADE, et sur les conclusions et recommandations d'une consultation d'experts.

Concernant les vaccins à utiliser pour endiguer les flambées, les populations cibles et la composition des stocks de l'OMS, le SAGE a émis les recommandations suivantes:

i. Les vaccins recommandés en cas de flambées de variole doivent être lyophilisés (maximisation de la durée de vie

shelf-life of the stockpile) and administered via bifurcated needles (allowing a reduction of the vaccine dose), and should produce a visible major cutaneous reaction as a correlate of protection (i.e. vaccine "take").

ii. In controlling an outbreak, countries should use any available smallpox vaccine that meets WHO standards of potency, purity, and stability.[15]

iii. For the WHO stockpile, both licensed ACAM2000 (2nd generation vaccine) and LC16m8 (3rd generation vaccine) are preferred. If they are not available, 1st generation vaccines used during the eradication campaign can be used.

iv. Countries donating vaccines to the WHO stockpile should provide the same vaccine as that in their country's stockpile (except for Imvanex-MVA which is currently not recommended).

v. Donated vaccines should be bundled with bifurcated needles, in freeze-dried presentation, and produce a visible cutaneous reaction after administration.

vi. In case of a smallpox outbreak, mass vaccination is not recommended, and vaccination should be limited to close contacts and first responders who are likely to have direct contact with symptomatic patients (including ambulance and clinical staff) and laboratory workers expected to have direct contact with specimen collection and/or processing.

vii. WHO should ensure rapid and equitable access to smallpox vaccines to countries facing outbreaks and which do not have a national stockpile.

viii. In view of the impossibility of predicting the likelihood and extent of a potential virus release and of disease outbreaks, an optimal stockpile size cannot be estimated. SAGE considered that with a total of 600–700 million doses of smallpox vaccine available worldwide (WHO and national stocks) and with production capacity that could rapidly reach up to 250 million doses per year, the current size of the WHO stockpile is sufficient for response to an epidemic.

ix. 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.

With respect to preventive use of the smallpox vaccines, SAGE recommended that:

i. Based on a risk–benefit assessment, and the low risk for reappearance of smallpox, preventive vaccination should be limited only to laboratory personnel working with orthopox viruses.

ii. Each country should decide which vaccine to use, provided the vaccine meets the WHO recommendations.[15]

des stocks) et administrés par l'intermédiaire d'aiguilles bifurquées qui économisent la dose de vaccin, et produire une réaction cutanée importante et visible qui est corrélée à la protection conférée (autrement dit «font effet»).

ii. Pour endiguer une flambée, les pays doivent utiliser n'importe quel vaccin antivariolique à disposition répondant aux critères d'activité, de pureté, et de stabilité fixés par l'OMS.[15]

iii. Pour les stocks de l'OMS, les vaccins homologués ACAM2000 (vaccin de 2e génération) et LC16m8 (vaccin de 3e génération) sont à privilégier. S'ils ne sont pas disponibles, il est possible d'utiliser des vaccins de 1e génération employés pendant la période d'éradication.

iv. Les pays qui donnent des vaccins à l'OMS pour sa réserve doivent fournir le même vaccin que celui qu'ils ont dans leurs propres réserves nationales (sauf pour Imvanex-MVA qui n'est pas recommandé à l'heure actuelle).

v. Les vaccins donnés doivent être livrés avec la quantité correspondante d'aiguilles bifurquées, sous une forme lyophilisée, et produire une réaction cutanée visible après administration.

vi. En cas de flambée de variole, la vaccination de masse n'est pas recommandée, et la vaccination doit se limiter aux personnes proches et aux intervenants de première ligne qui sont susceptibles d'avoir un contact direct avec des patients symptomatiques (par exemple, le personnel ambulancier) et les agents de laboratoire censés avoir un contact direct avec le prélèvement et/ou le traitement des échantillons.

vii. L'OMS doit garantir un accès rapide et équitable aux vaccins antivarioliques à tous les pays confrontés à des flambées qui ne disposeraient pas de leur propre stock.

viii. Devant l'impossibilité de prévoir le risque et l'ampleur d'une éventuelle propagation ou flambée du virus, et donc de déterminer la taille de stock optimale, le SAGE a indiqué que vu les 600-700 millions de doses de vaccin antivariolique disponibles en tout dans le monde et la possibilité pour les capacités de production de rapidement monter à 250 millions de doses par an, la taille actuelle des stocks de l'OMS convient pour faire face à une épidémie.

ix. Le SAGE recommande à l'OMS d'entamer des négociations avec les pays en possession du vaccin antivariolique pour mettre en place des mécanismes permettant de reconstituer les stocks de l'OMS en cas de besoin.

Concernant l'utilisation préventive des vaccins antivarioliques, le SAGE a formulé les recommandations suivantes:

i. À partir d'un rapport bénéfice/risque calculé, et compte tenu du faible risque de réapparition de la variole, la vaccination préventive doit être exclusivement réservée au personnel de laboratoire manipulant les orthopoxvirus.

ii. Chaque pays doit décider du vaccin qu'il utilisera, tant qu'il respecte les recommandations de l'OMS.[15]

[15] *WHO Expert Committee on biological standardization* (53rd Report1). Geneva, World Health Organization, 2004, WHO Technical report series 926. Available from http://whqlibdoc.who.int/trs/WHO_TRS_926.pdf; accessed November 2013.

[15] *WHO Expert Committee on biological standardization (53ème Rapport).* Genève, Organisation mondiale de la Santé, 2004, série de rapports techniques de l'OMS No 926. Disponible uniquement en langue anglaise sur http://whqlibdoc.who.int/trs/WHO_TRS_926.pdf; consulté en décembre 2013.

iii. There is not enough scientific evidence to support any recommendation on the need for, or frequency of, booster immunizations.

iv. SAGE considered that more clinical data on efficacy and safety of Imvanex-MVA should be provided before recommending its use in place of 1st and 2nd generation vaccines. However, in countries where it is licensed, this vaccine may be considered for individuals at high risk of exposure and for whom standard replicating vaccine is contraindicated because of immunodeficiencies, immunosuppression therapies or atopic dermatitis.

Immunization supply chains: key challenges impacting national immunization programmes

The success of national immunization programmes is highly dependent on the supply chain systems for delivery of vaccines and equipment. Without a functional system that meets the "6 rights" of a supply chain (the right vaccine, in the right quantities, at the right place, at the right time, in the right condition (no temperature breaks in the cold chain) and the right cost) and assures an uninterrupted availability of quality vaccines at the point of vaccination, immunization programmes would become marginalized and the fourth objective of the Millennium Development Goal (MDG-4) could not be achieved.

The availability of new vaccines over the past decade has resulted in markedly increased pressure on in-country vaccine supply chains. Between 2010 and 2015, 5 times more new vaccine introductions are expected in GAVI-eligible countries compared to the period 2000–2005. The storage volume of vaccines to fully immunize a child has markedly increased during the past decade and risen 11-fold in some countries. In the same period there has been a 10-fold increase in the value of vaccines procured through UNICEF whereas the overall investment in the supply chain has lagged behind.

Recent WHO-UNICEF assessments in 57 low-income countries revealed that national vaccine supply chains are under-performing and that none of these countries' supply chains met all of the minimum requirements set by WHO for effective vaccine management (EVM). Data systems to support the immunization supply chain have not kept pace with technological developments.

SAGE expressed deep concern about the mounting challenges faced by countries and recognized the need to draw the attention of all partners to this issue and encourage greater investments for strengthening in-country immunization supply chain systems.

In preparation for its the next session in April 2014, when SAGE will review a proposed vision and strategy for addressing these challenges, SAGE requested the following additional information: evidence and root-cause analyses of the EVM data, quantified evidence on invest-

iii. Il n'y a pas assez de données scientifiques pour pouvoir émettre la moindre recommandation sur la nécessité de rappels, et leur fréquence.

iv. Le SAGE considère qu'il faudra disposer de davantage de données cliniques sur l'efficacité et la sécurité d'Imvanex-MVA avant de pouvoir recommander son utilisation en lieu et place des vaccins de 1re et 2e génération. Toutefois, dans les pays où il est homologué, son utilisation peut être envisagée chez les individus à haut risque d'exposition et pour lesquels le vaccin réplicatif standard est contre-indiqué (immunodéficiences, thérapies d'immunosuppression, ou dermatite atopique).

Chaînes d'approvisionnement en vaccins: principales difficultés rencontrées ayant une incidence sur les programmes nationaux de vaccination

Le succès des programmes nationaux de vaccination dépend largement des systèmes de la chaîne d'approvisionnement en vaccins. Sans système fonctionnel répondant aux 6 critères d'une «bonne» chaîne logistique (le bon vaccin, en bonnes quantités, au bon endroit, au bon moment, dans les bonnes conditions (aucune rupture de la chaîne du froid) et au bon prix) et mettant à disposition sans interruption des vaccins de qualité au point de vaccination, le programme de vaccination jouerait un rôle marginal et le quatrième objectif du Millénaire pour le développement (OMD-4) ne pourrait pas être atteint.

La création et la mise à disposition de nouveaux vaccins au cours des 10 dernières années a fini par exercer une pression nettement accrue sur les chaînes d'approvisionnement en vaccins au sein des pays. Entre 2010 et 2015, on s'attend à 5 fois plus d'introductions de nouveaux vaccins dans les pays qui remplissent les conditions pour une aide de GAVI, qu'au cours de la période 2000-2005. L'espace de stockage nécessaire pour les vaccins destinés à vacciner complètement un enfant a nettement augmenté depuis 10 ans, jusqu'à être multiplié par 11 dans certains pays. Au cours de la dernière décennie, il y a eu une augmentation d'un facteur 10 de la valeur des vaccins achetés par l'intermédiaire de l'UNICEF, alors que l'investissement global dans les chaînes logistiques accuse un sérieux retard.

De récentes études réalisées par l'OMS-UNICEF dans 57 pays à faible revenu ont révélé que les chaînes d'approvisionnement en vaccins de ces pays ont des performances insuffisantes, et qu'aucun de ces pays ne possède une chaîne d'approvisionnement respectant les exigences minimales établies par l'OMS en matière de gestion efficace des vaccins (GEV). Les systèmes de données à l'appui des chaînes d'approvisionnement en vaccins n'ont pas évolué au rythme des innovations technologiques.

Le SAGE s'est vivement inquiété des difficultés croissantes auxquelles sont confrontés les pays et souhaite attirer l'attention de tous les partenaires sur cette question et encourager des investissements plus importants, en prêtant davantage attention au renforcement de la chaîne d'approvisionnement en vaccins au sein des pays.

En vue de la préparation d'une session prochaine en avril 2014 où il sera invité à examiner un projet de vision et de stratégie permettant de résoudre ces difficultés, le SAGE a demandé que lui soient fournies les informations supplémentaires suivantes: analyse des données de la GEV fondée sur l'examen des causes

ments needed to address the challenges (particularly on the relative expenditures on vaccine and cold chain equipment), information on the challenges in middle-income countries; promising and innovative approaches (controlled temperature chain; supply chain integration; public-private partnerships in immunization supply chains), information on the GAVI end-to-end supply chain strategy and the role of the WHO-UNICEF immunization supply chain hub.

Strategic review of the global sentinel hospital surveillance networks for invasive bacterial vaccine preventable disease (IB-VPD) and rotavirus (RV)

In 2008 existing local and regional surveillance systems were brought together in a WHO coordinated global sentinel hospital surveillance network. This was designed primarily to support low to middle income countries in surveillance for IB-VPD and RV diarrhoea, to generate national data for decision-making on introduction of pneumococcal conjugate vaccine (PCV) and RV vaccines. The networks' objectives are to document presence of disease, describe disease epidemiology, provide data for inclusion in disease burden estimation in the pre-vaccine introduction period, assess disease trends over time, and to monitor vaccination programme impact during the post-vaccine introduction period.

In February 2013, WHO with its informal Technical Advisory Group for new vaccines surveillance (iTAG), initiated a strategic review of both IB-VPD and RV surveillance networks to assess whether the objectives were met and decide on measures needed to fill gaps and enhance performance. Since many countries have now introduced PCV or RV vaccines or both, the focus is shifting from data for decisions on vaccine introduction to documentation of impact. The review comprised: surveillance data analyses; questionnaires to obtain national perspectives on the value and performance of the surveillance system; independent reviews of laboratory activities and data management systems; review of the published literature and GAVI applications to evaluate whether national surveillance data had been used in vaccine introduction decision-making; internal review of WHO activities and resource availability to support these activities.

From 2008 to 2012, 195 sites in 65 countries participated in IB-VPD surveillance and 265 sites in 67 countries in RV surveillance. Fewer than 50% of sites had data that met inclusion criteria for the strategic review. The strategic review concluded that both systems have documented the presence of disease and that the data contributed to country decisions to introduce RV vaccine

et des faits, éléments d'appréciation quantifiés sur les investissements nécessaires pour résoudre les difficultés (en particulier sur le contraste entre les dépenses liées aux vaccins et celles liées aux équipements de chaîne du froid); informations sur les difficultés rencontrées dans les pays à revenu intermédiaire; approches prometteuses et novatrices (chaîne sous température contrôlée, intégration des chaînes d'approvisionnement; partenariats public-privé dans le domaine des chaînes d'approvisionnement en vaccins); informations sur la stratégie de l'Alliance GAVI relative à l'ensemble de la chaîne d'approvisionnement et sur le rôle de la plateforme OMS-UNICEF en matière d'approvisionnement en vaccin.

Examen stratégique des réseaux mondiaux de surveillance par des hôpitaux sentinelles des maladies bactériennes invasives à prévention vaccinale (MBI-PV) et du rotavirus (RV)

En 2008, les systèmes de surveillance locaux et régionaux existants ont été regroupés pour former un réseau mondial de surveillance par des hôpitaux sentinelles coordonné par l'OMS. Ce réseau a été conçu principalement pour soutenir les pays à revenu faible ou intermédiaire dans leurs activités de surveillance de la diarrhée imputable aux MBI-PV et au RV, afin de produire des données nationales destinées à la prise de décisions concernant l'introduction du vaccin antipneumococcique conjugué et du vaccin antirotavirus. Les objectifs de ces réseaux étaient de documenter la présence de la maladie, décrire son épidémiologie, fournir des données susceptibles d'être incluses dans les estimations sur la charge de morbidité pendant la période ayant précédé l'introduction du vaccin, évaluer les tendances épidémiologiques au cours du temps et suivre l'impact du programme de vaccination pendant la période ayant suivi l'introduction du vaccin.

En février 2013, l'OMS avec son Groupe technique consultatif informel pour la surveillance des nouveaux vaccins a entamé un examen stratégique des réseaux de surveillance des MBI-PV et du RV, afin de savoir si les objectifs étaient atteints et définir les mesures nécessaires pour combler les lacunes et améliorer les performances. Puisque de nombreux pays ont à présent introduit le vaccin antipneumococcique conjugué ou le vaccin antirotavirus, la priorité ne va plus aux données destinées à la prise de décisions concernant l'introduction du vaccin, mais aux données permettant de documenter l'impact de cette introduction. L'examen s'est basé sur des analyses des données de surveillance; des questionnaires destinés à recueillir le point de vue des pays sur l'utilité et l'efficacité du système de surveillance; des évaluations indépendantes des activités des laboratoires et des systèmes de gestion des données; un examen de la littérature publiée et des demandes de soutien présentées à l'Alliance GAVI pour savoir si les données de surveillance nationales avaient été utilisées pour la prise de décisions concernant l'introduction des vaccins; un examen interne des activités de l'OMS et de la disponibilité des ressources qui facilitent ces activités.

De 2008 à 2012, 195 sites dans 65 pays ont participé à la surveillance des MBI-PV et 265 sites dans 67 pays à la surveillance du RV. Moins de 50% des sites présentaient des données répondant aux critères d'inclusion établis pour l'examen stratégique. L'examen stratégique a conclu que les 2 systèmes ont documenté la présence de la maladie et que les données ont contribué aux décisions prises par les pays d'introduire le vaccin

and PCV. The RV network has promising results for the potential ability to monitor impact of vaccine introduction and has successfully initiated monitoring of RV genotype distributions. The IB-VPD network has successfully enhanced the rate of isolation of pneumococcus at many sites and allowed the detection of illnesses due to other bacteria, including detection of meningococcal meningitis outbreaks. Pneumococcal serotype information has been collected from previously underrepresented countries and regions. The ability to monitor the impact of PCV introduction, or serve as a platform for specially designed PCV impact projects, has been demonstrated in a few sites but its potential to do so across the network remains to be demonstrated.

antirotavirus et le vaccin antipneumococcique conjugué. Le réseau de surveillance du RV a affiché des résultats prometteurs quant à sa capacité à suivre l'impact de l'introduction du vaccin, et a entrepris avec succès de suivre la répartition des génotypes du RV. La surveillance des MBI-PV a réussi à améliorer dans de nombreux endroits le taux de mise en évidence des pneumocoques, et a permis de détecter des infections causées par d'autres bactéries, notamment des flambées de méningite à méningocoque. Les informations sur le sérotype des souches de pneumocoques ont été recueillies auprès de pays et de régions auparavant sous-représentés. Les compétences affichées par ce réseau pour suivre l'impact de l'introduction du vaccin antipneumococcique conjugué ou lui faire jouer le rôle de plateforme pour des projets bien précis d'étude d'impact du vaccin antipneumococcique conjugué ont été démontrées seulement sur quelques sites, et il reste donc à démontrer qu'elles sont bien présentes partout dans le réseau.

The strategic review confirmed that the capacity needed for a site to successfully implement RV surveillance differs from that needed for IB-VPD surveillance. Gastroenteritis is common, easily recognized, and sample collection to test for RV, and other enteric pathogens, is non-invasive. IB-VPD sites conduct surveillance for meningitis, an infrequent condition, requiring a substantial population to detect more than a small number of cases, and the collection of cerebrospinal fluid. For the IB-VPD sites that also conduct surveillance for bacteremia, sepsis and pneumonia, pathogen-specific confirmation is insensitive. Establishing laboratory capacity to isolate bacteria from reliably normally sterile body fluids remains a challenge in many sites; the laboratory testing required for the RV network is less complex and yields a much larger number of positive samples.

L'examen stratégique a confirmé que les capacités d'un site nécessaires à la mise en œuvre réussie de la surveillance du RV sont différentes de celles nécessaires pour la surveillance des MBI-PV. La gastroentérite est courante, facile à reconnaître, et la collecte d'échantillons pour dépister le RV, et d'autres agents pathogènes intestinaux, est non invasive. Les sites surveillant les MBI-PV exercent également une surveillance de la méningite, une maladie rare, qui exige d'une part une population importante pour pouvoir détecter un nombre de cas qui ne soit pas trop petit, et d'autre part le prélèvement de liquide céphalorachidien. Dans les sites surveillant les MBI-PV qui exercent également une surveillance de la bactériémie, de la septicémie et de la pneumonie, les tentatives de confirmation en laboratoire des agents pathogènes spécifiques ont échoué par manque de sensibilité des tests pratiqués. Il est encore difficile dans de nombreux endroits d'établir la capacité d'un laboratoire à isoler des bactéries à partir de liquides organiques normalement stériles; l'épreuve de laboratoire requise pour le réseau de surveillance du RV est moins compliquée et donne un nombre d'échantillons positifs beaucoup plus grand.

SAGE affirmed the benefit to participating sites and countries of having a coordinated network of sentinel site surveillance. SAGE agrees that the IB-VPD and RV networks should leverage the experience of the past 5 years to meet future surveillance needs, which include monitoring changes in disease epidemiology. These data will be essential in some countries to secure long-term national funding for vaccines. Demonstrating vaccine impact in epidemiologic settings that are not reflected by existing impact data is also important.

Le SAGE a confirmé le bénéfice, pour les sites et les pays participants, d'avoir un réseau coordonné de surveillance par sites sentinelles. Le SAGE a convenu que les réseaux de surveillance des MBI-PV et du RV devaient mettre à profit l'expérience acquise ces 5 dernières années pour répondre aux futurs besoins de surveillance, et notamment suivre les évolutions de l'épidémiologie des maladies. Ces données seront essentielles dans certains pays pour garantir le financement national des vaccins sur le long terme. Il est également important de démontrer l'impact des vaccins dans des situations épidémiologiques qui ne se reflètent pas dans les données d'impact existantes.

SAGE endorsed the strategic review findings to strengthen and refocus the efforts. Key review findings include, inter alia, the following needs for both networks:

i. Revision of the surveillance objectives to align more closely with the current and future vaccine introduction landscape;
ii. Further standardization to ensure the generation of cohesive, credible, well-defined data and real-time monitoring of system performance;
iii. Sharing of standardized, case-based data at all levels, use of identifiers for linking of clinical and

Le SAGE a approuvé les conclusions de l'examen stratégique qui sont d'intensifier et de recentrer les efforts. Les principales conclusions de cet examen comprennent entre autres la nécessité pour les 2 réseaux de:

i. Actualiser les objectifs de la surveillance pour les mettre plus en adéquation avec le paysage actuel et futur des introductions de vaccins;
ii. Subir une nouvelle normalisation pour assurer la production de données homogènes, crédibles et bien définies, et le suivi en temps réel des performances du système;
iii. Partager des données basées sur l'identification des cas et normalisées, à tous les niveaux, utiliser des identificateurs

laboratory results, zero/negative reporting to differentiate absence of cases from lack of reporting, and progress on data management including the use of software with editing and verification capability;

iv. Development of performance measures and agreements on: (1) sentinel site eligibility for on-going participation in the network; (2) standards for the reference laboratories for support to sentinel site laboratories including site visits, conduct of specialized testing, and testing of a systematic sample of specimens from all sites for laboratory quality control; and (3) WHO roles in support of the network;

v. Additional human and financial resources are required to strengthen the networks including support to sites, access to technical assistance, laboratory quality assurance/control processes, data reporting systems, exchange of lessons learnt, and collaboration. The current year-to-year funding strategy does not encourage longer-term planning and investment.

vi. For the IB-VPD network, management of the programme should focus the limited resources on support for a smaller number of sites to generate better quality data to inform policies.

SAGE noted that both sentinel surveillance networks are aligned with the priorities outlined in the GVAP which emphasizes the need for low- and middle-income countries to invest resources to establish and/or strengthen sentinel site surveillance systems, including laboratory confirmation of vaccine-preventable diseases. Looking ahead, 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 (e.g. Japanese encephalitis included in meningitis surveillance; other causes of acute gastroenteritis), laboratory procedures (identification of other bacterial pathogens in laboratories conducting IBD surveillance) 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. ■

pour relier les résultats cliniques et les résultats de laboratoire, recourir au signalement négatif/zéro cas pour différencier l'absence de cas de l'absence de signalement, et progresser en matière de gestion des données, notamment en faisant appel à des logiciels ayant des fonctions d'édition et de vérification;

iv. Élaborer des outils de mesure de la performance et des accords sur: 1) les conditions à remplir par les sites sentinelles pour leur participation régulière au réseau; 2) les normes applicables aux laboratoires de référence concernant le soutien aux laboratoires des sites sentinelles, notamment les visites sur site, la réalisation de tests particuliers, et les tests pratiqués sur un échantillonnage systématique des échantillons de tous les sites en vue du contrôle de la qualité des laboratoires; et 3) les rôles qui incombent à l'OMS en matière d'appui au réseau;

v. Disposer de ressources humaines et financières supplémentaires pour renforcer les réseaux, ce qui inclut notamment l'appui aux sites, l'accès à une assistance technique, les processus de contrôle/assurance de la qualité dans les laboratoires, les systèmes de notification des résultats, l'échange des enseignements tirés, et la collaboration. La stratégie actuelle de financement annuel ne favorise pas la planification et les investissements à long terme.

vi. Concernant le réseau de surveillance des MBI-PV, la gestion du programme doit concentrer ses ressources limitées sur l'appui à un nombre plus réduit de sites afin de produire des données de meilleure qualité pour orienter les politiques.

Le SAGE a constaté que les 2 réseaux de surveillance sentinelle sont en phase avec les priorités décrites dans le GVAP qui insiste sur la nécessité pour les pays à revenu faible ou intermédiaire d'investir les ressources de manière à établir et/ou renforcer les systèmes de surveillance qui s'appuient sur des sites sentinelles, notamment la confirmation en laboratoire des cas de maladies à prévention vaccinale. Tourné vers l'avenir, le SAGE a demandé instamment que l'on accorde une plus grande attention à l'intégration des systèmes de données, qui faciliterait l'analyse en temps réel et le suivi des performances. Le SAGE a également noté qu'il est possible de mettre en œuvre une telle intégration en s'appuyant sur les capacités accrues développées par ces réseaux pour exercer une surveillance d'autres maladies au moyen d'une définition de cas similaire (par exemple encéphalite japonaise incluse dans la surveillance de la méningite, autres causes de gastroentérite aiguë), les procédures des laboratoires (identification d'autres agents pathogènes bactériens dans les laboratoires exerçant une surveillance des MBI) et le personnel formé pour appliquer et respecter des protocoles de surveillance rigoureux. Les 2 réseaux doivent continuer à partager leurs expériences avec le réseau de surveillance de la poliomyélite. Dans ce processus d'intégration, les efforts doivent être conçus dans une optique stratégique et déployés de façon logique et synergique. ■

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SAGE TRACKING RECORD OF RECOMMENDATIONS AND ACTION POINTS

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
General	SAGE recommended that ways to improve curricula for medical personnel should be explored.	Action	Nov 2008	Ongoing	The African region started to work with academia to develop a pre-service curricula for nursing and medical staff. Annual courses for medical and nursing staff take place in collaboration with Network for Education and Support in Immunization (NESI). An evaluation of the impact of pre-service training and curricula changes is ongoing in 9 countries in AFRO. An evaluation was conducted in late 2011 and a draft report has been prepared but it is not available for wider circulation yet. It first needs approval from countries involved. A report was expected for early 2013 but this report was not recieved by October 2013.
General	SAGE encouraged the European region to document and share its experiences in country profiling, tailoring responses and using novel communication strategies to effect behaviour change.	Action	Nov 2010	Ongoing	EURO is working to give countries tools to address vaccine hesitancy at the individual level. These include: 1. Development of the Tailoring Immunization Programs “TIP” toolkit, which allows a country or sub-national level authority to segment/profile a population based on behaviors rather than background characteristics. The resulting group profile can help inform programmatic responses that could be communication-oriented or inform improved service delivery. Best practices from other disease programs are included that can be adapted for country-specific issues. Pilot testing of the framework has been conducted in several European countries: TIP was implemented in Bulgaria and on three projects in Sweden (Somali immigrants, migrants, and anthroposophic communities) and Bulgaria. In 2013, TIP was implemented in France and the UK. Use of the tool in Switzerland is envisaged for 2014. A tool assessment is planned in 2014 and expansion to other regions that have expressed interest. TIP will be adapted for use on a global level and a second edition will be published later in 2014. 2. Strengthening the ability of member states to handle crises in vaccine confidence and trust through a guidelines document on vaccine safety communication was published in 2013. 3. Advocacy for immunization and strengthening the use of new media led to involvement of well-ranked bloggers who write in Russian and English to better engage around vaccine confidence. 4. A vaccines social media strategy and a smart-phone immunization tracker/reminder ‘app’ for parents has been launched and is currently being modified by national immunization programs in 10 countries to be adapted to local schedules. 5. An online vaccines resource centre was launched in 2012 and has been strengthened and improved through 2012-2013, with a number of MS using or translating the caregiver and health-care worker tools presented.
General	SAGE recommended strengthening national vaccination programs, integrating health services and strengthening health systems to promote universal health coverage.	Action	Apr 2013	Ongoing	A teleconference was held May 13 2013 with J. Abramson, P. Figueroa, and N. Arora and EPI (M. Zaffran and T. Goodman) to discuss issue and provide briefing on the integration activities that historically and presently EPI is working on. Subsequently, in early June a draft typology was produced and shared that summarizing this area of work. It was agreed that an effort would be made to highlight this area of work in a few slides of the IVB Director's next presentation to SAGE. Discussions are ongoing. The topic of integration is on the agenda of the April meeting.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
General	SAGE requested that a paper be developed, highlighting the circumstances under which off-label use of any vaccine can be recommended, while clarifying the differences between regulatory decisions and public health recommendations. Legal and programmatic implications of off-label recommendations and the need for clear communication should be considered.	Action	Apr 2012	Pending	Advice being sought through the ECBS - added to agenda of next meeting, 15-19 October 2012. SAGE had previously requested that a paper be developed, highlighting the circumstances in which off-label use of any vaccine could be recommended, while clarifying the differences between regulatory decisions and public health recommendations. During the November 2012 SAGE meeting, SAGE further requested that ECBS prepare guidance for national regulatory authorities on studies needed to support evidence-based, off-label use of vaccines which benefit public health. It was noted that for regulators, product specific data are paramount. SAGE requested that an additional document be prepared to advise the national immunization technical advisory committees about the type of data that might support a policy recommendation to use a vaccine outside its licensed schedule in order to achieve public health benefits such as operational simplicity or cost savings. The ECBS guidance document has been delayed and will be prepared after the 2014 meeting. The paper clarifying the differences between regulatory decisions and public health recommendations has been commissioned and is under development. The aim is to have it ready for submission to a peer review journal in the spring 2014.
General	SAGE encouraged the Regional Office in EMRO to pay special attention to countries affected by political turmoil and requested specific monitoring for any adverse impacts on immunization programmes in GAVI graduating countries.	Action	Apr 2011	Ongoing	There are no GAVI graduating countries in the EMR. EMRO is working closely with and is paying special attention to the countries affected by political turmoil. The following support was provided since the last SAGE meeting in November 2013: • implementation of routine vaccination in the 2 provinces hosting the refugees camps in Jordan • implementation of the national MR/Polio synchronized campaigns in Syria and the surrounding countries (Syria, Jordan and Iraq) • provision of support to Tunisia for recruiting technical staff to support EPI • Conduction of comprehensive EPI review in Sudan, including DQS and PIE • Conduction of EVM in Sudan. • Introduction of Hib (Pentavalent) vaccine in Egypt.
Accessibility of affordable vaccines: gaps and WHO's role in supporting emerging manufacturers	SAGE suggested to monitor gaps and opportunities and consecutively develop a systematic process to responds to these needs in collaboration with keys partners. A perspective is to be presented at a future SAGE meeting on accessibility of affordable vaccines.	Pending	Nov 2010	Ongoing	WHO is actively contributing to increasing global access to vaccines through the following activities: 1) close collaboration (participation in annual meetings and bilateral meetings) with IFPMA and DCVMN as federations of manufacturers form developing and industrialized countries to ensure that they all have clarity on the needs of developing countries both in terms of types of vaccines but also in terms of their programmatic suitability; 2) Active participation in the annual DCVMN meeting to update them on new developments, concerns, and issues related to vaccine presentations, prequalification, regulation financing and priority country need. 3) WHO has resurrected and chaired the VPPAG (Vaccines Presentations and Packaging Advisory Committee) a forum for discussion between the public and private sectors on the characteristics of vaccines required for developing countries. The full participation of industry enables them to have more visibility of the needs and constraints of countries; 4) The DoV work stream on global access and vaccine price indicator which gets reported every years to the SAGE working group on the DoV. 5) General discussions on the process of technology transfers are taking place under the leadership of the Evidence Information and Research Cluster. 6) the Vaccine Product, Price and Procurement project (V3P) to support GAVI graduating and middle income countries through the provision of improved vaccine product and price information for decision-making. This 3-year project funded by the BMGF has conducted a number of assessments. It has also reviewed experiences on price information sharing mechanisms for medicines. The V3P database development is almost completed and should be live by the time of the April 2014 SAGE meeting. Capacity building activities are under development in close collaboration with partners to support countries and facilitate dialogue on price transparency and pricing policies.

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Childhood mortality	SAGE noted the recommendation by IVIR-AC that WHO would encourage countries to collect local data at country level and not only estimated age specific mortality rates by epidemiological modeling or expert elicitation.	Action	Nov 2010	Ongoing	All models reviewed by IVIR-AC are hampered by the lack of primary data, and more efforts should be made to make such data readily available. Specically, for pertussis disease burden estimation IVIR-AC suggests validating the parameter estimates against data from Senegal and Europe as a first step, although primary data from developing countries that is currently not publicly available would provide a more compelling comparator for validation. For polio more primary data should be made available for all models. IVIR-AC recommends that polio related data should be made available for multiple modeling groups to encourage comparison of results using different approaches.Ongoing/standing issue for many other diseases.
Cholera vaccines	Oral Cholera Vaccines(OCVs) - SAGE will further consider their use in endemic countries and whether a stockpile should be developed, particularly as current manufacturing capacity is limited.	Action	Apr 2011	Completed	OCV stockpile: A meeting on use of oral cholera vaccines (OCVs) in complex emergencies was held in early May 2011. Also in May 2011, the WHA passed a resolution (64.15) calling for an integrated, comprehensive strategy of cholera prevention and control. In April 2012, a meeting of the WHO Technical Working Group on creation of an oral cholera vaccine stockpile was convened by the Pandemic and Epidemic Diseases Dept (WHO HQ) to develop SOPs for implementation of the OCV stockpile for outbreak response, including definition of specific criteria for deployment of vaccine from the stockpile. An agreement for procurement of 2 million OCV doses for the stockpile was issued in June 2013 (with financial support from EU-ECHO, USAID, USFDA and three private entities). In Nov 2013, the GAVI Board approved a contribution towards a global OCV stockpile for the period 2014-2018 to increase OCV access in outbreak situations and endemic settings. OCV use in endemic countries: A meeting was held in Feb 2012 to review the experiences of the Zanzibar study on pre-emptive use of OCV (2006-2012) and the Zanzibar Government developed a proposal for island-wide use of OCV in risk groups with the aim to eliminate cholera and to scale up WASH interventions. OCV campaigns for outbreak control were implemented in 2012 in Haiti and Guinea Conakry with positive results in both.
Decade of vaccines/GVAP	SAGE requested consideration of the establishment of a SAGE standing working group to monitor GVAP implementation.	Action	Apr 2012	Completed	A SAGE DoV-GVAP standing working group has been established. The group met for their first face-to-face meeting from 9-11 September 2013 in Geneva. During this meeting the working group reviewed the indicators related to the GVAP strategic objectives. The group presented the first review of progress on the GVAP implementation at the November 2013 SAGE meeting and SAGE prepared the first progress report for the 2014 World Health Assembly. The GVAP working group met in February 2014 and will meet again in September 2014 to prepare for the next yearly review of progress to be presented at SAGE at its October 2014 meeting.
Decade of vaccines/GVAP	SAGE also recognized the urgency for having approximate cost and impact estimates and recommended that the technical group provide preliminary estimates for SAGE review in November 2013.	Action	Nov 2012	Ongoing	As part of GVAP resources invested in immunization will be tracked and monitored on a yearly basis throughout the decade, using the System of Health Accounts (SHA 2011) framework, the global standard to report spending in the health sector. The process to monitor resources invested in immunization will put emphasis on strengthening country capacity and creating a single platform for collecting, analyzing and reporting annually on all health expenditures, including those on priority diseases or programmes like immunization. This is intended to unify under a single platform other existing resource-tracking efforts, such as those being undertaken on national health accounts, and those for the Commission on Information and Accountability for Women's and Children's Health, and for the Global Fund to Fight AIDS, Tuberculosis and Malaria. This exercise will not only ensure regular and efficient reporting of good-quality data as part of the monitoring process, but also promote accountability and sustainability for immunization financing.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
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.	Action	Nov 2012	Ongoing	The SAGE report of progress with GVAP was presented to the WHO Executive Board on January 20, 2014. The concerns expressed by SAGE on lack of progress in some areas was noted by the EB. The EB Members also acknowledged the importance of data quality for monitoring programs and taking corrective actions. The WG met again in February 2014 where it specifically addressed the formulation of indicators that they found problematic in their review of progress and proposed reformulation.
Decade of vaccines/GVAP	IVR was encouraged to contribute actively to the research component of the DoV.	Action	Apr 2011	Ongoing	The Global Vaccines and Immunization Research Forum (GVIRF), to be held on 4-6 March 2014 in Bethesda, MD, will review and discuss progress on R&D and implementation research related to the GVAP. R&D indicators will be reported in 2014 and are being discussed at SAGE working group.
Dengue Vaccine	SAGE requested that future recommendations on dengue vaccine safety be linked to the dengue vaccine development strategy.	Action	Apr 2012	Ongoing	The dengue vaccine safety profile will be updated once an application for licensure has been filed.
Financing	SAGE identified the need to support countries that become ineligible and lower middle income countries through pooled procurement.	Action	Oct 2009	Ongoing	Various activities are conducted at global and regional level to support non GAVI and Lower Middle Income Countries (LMICs) - At global level: a study to enhance global knowledge and understanding of the challenges that Lower Middle Income Countries face as they explore potential adoption of new vaccines. The study was completed in March 2011. Finding and preliminary conclusions and recommendations were presented to the SAGE in November 2010. At regional level: EMRO is working with MICs in the region to set up a pooled procurement system with the support of UNICEF SD, CDC and PAHO and other partners. Identification of graduating countries and their potential constraints and issues is ongoing with GAVI and UNICEF to define measures and activities to overcome the obstacles and develop transition plans. 2 regional and 6 country assessment were conducted in 2012 on GAVI graduating countries. 4 country assessments and transition plans were conducted in 2013. Despite some progress, the challenges are enormous not only on the financial aspects but also on ownership, decision making, capacity, pricing, regulation and procurement aspects. The establishment of a pooled procurement in EMRO has been decided by the Regional Committee in 2012 and is under development despite the unstable political situation in the region. In November 2012, SAGE reviewed the situation faced by middle income countries including countries graduating from GAVI support and made strong recommendation calling for a global and coordinated effort to support MIC and for the establishment of a task force on Middle Income countries to advocate and support the implementation of the platform discussed at the November 2012 session on MIC. Terms of Reference were drafted, potential composition was identified, and contact with key partners was done to set up the SAGE recommended task force and working group. First teleconference to be held by 31 October 2013. The group was not convened as scheduled. Change in staff at HQ has resulted in delays in this area of work. The new staff has now started and we will regroup and revisit this area of work in the context of similar effoirts also being undertaken by GAVI and the Task Force for Global Health. An update on progress will be provided by June 2014.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Global vaccine safety Blueprint	The Blueprint implementation should be led by WHO and its partners. It should be aligned with other related WHO capacity-building efforts. This includes in particular immunization programme and national regulatory authorities strengthening together with the development of national expert advisory bodies. SAGE suggested that a mechanism be developed to enable prioritization of both activities and countries in the implementation of the Blueprint. SAGE invited the GAVI Alliance and other partners to support this implementation.	Action	Nov 2011	Ongoing	The Global Vaccine Safety Initiative has been launched and hosted its second annual meeting in November 2013. The portfolio of activities is now publicly available covering all 8 strategic objectives with priorities endorsed by the Planning Group.
HIV	SAGE requested regular updates on the progress of HIV-vaccine research.	Action	Apr 2010	Ongoing	In 2010/2011, with an objective of addressing ethical and regulatory challenges for follow up activities after the announcement of the Thai RV144 trial, which demonstrated for the first time a moderate (31.2%) level of efficacy in preventing HIV infection. Following SAGE recommendation on these aspects WHO/IVR/HVI and UNAIDS implemented the following 2 activities: 1. Development of a new ethics guidance point on ethical involvement of populations with high risk for HIV infection (i.e. people who injecting drugs) through extensive regional consultations. In 2013-14, the focus of work in this area is on "standards of prevention", i.e. the development of a framework that provides guidance on the non-vaccine preventive interventions, e.g. pre-exposure prophylaxis, to be provided during HIV vaccine trials. 2. In support of regulatory frameworks, WHO/IVR/HVI and UNAIDS have initiated a project on the development of a policy/discussion paper to facilitate national decision making with regard to the novel strategies for testing HIV vaccines; namely, most recently HIV vaccine trials in adolscents, adaptive trial design, etc. Currently, i.e. in Q1 2014, guidance on the future use of adenoviral vectors in HIV vaccine research. In October 2013, a written update was provided to SAGE on the progress of HIV-vaccine research, and the next update will be provided for the October 2014 SAGE meeting.
Hepatitis A	Long-term protection from single or 2-dose schedules should be regularly monitored by countries and reviewed by SAGE.	Action	Apr 2012	Ongoing	Post-market surveillance continues in Argentina and a detailed report on the recent epidemiological situation was provided to WHO in February 2014. There is still no identified breakthrough case among vaccinated children since the introduction of hepatitis A in the national immunization program in 2005. Hepatitis A cases have reached an all time low in 2013. Still occurring cases indicate that the risk persists in the population. As also requested by SAGE, an economic analysis of the impact of the single dose immunization strategy against hepatitis A in Argentina has been done. Estimated total vaccination cost for the 2006-2010 post vaccination period was ~US$ 45 million. The total of medical and societal costs plus immunization cost decreased from ~US$ 105 million for 2000-2004(prevaccination) down to ~US$ 56 million for the 2006-2010 post vaccination period i.e. a reduction rate of 46.5%. Both Colombia and Paraguay also introduced a single dose national immunization schedule for 1 year old children. Yearly review of the Argentina surveillance data will continue.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Hepatitis B	SAGE recommended that the timely delivery of a birth dose of hepatitis B vaccine (that is, within 24 hours of birth) should be used as a performance measure for all immunization programmes. Reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose.	Action	Apr 2009	Ongoing	A consultation on implementation of new universal birth dose recommendation was conducted in December 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. IPAC reviewed this work in early 2011 and again in April 2012, and endorsed 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 (Joint Reporting Form) and associated materials have been revised to improve reporting of birth dose with a particular focus in WPRO and now steps are being taken to make HepB birth dose a WHO/UNICEF "best estimate" in line with previous SAGE recommendations. 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 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 GIVS goals. In 2012, WPRO convened EPI and MCH managers from the five priority counties to jointly propose actions towards improving birth dose uptake.
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.	Action	Nov 2008	Ongoing	In 2012, WHO HQ has published a framework for global action to control viral hepatitis (http://www.who.int/csr/disease/hepatitis/Framework/en/index.html). EMRO is working with Member States to ensure achievement of the Regional Committee goal for HBsAg reduction in vaccinated children. During the 2013 WPR's Regional Committee Meeting, 2017 was set as the target year to achieve the goal of reducing childhood hepatitis B prevalence to <1%. SEARO has a drafted regional strategy. AFRO has convened a regional hepatitis TAG and plans to present a plan for comprehensive viral hepatitis control during the 2014 RC Meeting. EURO will consider a regional hepatitis B control goal. PAHO has resolved to eliminate hepatitis B virus transmission and is formulating a regional strategy. Documenting the Impact of Hepatitis B Immunization: best practices for conducting a serosurvey (WHO/IVB/11.08) has been published by the department of Immunization, Vaccines and Biologicals.
Hepatitis E	SAGE approved draft ToRs for a Working Group on Hepatitis E and requested that WHO establishes this group in the summer 2013.	Action	Apr 2013	Completed	The SAGE Hepatitis E working group has been established and started its proceedings by teleconference. The group will have a face to face meeting in the summer of 2014 and aim to report at SAGE in October 2014 or at the subsequent meeting.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Immunization safety	SAGE encourages development of simple technological solutions with improved environmental characteristics, and encourages donors to support such work as a priority.	Action	Nov 2007	Ongoing	- The WHO manual: Safe Management of Wastes from Health Care Activities second edition was published in 2013. http://apps.who.int/iris/bitstream/10665/85349/1/9789241548564_eng.pdf A series of 25 training modules for use in implementation of the manual and training health workers including waste handlers in the safe handling, treatment and disposal of health care waste has been completed. -Work is on-going through Project Optimize in collaboration with the Vaccine Packaging and Presentation Advisory Group to explore vaccine packaging that minimizes the impact on environment. VPPAG has 2 related streams of work: 1) Developing recommendations to minimize primary, secondary, and tertiary container packaging, and 2) Drafting a consensus statement with industry about use of materials for vaccine packaging that will minimize environmental impact. - A document on Environmental due diligence procedures has been developed and shared with GAVI. It expresses steps to be taken to minimize and manage waste from immunization activities in an environmentally friendly manner. The WHO reference document is: WHO policy paper on Health Care Waste Management(see http://www.who.int/water_sanitation_health/medicalwaste/hcwmpolicy/en/index.html) - The health care waste component of Global Environment Facility (GEF) project is developing a small autoclave in Tanzania to treat waste produced in low income countries. The technology is ready and was launched at the final GEF meeting in December 2012 in Tanzania and is planned for use in a new GEF-funded project together with UNDP beginning in 2014 in four African countries: Ghana, Madagascar, Tanzania and Zambia. Replication of the design for scale-up in southeast Asia is in planning stages. - The issue of needle-cutters and WHO recommendation about their use have been in debate for at least 6 years now during every SIGN meeting. At the 2010 SIGN meeting, there was a special session on needle cutters. A Bangladesh study on the safety of using needle removers was reviewed. The results showed that hub cutters do not lead to increased needle-stick injuries among HCWs. Based on the findings of this study, although there was no unanimity among the group, it was decided to state that WHO doesn't object (nor recommends) to the use of needle cutters, but their introduction should be associated with training HCWs on their use. An RCT on hub cutters has subsequently been completed in Ghana with WHO collaboration.
Immunization schedules	SAGE encouraged WHO to complete the project promptly. SAGE requested a critical appraisal of alternative schedules for pneumococcal conjugate vaccine, rotavirus vaccine and Hib vaccine in 2011.	Action	Nov 2010	Ongoing	PCV: evidence was reviewed by SAGE on November 2011. New recommendation on schedules was issued and data was used to update the position paper. 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 on the use of rotavirus vaccines was published in February 2013. Hib: No resources for model and/or ICEA. Evidence review is being completed; an ad hoc consultation was held in September 2012 and outcomes were proposed for SAGE consideration at the November 2012 meeting. During the discussion, SAGE members noted that the evidence on the number of primary doses and the need for booster doses requires further evaluation before recommendations can be made on optimizing the current schedule. The issue was revised during the April SAGE 2013 meeting. For all: review of number of contacts during first years of life (ongoing); cost of contacts (planned); update on actual age at vaccination data (completed and used in conjunction with rotavirus epidemiology). Completed for PCV, Rotavirus and Hib vaccines. Evidence on DTP, TT and Hep B will be presented to SAGE in October 2014

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Immunization supply chains	SAGE requested the following additional information: evidence and root-cause analyses of the EVM data, quantified evidence on invest ments needed to address the challenges (particularly on the relative expenditures on vaccine and cold chain equipment), information on the challenges in middle income countries; promising and innovative approaches (controlled temperature chain; supply chain integration; public-private partnerships in immunization supply chains), information on the GAVI end-to-end supply chain strategy and the role of the WHO-UNICEF immunization supply chain hub.	Action	Nov 2013	ongoing	A deeper analyses of the EVM data is ongoing and more insights on the root-causes of the EVM scores in countries will be presented in April together with an econometric analysis trying to understand whether there is a relationship between supply chain performance (as measured by the EVM) and immunization performance (as measured by coverage). The Secretariat is working on preparing for the SAGE Session in April. The content of the presentation will include promising and innovative approaches (controlled temperature chain; supply chain integration; public-private partnerships in immunization supply chains) and information on the GAVI end-to-end supply chain strategy and the role of the WHO-UNICEF immunization supply chain hub. At the moment it is unlikely that we will be able to analyse the situation in middle income countries given the paucity of date from this group of countries. Question to SAGE: on the quantified evidence on investments needed to address the challenges, would it be sufficient to present the estimates generated for the GVAP related to immunization supply chains?
Impact of the introduction of new vaccines on immunization and health systems	SAGE recommended that the ad-hoc working group work towards producing guidelines and tools for WHO to assist decision-makers and EPI managers contemplating the introduction of new vaccines, in order to take account of collateral effects inherent in introduction. The guidelines should provide a set of indicators that would enhance the potential positive effects, and reduce any potential negative effects, both on the immunization system and the health system. The guidelines should accommodate vaccines with different characteristics.	Action	Apr 2010	Ongoing	Further information was collected through a search of the published, unpublished and grey literature (such as post-introduction evaluation reports), as well as through key informant interviews. An in-depth study in 7 countries was conducted by LSHTM in 2011-12 to gather further information. Final results were presented in a meeting in London in November 2013. The ad-hoc group has updated the framework based on the data obtained and has drafted a guideline (Vaccine Introduction Guidelines – Adding a vaccine to national immunization programme) to assist country decision makers and EPI managers to take account of the potential effects/impacts of new vaccine introduction on the immunization and health systems. The 'Principles for adding a vaccine to a national immunization programme while strengthening the immunization and health systems' were endorsed by SAGE in April 2012 and form part of this guideline document, to be published in 2014.
Impact of the introduction of new vaccines on immunization and health systems	SAGE noted the importance of the ad hoc working group continuing to include a broad range of partner agencies, and encouraged to seek endorsement of this work at senior levels of partner agencies.	Action	Apr 2010	Ongoing	The ad hoc working group included a broad range of partner agencies (WHO, UNICEF, WB, CDC, PATH, JSI, LSHTM, JHU) and has sought endorsement of this work at senior levels of partner agencies. The revised Vaccine Introduction Guidelines, about to be published in 2014 as a result of the proceedings of the ad hoc working group, have been vetted by the partner agencies and endorsed by their senior personnel.
Implementation research	SAGE suggested that implementation research on vaccines should be linked with the WHO Implementation Research Platform.	Action	Nov 2013	ongoing	
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.	Action	Nov 2013	ongoing	This recommendation is now part of the new IVIR-AC agenda under research to minimize barriers and improve coverage of vaccines currently in use.

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Influenza	SAGE requested that WHO report on epidemiology and surveillance of H7N9 as well as on the development of a potential vaccine candidate.	Action	Apr 2013	Ongoing	1/03/2014-There is no sustained human to human transmission of H7N9. As of February 25, 368 cases have been confirmed with a minimum of 112 deaths occuring in two waves ((1) Feb-May 2013, (2) Oct. 2013 – present). WHO updated its recommendation for vaccine development in February 2014. The recommended strain, A/Anhui/1/2013-like, remains the same. An update was provided to SAGE during the 2nd preparatory teleconference in March 2014 and a discussion on H7N9 and the influenza WG will be added to the agenda for one of the breakfast meetings during the April 2014 SAGE meeting, depending on H7N9 progression.
Influenza	SAGE recommends WHO continue urgent development of H5N1 stockpile. Further SAGE noted that WHO needs, concurrently with the acquisition of a stockpile, to develop the operational guidelines that would govern the management and release of the stockpiled H5N1 influenza vaccine, and to define appropriate methods for monitoring its use and evaluating outcomes. SAGE further recommended a feasibility study on the management and use of the stockpile.	Action	Nov 2010	Ongoing	This project is being taken forward by the SAGE influenza working group for influenza vaccines and immunization. Discussions are ongoing and continued during the last 3 face to face meetings. During the 2nd meeting in February, 2011, the WG favored the option of keeping the stockpile mainly as a virtual stockpile with a small physical stockpile of filled and finished doses of H5N1 vaccine for rapid response and outbreak control in case of need. WHO should ensure that it has procedures in place to facilitate the deployment of pandemic vaccine to countries in need of support. Lessons learned from the deployment of the H1N1 pandemic vaccine in 2009 and 2010 are used to develop guidance and procedures for future vaccine deployment activities. Guidance document and associated work plans are available in all UN languages from: http://www.who.int/influenza_vaccines_plan/resources/deployment/en/index.html. WHO H5N1 stockpile is also being discussed in the Pandemic Influenza Preparedness (PIP) framework. The issue of the stockpile and the pre-pandemic use of H1N1 vaccine was reviewed by SAGE once more in Nov 2013. In view of the fact that (a) the PIP Framework secures access to pandemic vaccine production, (b) there is no significant change in A(H5N1) epidemiology, (c) there is a substantial risk of poor antigenic/strain match between the actual pandemic virus and stockpiled A(H5N1) vaccine and (d) the value of a stockpiled vaccine for containment of a nascent pandemic remains doubtful, SAGE recommended that WHO should not create a stockpile of A(H5N1) vaccine, but should ensure immediate access to pandemic vaccines under the PIP Framework. SAGE also highlighted the need for WHO (a) to ensure equitable access by low and middle-income countries and (b) to put in place a strategy for timely communication of any delays in vaccine availability in case of a pandemic. Regarding the question of inter-pandemic use of A(H5N1) vaccines (if and when available), SAGE agreed that (a) no clear change in the low level of risk to exposed populations has been observed, (b) no changes in populations at risk for highly pathogenic avian influenza (HPAI) H5N1 virus infection have been observed and (c) while risk remains low, even in exposed populations, certain high-risk groups may benefit from vaccination given the severity of the disease. Therefore, SAGE concluded that its previous recommendations on the use of A(H5N1) vaccine during inter-pandemic periods, mainly focusing vaccination of persons at high risk of A(H5N1) disease through occupational exposure, should remain unchanged.
Influenza	SAGE recommended that the Influenza Vaccines and Immunization Working Group develop a research agenda.	Action	Nov 2010	Ongoing	Elements of an influenza research agenda were identified by the SAGE working group on influenza and a consultation on clinical trials of new influenza vaccines was done in 2013. Together with a consultation planned to be held in May 2014, a more formal influenza research agenda will be developed jointly with the global influenza programme of WHO.
Integration of vaccine services	SAGE requested a session during the April 2014 meeting on integrated approaches in immunization and other healthcare programs.	Action	Nov 2013	ongoing	A session on integrated approaches in immunization and other healthcare programs was added to the agenda of the upcoming SAGE meeting in April 2014.
Japanese encephalitis	Interference with the immune response to other vaccinations, number of doses required and the duration of protection need to be assessed.	Action	Apr 2006	Ongoing	WHO secretariat is currently reviewing existing evidence (one new publication on the subject) in context of the SAGE JE working group.

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Japanese encephalitis	Commercial kits for detection of JE-specific IgM should be compared and validated.	Action	Apr 2006	Ongoing	Assessment using serum was carried out by PATH and published Am J Trop Med Hyg July 07. Field validation of serum and CSF in India and Bangladesh was assessed in a joint WHO/CDC meeting, SEARO, February 2008. Nepal and Cambodia field evaluation of JE assays is complete and paper has been submitted to JID. Assessment of kits using CSFs accepted for publication in Am J Trop Med Hyg. CDC Fort Collins will distribute the 3rd serum and CSF proficiency test panel to evaluate in-house and commercial JE ELISA assays to WPRO JE labs 4ht quarter 2012. The three WPR JE regional reference labs (Japan, China and Republic of Korea) held their annual coordination meeting in Chengdu, China in the 2nd quarter 2012. China CDC JE regional reference Lab was fully accredited by WPR and HQ Lab Coordinators, August 2012. A WPR JE labnet meeting took place on 15 March 2013 and a Regional JE workshop for WPR is planned the week of 17 June in Seoul. Submission for publication of a paper summarizing the development of the JE LabNet is pending. The Regional Reference Laboratory for JE in the Western Pacific Region at the Victorian Infectious Diseases Reference Laboratory, Melbourne, has been fully accredited in Oct 2013. The Global Specialized Reference Laboratory for JE at the National Institute of Infectious Diseases, Tokyo, has also been fully accredited in Oct 2013. The diagnostic assay produced by PanBio ceased production at the end of 2013. An alternative assay produced by InBios with similar performance will be used in the WHO laboratory network. The training workshop at the Korean CDC in June was intended to introduce the network to this kit.
Japanese encephalitis	SAGE looked forward to better assessment of the disease burden and identification of target populations for immunization and to reviewing the regional JE control goal currently under development and the activities to achieve this goal.	Action	Nov 2008	Ongoing	WHO is reviewing evidences in context of the SAGE working group on JE.

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Lower middle-income countries: sustainable adoption and financing for new vaccines	SAGE requested that WHO facilitate the establishment of a partnership among all relevant stakeholders to consider: pooled procurement; tiered pricing; greater transparency of pricing; and exploring the role that UNICEF, the Pan American Health Organization and foundations can have in assisting these countries with procuring and financing vaccines.	Action	Nov 2010	Ongoing	Establishing a partnership among all relevant stakeholders to support middle income countries is our aim and has been clearly recommended by SAGE in 2011 and 2012. WHO has already started consulting with agencies towards projects and initiatives to explore possibilities to collaborate and support middle income countries with procuring and financing vaccines and immunizations. This is the case with UNICEF, PAHO, SIVAC, OPTIMIZE, PROVAC and others. We have also consulted with the Bill and Melinda Gates Foundation (BMGF) on their concerns and plans. They showed a great interest and are trying to identify the best approaches to support this objective. We have organized in January 2011 a successful brainstorming meeting on vaccine price and vaccine pricing focusing on issues faced by GAVI-graduating and middle income countries. A proposal was submitted and is now funded by the BMGF on vaccine product, price, and procurement (V3P project). This is a 3-year project aiming to identify, develop, and establish the most appropriate and comprehensive method(s), mechanism(s) and/or tools to provide countries with accurate, reliable, and useful data on vaccine product, price and procurement. This project has completed phase one (assessment of country needs and lessons learnt from other health sector) and is now starting phase two (V3P tool development and roll out, testing with countries and capacity building activities). In parallel, we have raised the LMIC issue within the Decade of Vaccines collaboration, it has been considered as one the priority of the decade of vaccines and is now reflected in the Global Vaccine Action Plan.(GVAP). Multiple consultations took place on GAVI graduating and middle-income countries activities and issues. The results of this consultative process were presented at the November 2012 SAGE meeting. SAGE appreciated the efforts made by WHO, UNICEF and GAVI and other partners to extend discussions about vaccine supply and pricing to MICs where appropriate, and the adaptation of some activities to suit MIC-specific needs. However, SAGE noted with concern that these efforts are fragmented and are failing to optimize synergies in the work being undertaken by each agency. SAGE noted that with a modest investment in technical assistance and capacity building could be significantly strengthened. SAGE requested that this issue and achievements be revisited in a subsequent meeting and that a task force is establish by WHO to coordinate policies and efforts of partners. At regional level, EMRO is working to launch, by the end of 2013, the EMR Initiative on pooled procurement, and to contribute to the UNICEF SD initiative on MIC and new vaccines. The political and general situation in Middle-East might delay concrete actions in that domain. This question was discussed during the 2013 EMRO regional Committee meeting.
Malaria	SAGE noted the utility of 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.	Action	Apr 2013	Ongoing	Development of malaria vaccine Preferred Product Characteristics is underway and scheduled for finalization by end 2014. A pre-final version will be sent to SAGE for comments in July 2014. A workshop was being held on the concept of WHO Preferred Product Characteristics at the Global Vaccine & Immunization Research Forum in March 2014.

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Malaria	SAGE requested that it be kept informed of developments in the ongoing multi-country Phase 3 trial and indicated that further discussion on the optimal schedule for a malaria vaccine will need to occur.	Action	Oct 2009	Ongoing	The timing for the "Decision" session depends on the outcome of the regulatory process. The European Medicines Agency is expected to make a regulatory decision in June 2015. If those timelines remain unchanged, a SAGE/MPAC (Malaria Policy Advisory Committee) joint session is expected in Oct 2015. The third set of results from the Phase 3 trial of RTS,S/AS01 was made publicly available on 8 Oct 2013. These results include site-specific efficacy and 18 month follow-up in both the 5-17 month age group and 6-14 week age group. In Jan 2014, SAGE members received the JTEG meeting report summarising these most recent results. Depending on the booster dose results, expected by Sep 2014, JTEG may propose recommendations for use in the 5-17 month age range. It is considered unlikely that JTEG will propose recommendations for use in the 6-14 week age range given the results to date, unless booster dose results in this age group give higher efficacy than after the primary immunization series. Any recommendation for use in the 5-17 month age range would require at least 2 new immunization visits. One possible schedule is 6 months (with vitamin A), 7-8 months (new visit) and 9 months (with measles first dose). JTEG considered that the data on co-administration with measles first dose is acceptable. Further exploration of possible schedules is underway. The first wave of 5 African national regulatory submissions will be to Kenya, Tanzania, Ghana, Senegal and Burkina Faso, where Phase 4 studies of safety and effectiveness are planned.
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.	Action	Nov 2013	ongoing	Secretariat is working with a public heath/regulatory consultant on an options paper that will be available at the time of the April SAGE meeting. Recommendations from that work will also be considered in the implementation of the influenza maternal immunization project, that begun Januray 2014.
Non-specific effects of vaccines	SAGE supported the two proposed literature reviews that include documentation of the current and proposed studies in the field. SAGE insisted that the reviewers should make efforted to include all available evidence and access all relevant data sets.	Action	Apr 2013	Ongoing	Working group constituted and functional. The results of the two systematic reviews were presented to the working group during their face-to-face meeting in January and will be presented to SAGE in April 2014.
Optimizing immunization schedules	SAGE recommended that WHO provide support to country-level policy-makers on the rational use of analyses generated by the tool.	Action	Nov 2010	Completed	We have approached SIVAC to collaborate in one African country as a case study (initially Cote d'Ivoire now considering Mozambique). After consulation with AFRO colleagues and, bearing in mind that the NITAGs have been only recently constituted, this activity has been postponed and no new date has been set yet. A draft of the website tool was presented to NUVI meeting participants in June 2013. It was well received and appreciated. The tool will be finalized once the systematic review of evidence on the remaining vaccines is completed and presented to SAGE.

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Pertussis control	SAGE endorsed the establishment of a pertussis-vaccine strain repository and a database on the genealogy and characteristics of different vaccine strains. A proposal should be presented to the Expert Committee on Biological Standardization.	Action	Apr 2010	Closed	The initial offer of the pertussis strains made by Dr. Nicole Guiso from the Institut Pasteur was not presented to the ECBS in 2010 due to the lack of information regarding the use of the strains and the related data. Discussions took place within the Institut Pasteur and their legal department advised that as strains had been received under specific contract from the vaccine manufacturers they could not be shared. However, they provided a list of strains received so that WHO can request permission directly from the vaccine manufacturers themselves for the strains to be used as needed for research purposes and for the genetic filiation of the strains to be publicly released.
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.	Action	Apr 2013	Ongoing	The GPEI has constituted a Legacy Working Group (LWG), currently comprised of representatives from the spearheading partners (Rotary, WHO, CDC and UNICEF) and the Bill and Melinda Gates Foundation to take forward the legacy planning work. The LWG is finalizing its workplan. One of the major activities within the workplan will be to hold broad consultations with relevant stakeholders to document the lessons learnt and knowledge of the programme, to guide the direction of the legacy work, and to establish what benefit the lessons and resources of the GPEI could be to other initiatives. These consultations will begin in early 2014 and continue through the rest of the year. The consultation will include plans for soliciting contributions from communities and front-line health workers' on their experiences of polio eradication.
Polio	Sufficient capacity should be established at the global level to provide technical and programmatic support to countries to plan and implement all activities associated with OPV2 withdrawal and introduction of IPV.	Action	Apr 2013	Ongoing	The Immunization Systems management group, co-chaired by WHO and UNICEF, has been established to coordinate efforts towards the activities relating of OPV2 withdrawal and IPV introduction. The multi partner group has been operating since mid-April 2013 in five areas of work : Regulatory, vaccine implementation, communication, financing and routine immunization strengthening. The time investment dedicated by the staff of the six agencies engaged in the IMG (CDC, WHO, UNICEF, BMGF, Rotary and GAVI) since April 2013 has been impressive. WHO/EPI has filled an additional 3 professional staff positions at HQ to contribute to this effort. UNICEF HQ has filled one additional position. Similar positions will also be supported at Regional levels. These have yet to be filled.
Polio	SAGE encouraged a technical briefing on key OPV2 withdrawal issues at the WHA 2014, in advance of a potential WHA resolution in 2015 on a target date for the withdrawal of OPV2 from all routine immunization programmes globally.	Action	Apr 2013	Ongoing	A side-event on the IPV introduction and OPV2 withdrawal is being planned during the WHA in 2014.
Polio	SAGE recommended working closely with countries on activities towards OPV2 withdrawal.	Action	Apr 2013	Ongoing	A joint letter to all OPV only using countries was sent by the WHO DG and UNICEF ED, and the GAVI CEO where applicable, highlighting the importance of IPV introduction and outlining the SAGE recommendation on IPV introduction schedules and planning timelines. At the same time all WHO and UNICEF regional Offices have advanced in this area, with IPV being discussed at key meetings in all regions in Q4/2013 and Q1/2014. Further briefings to countries are planned at EPI manager meetings and regional working group meetings in February and March. Joint WHO/UNICEF regional coordination mechanisms are being established to ensure countries are suitably supported in the decision making process and in the development and implementation of introduction plans.

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Polio eradication	SAGE recommended that tight deadlines should be set for the completion of each step required to implement the switch from tOPV to bOPV. Similarly, urgent plans must be in place for the development of a low-cost IPV, and for its introduction by countries which choose to adopt this strategy. For countries planning to introduce IPV, including the low-cost IPV option, similar planning must take place.	Action	Apr 2012	Completed	Discussions among the GPEI partners, and activities of the SAGE Polio Working Group have continued since the November 2012 SAGE meeting to further refine the definition and timeline for the programme of work on the six main pre-requisites that need to be in place before the withdrawal of OPV2 (i.e. replacement of tOPV by bOPV for routine immunization) can be considered. As requested by SAGE, the considerably expanded work-streams on the OPV2 withdrawal pre-requisites - including lab containment of polioviruses, introduction and uptake of affordable IPV, IPV and bOPV product development and licensing, and MOPV2 stockpile and outbreak response, and anticipated time-lines within the polio endgame - were presented at the April 2013 SAGE meeting.
Polio eradication	SAGE requested that the Polio working group draft the necessary protocols for the 5 major components of the proposed strategy for type 2 virus detection and response after OPV2 cessation, in the areas of virus notification, surveillance, vaccine stockpiles, response and management of travellers for presentation to the SAGE in 2014.	Action	Nov 2013	ongoing	It is ongoing in collaboration with HSE cluster. It is planned to be submitted for SAGE October 2014 for review.
Polio eradication	"To facilitate prioritization, planning and implementation of IPV introduction at country level, SAGE recommended that consideration be given to developing a resolution on accelerated IPV introduction for submission to the World Health Assembly (WHA) in 2014."	Action	Nov 2013	ongoing	It is planned to be proposed and discussed during the WHA 2014.
Polio eradication	SAGE encouraged WHO to specifically assess how existing international mechanisms could be used to strengthen and implement vaccination recommendations for travellers entering and leaving polio-infected countries and areas and, for areas of uncontrolled transmission, to consider travel advisories.	Action	Nov 2011	Ongoing	This topic was extensively discussed during the SAGE polio WG meeting in February 2014, and will be subsequently presented to SAGE in April 2014.
Polio eradication	Update SAGE Polio Vaccine position paper, including recommendations from the November 2013 SAGE meeting on the introduction of at least one dose of IPV in national schedules.	Action	Nov 2013	ongoing	The updated polio position paper including the recommendations from the November 2013 SAGE meeting was published in the WER on the 28th of February 2014 (http://www.who.int/wer/2014/wer8909.pdf).
Polio eradication	SAGE requested that WHO/GPEI draft a 'GPEI Strategic Plan/Budget for 2013-2018' by November 2012 that incorporates OPV2 cessation and eventual bOPV cessation, with different scenarios for the timing of IPV introduction for the period of the tOPV/bOPV switch and longer term IPV uptake following complete OPV cessation.	Action	Apr 2012	Completed	Following this request from SAGE and a similar recommendation from the GPEIs Independent Monitoring Board (IMB), a Strategic Plan for the Polio Endgame and Legacy Options 2014 to 2018 has been drafted. This document was developed in close consultation with GPEI spearheading partners and other initiatives (i.e. GAVI), as well as with WHO Regional Offices; the SAGE Polio Working Group also reviewed the draft and provided comments. The document has three main sections: a) the endgame strategic plan, including the eradication of polio and management of associated risk, b) the financial requirements 2014 to 2018 (i.e. a 2014 to 2018 indicative budget), and c)the legacy, i.e. to define the broader global health benefits of the global polio programme. In November 2012, SAGE welcomed the long-term vision of the draft GPEI Polio Eradication and Endgame Plan, 2014-2018 and endorsed the 4 major components.

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Reports from other advisory committees	SAGE recommended appointment of appropriate programmatic and implementation expertise to IVIR-AC membership including representation of experts from low and middle-income countries.	Action	Nov 2011	Ongoing	Since 2013 IVIR-AC includes two programmatic and implementation research members from AFR and SEAR. Recruitment of new IVIR members is ongoing in 2014 to replace members who will rotate off and to fill existing vacant positions. Call for nomination will be posted soon for economists, mathematical modelers, social scientists, epidemiologists and an EPI manager (rotating membership).
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.	Action	Nov 2006	Pending	A comprehensive review of the work of the ECBS is still pending. The review will include (but not be restricted to) consideration of communication of ECBS outcomes. This will be linked with an overriding review of Expert Committees by the department of Essential Medicines and Health Products. SAGE will be invited to participate as soon as the review is terminated.
Security of vaccine supply	SAGE requested WHO to produce a report on the security of the supply of affordable vaccines and encouraged donors to invest in the development of new vaccine technologies that facilitate the delivery of effective, affordable vaccines to populations most at risk.	Action	Apr 2012	Ongoing	Discussion with donors has advanced well and planning for meeting on new vaccine technologies being initiated. Internal WHO discussions are in progress. Meeting on new vaccine technologies held in February 2014. The work on the supply of affordable vaccine is an on-going effort in which all immunization partners are engaged. Affordability of vaccine remains an on going challenge for a number of countries however recent accomplishments in the area of IPV supply and financing are a good indication that the trend is evolving positively through strong partnership between the public and the private sectors. Given the amount of work going on in this area under several other initiatives includign those reflected under item "Financing", we have discussed internally and have decided that, for the time being the production of a report was not warranted. SAGE will be kept informed on an on-going basis of propgress made and new developments .
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.	Action	Nov 2013	ongoing	Negotiations have already started. An operational framework for vaccine donation has been developed with USA and Germany. A working group of GHSI is going to meet 17-18 March, 2014 to finalize the legal aspects of the framework. WHO and Japan are also working on material transfer agreement. WHO and France have sent an official letter to donate vaccine.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Surveillance	SAGE endorsed the recommendations of the ad hoc TAG for improving the quality of the IB-VPD surveillance network and urged that the objectives of this network be more clearly defined, that collaboration with other surveillance systems and laboratory networks (i.e. the polio/measles laboratory networks) be continued, and that, where feasible, activities be linked with other programmes enhancing country capacity, including implementation of the International Health Regulations. SAGE urged greater attention to integration of data systems, which would facilitate real-time analysis and performance monitoring. SAGE also noted the opportunities for integration by building upon the enhanced capacity developed by these networks to conduct surveillance for other diseases using a similar case-definition and personnel trained in applying and adhering to rigorous surveillance protocols. Both networks should continue to share experiences with the polio surveillance network. Integration efforts must be strategically designed in ways that are logical and synergistic.	Action	Nov 2013	ongoing	During 2013, a strategic review of the invasive bacterial vaccine preventable diseases (IB-VPD) and rotavirus surveillance networks was undertaken by WHO and its informal Technical Advisory Group for new vaccines surveillance and presented to SAGE in November 2013. WHO is now developing a sentinel surveillance management framework to prioritize and guide actions to implement all SAGE recommendations from the 2013 meeting. Actions already implemented related to data include: development of an agreed IB-VPD variable list for sentinel sites and Regional Reference Laboratories; development of a draft rotavirus list for sites and an agreed list for rotavirus Regional Reference Laboratories; agreement to share case-based sentinel site data throughout the network and to increase data reporting frequency to a quarterly basis for sentinel sites and to twice yearly for IB-VPD RRL data; discussion with AMRO & SEARO countries regarding web-based data reporting with realtime data entry, verification and analysis; initial steps taken to pilot such a web-based data system in one to two AMRO countries, with additional discussions in SEARO and with WPRO regarding lessons learned from their new web system that will be launched in 2014. To better integrate with other VPD surveillance networks, the sentinel site surveillance laboratory coordinator will continue to have monthly meetings with the polio and measles laboratory coordinators.
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.	Action	Nov 2011	Ongoing	Written update to SAGE was provided ahead of the November 2013 SAGE meeting. In December 2012, the first consultation of the TB TEG was held to review clinical trial plans for two advanced new TB vaccine candidates, VPM1002 (VPM, Germany) and M72 (GSK Biom, Belgium). Another meeting is planned for Q3 with the remianing (advanced) developers of new TB vaccines, and a report will be provided to SAGE together with the 2014 annual update on TB vaccines, in Oct. 2014.
Typhoid	Need for advocacy and prioritization at international level. To include prioritizing WHO's prequalification for new-generation typhoid vaccines and the need for international financing mechanisms.	Action	Nov 2007	Ongoing	As previously reported to SAGE, the first (and to date the only) typhoid polysaccharide vaccine was prequalified in June 2011. However Vi polysaccharide vaccine uptake has remained low for multiple reasons, including lack of funding. In November 2011, the GAVI Board re stated its 2008 commitment to fund typhoid conjugate vaccines in the GAVI Vaccine Investment Strategy; it is expected that a typhoid vaccine support window will be opened when a WHO prequalified vaccine is available. Currently, 2 typhoid conjugate vaccines have been licensed by NRAs, one vaccine is undergoing review for national licensure, and several others are in clinical trials. A first application to WHO for pre-qualification is expected in late 2014. WHO guidelines on the quality, safety and efficacy of typhoid conjugate vaccines were approved by the ECBS in Oct 2013 and published. WHO/IVB is planning an expert meeting in 2014 to review the availability of clinical data to inform the future SAGE policy process. An initial 3-year grant (2011-2013) from the Bill and Melinda Gates to the Coalition against Typhoid (CaT) and Sabin Vaccine Institute was renewed for an additional two years to support typhoid control and prevention activities, including immunization. The International Conference on Typhoid Fever and Other Invasive Salmonelloses held 1-2 March 2013 in Dhaka served as testament to increased advocacy and prioritization efforts.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Un/under-immunized children	SAGE requested that WHO quickly roll out tools so that other countries can address low coverage of vaccination.	Action	Nov 2010	Ongoing	A set of one diagnostic tool and 6 in-depth tools had been envisaged. The basic tool (diagnostic tool) has been developed at HQ. The EURO, AMRO/PAHO and AFRO regional offices and HQ of WHO; UNICEF; and MCHIP are working on developing the 6 in-depth tools to address different facets of the problem. The in-depth tool "A Guide to Tailoring Immunization Programmes (TIP) has already been developed by WHO-EURO and is available at http://www.euro.who.int/__data/assets/pdf_file/0003/187347/The-Guide-to-Tailoring-Immunization-Programmes-TIP.pdf
Vaccination in humanitarian emergencies	SAGE also suggested that the framework approach to vaccine decision-making could be considered for other health interventions in emergencies.	Action	Apr 2012	Ongoing	Due to lack of staff and three Level 3 emergencies in 3 months, The Emergency Risk Management and Humanitarian Response (ERM) Department lacked the capacities to complete this task. The relevance and applicability of this recommendation will be reviewed in the coming months, once the demands on ERM staff for field deployments to assist in emergencies have settled down.
Vaccine Hesitancy	SAGE suggested that the definition include “when uptake of a vaccine or immunization programme in a community is lower than would be expected in the context of information given and services available”.	Action	Apr 2013	Completed	The Working Group reworded the definition of vaccine hesitancy taking into account the proposed wording by SAGE: "Vaccine hesitancy is an emerging term in the discourse on determinants of vaccine acceptance where uptake of a vaccine or immunization program in a community is lower than would be expected in the context of information given and services available. Vaccine hesitancy recognizes that issues of complacency, convenience and/ or confidence in vaccine(s) or immunization programs may all contribute to the delay or refusal of one, some or almost all vaccines. These factors which influence vaccine acceptance vary by setting and responses need to be locally assessed." During the face to face meeting in December 2013, the working group revisited the definition to shorten and make it more comprehensive. The wording of new definition is: "Vaccine hesitancy refers to delay in acceptance or refusal of vaccines despite availability of vaccine services. Vaccine hesitancy is complex and context specific varying across time, place, and vaccines. It includes factors such as complacency, convenience, and confidence."
Vaccine Hesitancy	SAGE recommended close linkages and interaction with key WHO and UNICEF initiatives to address the unvaccinated or under-vaccinated groups and relevant interventions.	Action	Apr 2013	Ongoing	Close collaboration with partners, initiatives, and key stakeholders in the field of vaccine hesitancy is sought. During the Working Group's monthly teleconferences, partners are invited to present their work (e.g. UNICEF on their polio-related work) and link with the Working Group directly. In addition, WHO colleagues from other departments such as Communications and the Vaccine Safety and Vigilance Team, as well as UNICEF staff, were attending the 3rd face-to-face meeting of the Working Group in December 2013.
Vaccine Supply	It was noted that SAGE needs to address the constraint experienced across Regions of repetitive shortfalls in vaccine supply, both for existing vaccination programmes (in particular for DTP-containing vaccines) as well as for new/emerging vaccines, and the impact on vaccine coverage in several countries.	Action	Nov 2012	Ongoing	Discussions have been initiated with UNICEF Supplies Division, and UNICEF Programme Division to work on global vaccine supply issues. A meeting was held in Copenhagen on 28 September 2013 to review the supply of traditional vaccines. Both DTP vaccine and to a lesser extent mono-HepB vaccine are increasingly of limited supply. Further intelligence is needed on countries plans to start DTP booster doses and Hep B birth doses, both of which require the vaccines without further combination.

Topic	Recommendations/Action item	Category	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.	Action	Nov 2011	Ongoing	As the Bill & Melinda Gates Foundation is now accepting Letters of Inquiry for the development of an easy-to-use tool that rapidly assesses the immune status of children against select vaccine-preventable diseases. Inquiries will be welcome that focus on prototype development and detail plans for future commercialization possibilities.
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.	Action	Nov 2011	Ongoing	To improve the precision and usefulness of survey results and to reduce the cost of surveys, SIG proposes to explore 1) recent advances in sampling methodology, 2) new technologies for constructing sampling frames, supervision of field work, data collection, and analysis and 3) alternative content, collection, analysis, presentation and linkages with other data sources. An explicit description of precision, usefulness and cost of various trade-offs between alternative methods will constitute part of the exploration. An initial meeting was convened of the IVB Informal Advisor Group on Monitoring Immunization Programme Performance through Household and Community Surveys. First meeting addressed the need to modify Demographic and Health Surveys (DHS) - implemented by ICF International; the UNICEF Multiple Indicator Cluster Surveys and the WHO Immunization Cluster Survey to accommodate changes in immunization system strategies. On 17-18 September 2012 a meeting was held with representatives of ICF and UNICEF to discuss modifications to their standard recommendations on data collection, analysis and presentation of immunization coverage data. WHO and UNICEF will provide written recommendation to these agencies. An informal working group has been created to review and revise WHO guidance on measuring immunization coverage through household and community surveys. The working group met in July 2013 to agree on the scope of work, to identify initial products, and establish a plan of document production, review, pilot testing, and clearance. Guideline drafting has been begun and a working group meeting to finalize a draft for external review is scheduled for March 2014. Regional offices have been contacted for suggestions regarding potential countries for pilot testing. A protocol for pilot test is being developed and a consultant has been identified to coordinate test.
Vaccine coverage	WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage.	Action	Nov 2011	Ongoing	WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage. A draft document which reviews, for a selected list of vaccine-preventable diseases, laboratory test available and associated requirements for specimen collection/transport, personal experience and training, and laboratory supplies and equipment has been prepared. The draft will be reviewed internally and following recommended changes will be submitted for review by external experts. For each selected disease study populations, sampling methods, data/specimen collection, laboratory/statistical analysis, and implications of results were summarized in an accompanying document. Work in progress was presented to WHO and UNICEF Regional Focal Points for immunization during the Meeting on Monitoring National Immunization Systems, 9-11 October 2012 for their comments. Internal and external review of the document will continue and after incorporating the comments draft guidelines will be developed for use of sero-surveillance as an evaluation tool for immunization programmes.
Vaccine safety	SAGE highlighted the urgent need for a safety review of other important vaccines that could be used during pregnancy.	Action	Nov 2012	Ongoing	A sub-group of GACVS has been launched to address vaccine safety during pregnancy. A finalized version of the GACVS report on safety of immunization during pregnacy was published and has been made available to SAGE in November 2013. Publication of the report is to be expected in the first half of 2014. A more systematic review has been piloted for Rubella and is expected to become available in summer 2014.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Vaccines during humanitarian emergencies will be discussed at a forthcoming SAGE meeting.	The use of vaccines during humanitarian emergencies will be discussed at a forthcoming SAGE meeting.	Action	Nov 2010	Completed	A SAGE Working Group on vaccination in humanitarian emergencies was established in June 2011. Multiple teleconferences were held and two face-to-face meeting of the working group took place on 20-21 September 2011 and on 16-17 February 2012. The group reported to SAGE in April and November 2012. In November 2012, SAGE endorsed the complete framework for decision making on the use of vaccinations in humanitarian emergencies as a major step forward and considers that it fills an existing gap but acknowledged that the framework focuses on vaccination, which is only one priority consideration in humanitarian emergencies. SAGE strongly affirmed the potential utility of this framework and recommended pilot testing in the field. The working group was asked to adapt the document to take into consideration SAGE's comments and proceeds with its finalization. The working group has since then finalized the framework which following final editing has been published and is available on the web at http://www.who.int/iris/bitstream/10665/92462/1/WHO_IVB_13.07_eng.pdf. More efforts need to be made to disseminate the framework to partners and to evaluate its usefulness and update as necessary down the road.
Yellow Fever	SAGE requested WHO to revisit the IHR provisions relating to the period of validity for international certificates for vaccination against YF.	Action	Apr 2013	Ongoing	A proposed revision to the relevant provisions in the International Health Regulations (2005) (IHR) was endorsed by the WHO Executive Board in January 2014, and recommended for adoption to the World Health Assembly (WHA) which meets in May; any revision to the IHR must be adopted by the WHA, followed by an extended period prior to which the revised provisions enter into force for the 196 States Parties to the IHR (including all WHO Member States).

WHO/AFRO TASK FORCE ON IMMUNIZATION BRIEFING

SUMMARY REPORT

SANDTON, JOHANNESBURG, SOUTH AFRICA
02 TO 04 DECEMBER 2013

Background

In 2012, the World Health Assembly adopted the 2011-2020 Global Vaccine Action Plan (GVAP) which was thereafter discussed at the 65th WHO Regional Committee for Africa, which took place in Brazzaville, Congo, in September 2013. Effective 2014, all 47 countries that comprise the WHO African Region are required to report every year to the Regional Committee on lessons learnt, progress made, remaining challenges and updated actions to attain national immunization targets. This will require due diligence and dedication from all stakeholders across all sectors within the African context.

In light of the above, the WHO Regional Director for Africa reconstituted the Task Force on Immunization (TFI) earlier this year, to primarily advise his office on the adequacy of the regional immunization strategic plan and corresponding priority activities to achieve the GVAP goals as well as take into consideration the comparative advantages and the respective roles of partner organizations. Moreover, the Regional Director requested the newly reconstituted TFI to regularly advise his office on the adequacy of regional progress as well as highlight major risks/challenges that need to be addressed and propose recommendations to achieve GVAP goals within the WHO African Region.

Noting that 14 of the 18 TFI members are newly nominated, and taking into consideration that the mandate of TFI is not restricted to childhood vaccines and immunization but extends to the control of all vaccine-preventable diseases in the context of health systems strengthening, an in-depth TFI members' briefing/meeting convened at the Protea-Balalaika Hotel, Sandton, Johannesburg, South Africa, from 02 to 04 December 2013. The 3-day event concentrated on:

- Briefing TFI members on the work of WHO in general and its on-going reform;
- Apprising TFI members on WHO's regional priorities in the field of immunization;
- Agreeing upon *modus operandi* for TFI over the coming 3-year period; and
- Obtaining orientation from TFI members on: the development of the *regional strategic plan for immunization 2014-2020*; preparations for the immunization

ministerial conference, scheduled to take place in Ethiopia in June 2014; and setting the agenda and dates for TFI meetings in 2014.

Session 1 – Introduction

The meeting was opened by Dr Deo Nshimirimana, Director of the WHO/AFRO Immunization, Vaccines & Emergencies (IVE) Cluster, who welcomed participants to South Africa on behalf of the WHO Regional Director for Africa. The IVE Director thanked all 18 TFI members for accepting invitation to serve on the African TFI - 14 members for an initial period of 3-years and 4 members to serve for a second 3-year term. He also informed participants that the WHO Regional Director for Africa had nominated Professor Helen Rees to chair TFI.

The IVE Director then informed participants that an external evaluation was conducted earlier this summer on the 2009-2013 regional immunization strategic plan as a preparatory step towards the formulation of the next regional immunization strategic plan which would run from 2014 to 2020. This new regional strategic plan would give the region the opportunity to harmonize all stakeholders' strategic approaches to immunization which should align with GVAP. The IVE Director briefed participants that the overall conclusion of the external evaluation was that the African immunization programme had witnessed progress - from a virtual absence of routine infant immunization four decades ago to the current state of public awareness of the benefits of vaccine, the building of a competent workforce to procure, transport, store and administer these vaccines, and the production and dissemination of data revealing progress achieved and pitfalls encountered. Nevertheless, the external evaluation team noted a paradox - the routine coverage of each annual birth cohort has not increased significantly beyond the level of 80%, a level at which it seems to have stalled over the past two to three years. Moreover, inequities in the use of immunization was also highlighted in the external evaluation report with evidence within countries where the *Reaching Every District* strategy is in force, has not been sufficient to give every child an equal chance of accessing immunization.

The IVE Director then highlighted that the external evaluation team found that regional progress was made towards polio eradication and measles elimination targets, the introduction of the conjugate Men.A vaccine in the African meningitis belt, introduction of pneumococcal and rotavirus vaccines in the national routine immunization schedule, launching of the HPV demonstration projects. However, the evaluation report highlighted that gaps/systemic weaknesses prevail in the areas of: national ownership, data quality, knowledge transfer, communication strategies, integration of immunization with other primary health care components, human resources for immunization service delivery, and

procurement + supply chain management. The IVE Director highlighted that the external evaluation team made sound recommendations that will require innovative ways to achieve results and that TFI members will play a crucial role in supporting the region achieve results.

The newly nominated TFI Chair, Professor Helen Rees, then took the floor to welcome participants to Sandton, Johannesburg, South Africa. She underlined the unique role WHO plays in public health as the only organization who has the UN mandate to provide global guidance. The TFI Chair reminded members that in their advisory capacity to WHO, TFI can make a profound difference to achieving the target of full benefits of immunization to all people living in Africa. In this light, the TFI Chair stating that she is expecting every TFI member to be fully interactive throughout their term in office to advise WHO/AFRO appropriately in overall regional policies and strategies, ranging from vaccines and technology research & development, to delivery of immunization services and linkages between immunization and other health interventions.

Finally, the 3-day programme-of-work proposed by the WHO/AFRO secretariat was reviewed by TFI members and was adopted unanimously.

Session 2 – Overview of WHO, SAGE & TAGs

The key objective of this session was to brief TFI members on the work of WHO, its functioning and relationship with countries and partners, as well as brief TFI members on pertinent issues related to SAGE and Immunization Technical Advisory Groups (TAGs).

2.1 Overview of WHO

Presenter: Dr Deo Nshimirimana, IVE Cluster Director, WHO/AFRO

The IVE Director delivered a presentation on WHO which covered WHO's core values and technical priorities, the on-going reforms within WHO aimed at ensuring effective, efficient and fully funded programmes, the organizational structure of WHO/AFRO including the structure of the inter-country support teams. Current immunization priorities in the African Region were highlighted as follows:

a. interruption of poliovirus transmission;
b. reduction of the number of un- and under-immunized;
c. acceleration of immunization initiatives to include measles/rubella elimination, maternal & neonatal tetanus elimination, meningitis control, yellow fever control;
d. improvement in data quality; and

e. promotion of alliances between immunization and the health systems strengthening and maternal & child health programmes.

An overview of the trends in performance of immunization programmes in the Africa region was also presented.
TFI members appreciated the presentation made - particularly overview of the on-going WHO reforms (as depicted in Annex 1). Participants noted the success of the recently concluded WHO financing dialogue that took place in Geneva in November 2013 that has already mobilized 85% of WHO funding needs for 2014 and 2015.

Noting that the WHO African Region was lagging behind other regions in terms of meeting GVAP targets, it was suggested that AFRO should learn lessons from other WHO regions such as PAHO/AMRO that have successfully achieved/sustained high immunization coverage and other programme performance targets over the years. It was also suggested that efforts to further enhance immunization coverage in the African Region should be closely linked to efforts to strengthen national health systems.

Concern was raised with regard to the current dependence on both polio eradication funding and the polio infrastructure in the AFRO region. In this light, it was suggested that TFI should be fully engaged in the process of legacy planning as part of the polio endgame strategy.

The issue of data quality as a priority for the African region was well appreciated. Although it was noted that WHO/AFRO has a good data system in place which tracks coverage at the district level, there is an urgent need to enforce the culture of data validation and to utilize data analysis for corrective actions and informed decision-making.

2.2 Overview of the Immunization Strategic Advisory Group of Experts (SAGE)

Presenter: Dr Philippe Duclos, Senior Immunization Adviser, WHO/HQ

Presentation provided a summary of the immunization policy advisory framework in place at the global, regional and country level. Moreover, the membership and *modus operandi* of SAGE were described in detail and specific emphasis was placed on agenda setting, preparation for SAGE meetings, mechanisms for communicating and follow-up of the implementation of SAGE recommendations. Furthermore, an overview of the 2013 SAGE recommendations with particular relevance to the African Region was made to include: yellow fever vaccination - booster dose no longer required; introduction of IPV to the national routine immunization schedule, and measles and rubella elimination.

TFI Members were appreciative of information session on SAGE and recognized the importance of SAGE and its link with the work of TFI. It was thereby proposed that SAGE

members who represent the African Region be invited to participate at future TFI Meetings. Moreover, given the importance of African representation on all SAGE working groups, for current working groups with no African representation, TFI to propose candidates for SAGE to consider.

Annex 2 of report provides tentative topics for discussion at the next SAGE meeting in April 2014.

2.3 Overview of Technical Advisory Groups (TAGs) in the WHO African Region

Presenter: Dr Alex Gasasira, Polio Eradication Programme Area Coordinator, WHO/AFRO

Presenter outlined the historical background of the four TAGs in the region that were initially established to support countries achieve polio eradication targets, as well as the Regional TAG for Measles. The TAGs that are currently operational within the WHO African Region are as follows:

1. Polio/TAG for Angola, Congo, DRCongo, Namibia and Zambia;
2. Polio/TAG for Horn-of-Africa countries;
3. Polio/TAG for Chad and Central Africa Republic;
4. Nigeria Expert Review Committee on Polio Eradication and Routine Immunization; and
5. Measles Regional TAG.

The membership, terms of reference and overview of the recommendations of the most recent meetings of the TAGs were covered. Participants were also informed that in 2013, the terms of reference of the Regional TAG for Measles were expanded to include issues related to Rubella and Congenital Rubella Syndrome and was renamed the Regional TAG for Measles and Rubella. The membership of this Regional TAG was renewed in 2013 for a period of 3 years.

During the discussion session, the importance of establishing a strong link between TFI and the TAGs was highlighted to ensure complementarity. Noting that TFI serves as the principle advisory group to WHO/AFRO for immunization and that it has the capacity to undertake high-level advocacy if needed, it was proposed that all TAG chairpersons be invited to future TFI meetings to report back to TFI on TAG outcomes.

It was also pointed out that a key constraint faced by a number of TAGs is difficulty in ensuring effective implementation of TAG recommendations due to weak implementation oversight committees, insufficient in-country technical capacity, and/or insufficient focus and commitment by national authorities. Furthermore, the need for a clear vision on the

criteria for establishment and discontinuation of a TAG as well as a clear hierarchy between different advisory bodies within the Region was emphasized.

Session 2 – Recommendations

No	Recommendations/Follow-Up Actions	Responsible	Deadline
1.	Depending on topics for discussion, AFRO to invite relevant countries and appropriate expertise to actively participate in future TFI meetings.	WHO/AFRO	Ongoing
2.	The importance of establishing a mechanism to prioritize SAGE recommendations that have a particular relevance for the WHO African Region as well as establishing a follow up mechanism on the effective implementation of such recommendations was highlighted by TFI. WHO/AFRO to propose such a mechanism for review/approval by TFI when TFI next convenes.	WHO/AFRO	Next TFI Meeting
3.	Cognizant of the importance of African representation on all SAGE working groups, for current SAGE working groups with no African representation, TFI to propose candidates for SAGE to consider.	TFI Chair	Immediate
4.	WHO/AFRO to also establish mechanisms to strengthen the capacity of national programmes to ensure both the timely and effective implementation of country-specific and multi-country TAGs. Proposed mechanisms to be presented at the next TFI meeting.	WHO/AFRO	Next TFI Meeting
5.	To ensure complementarity between TFI and regional, sub-regional and country-level immunization TAGs, WHO/AFRO to commission a review of existing immunization TAGs within the African Region. The review team to take into consideration the criteria in place to establish and discontinue TAGs as well as the inter-relationships between the different TAGs. The review team to bear in mind the need for capacity building for potential TAGs at the country level and the need to avoid establishing a heavy bureaucratic architecture for immunization that many not be beneficial eventually. Report of review, to include clear recommendations that highlight a clear architecture for TAGs with link to TFI, to be presented at the next TFI meeting.	WHO/AFRO	Next TFI Meeting

Session 3 – Functioning of TFI

The key objective of this session was to collectively deliberate on future working arrangement and modalities of the TFI under the framework of the Decade of Vaccines and 2011-2020 Global Vaccine Action Plan.

3.1 TFI in the Era of Decade of Vaccines

Presenter: Professor Helen Rees, TFI Chair

The TFI Chair commenced presentation by stating the newly appointed/renewed TFI members will concentrate their efforts over the coming 3- to 6-years in support of the Decade of Vaccines (DoV) - an initiative which the Bill & Melinda Gates Foundation (BMGF) has committed US$10 billion over this decade to help research, develop and deliver vaccines for the world's poorest countries. The overarching vision of DoV is to avert deaths and promote country ownership by the increased investment in vaccines by governments and the private sector which would lead to supporting developing countries dramatically reduce child mortality by the end of this decade. The TFI Chair then dedicated time to present key elements of the 2011-2020 Global Vaccine Action Plan (GVAP), which was approved by the World Health Assembly in 2011. She highlighted the 6 guiding principles of GVAP as well as GVAP's time-limited strategic and transformative approaches. She also pointed out the lack of country-level accountability and equitable access to immunization as major challenges for the WHO African Region. Given WHO is the lead agency responsible for monitoring GVAP progress and that there is a clear GVAP monitoring and evaluation framework in place, WHO, with the support of TFI strategic orientation, will need to concentrate its efforts on guiding countries to produce high-quality data in an effort to rapidly reach the point where all stakeholders are confident with data produced. The TFI Chair ended her presentation by focusing on country ownership at all levels (given in most countries, lower levels do not have negotiating power) and the importance of putting-in-place competent, well-functioning NITAGs; as well as building grassroot-level support that would lead to demand for immunization delivery services.

The deliberations following presentation concentrated on how to stimulate community demand for immunization services as well as the importance of effectively communicating to communities on the benefits of vaccines. In this light, it was pointed out that social mobilization is part of demand creation and that social mobilization strategies should look at social norms, community perceptions, barriers faced, as well as increase quantitative and qualitative research in this area. Moreover, it was highlighted that the GVAP indicators concentrate on vaccine hesitancy; however, within the African context this issue is not as much about hesitancy but rather access to health facilities.

The importance of translating science into the local language/context was stressed as communities need to comprehend the benefits of vaccination in their own language and at their level of understanding. Furthermore, the need to work on data ownership at the service point was highlighted and the need for community and health workers to undertake data they collect/generate and use it for their own needs was stressed.

Finally, the issue of health as a human right was raised in the context of the need for immunization programmes to align with human rights groups to package immunization with other community health needs. Moreover, given health goes beyond the health sector, the importance of taking a multi-sector approach to achieve immunization goals was stressed.

3.2 TFI Future Working Arrangements & Modalities

For this session, participants split into two groups to brainstorm on the most effective working arrangements and modalities to institute for the newly reconstituted TFI over the coming 3- to 6-years. It was pointed out that GVAP and the 2014-2020 Regional Strategic Plan for Immunization would be TFI's guiding documents. When reporting back in plenary, both groups raised similar proposals to include:

- Effective 2014, TAG Chairs to partake in all TFI meetings in order to report back to TFI on key outcomes of most recent TAG meeting. Furthermore, TFI to designate a member of TFI to attend each TAG meeting. Finally, a review of the TAG ToRs in relation to the TFI ToRs to be undertaken to ensure uniformity.
- Develop a mechanism to monitor implementation of past TFI recommendations.
- Time-limited TFI Working Groups to be established for priority areas of work. Working groups would be organized similar to SAGE working groups. Established TFI Working Groups to report back at TFI Meetings on progress made and outcomes.
- There must be clear guidelines developed on: internal communication mechanisms for TFI members; and TFI communications with external groups.

The specific recommendations generated from Session 3 are outlined in the way forward section of report (Session 6) which were aptly summarized by the TFI Chair.

Session 4 – Briefing on Priority Areas of Work for IVE/AFRO

The key objective of this one-day session was to brief TFI members on progress made in the delivery of routine immunization services, introduction of new vaccines, measles elimination, rubella control, meningitis A elimination, yellow fever control, MNTe, polio eradication, building demand for immunization, immunization financing, and immunization in humanitarian emergencies within the African Region.

5.1 Routine Immunization & New Vaccines

Presenter: Dr Richard Mihigo, Routine Immunization & New Vaccines Programme Area Coordinator, WHO/AFRO

Presentation began by acknowledging the tremendous progress made in immunization coverage over the past few decades by demonstrating that there was a consistent increase in immunization coverage especially during the universal child immunization (UCI) period. After the UCI period, decline in coverage ensued until GAVI was launched in 2000, when the reach every child (RED) strategy was implemented; the rise in immunization coverage continued up to the 2010. During the past 2-3 years, it was reported that routine immunization coverage stagnation has occurred at around 70%.

The presenter then demonstrated that the number of unimmunized children within the African Region is not evenly distributed; 80% of unimmunized children are located in only 10 countries especially Nigeria and DRCongo. Thus, there has been some focused support to reduce the trend of unimmunized children in these countries. The presenter informed participants that there is beginning to be a drop in the number of missed children in Nigeria, Uganda, DRCongo and Chad, comparing the 2012 to the 2013 data.

An area of concern highlighted was the validity and reliability of data produced to show progress in the implementation of routine immunization. The presentation demonstrated that systems have been put in place to support countries to ensure that generated data are of high quality. There is also a step-wise data assessment process in place which includes logical processes for data processing, cleaning, data harmonization and data quality self-assessments.

With respect to the introduction of new vaccines, TFI members were informed that almost every country has introduced pentavalent vaccine, except South Sudan; and that the region has witnessed a progressive introduction of PCV and Rota in 27 and 10 countries respectively. In addition, TFI members were informed that the programme continues to collaborate with other partners to prevent and treat pneumonia and diarrhoea. The introduction and delivery of Men A was highlighted as a success story for the region given

over 150 million individuals have been reached in less than 3 years and no reported case of Men.A has been identified in vaccinated populations. Finally, TFI members learnt that HPV is gaining momentum, where Rwanda and Lesotho have introduced the vaccine and a number of countries have started demonstration projects.

The presenter then outlined key challenges the health system faces, to include:

- The introduction of new vaccines has increased the health workers workload yet the number of staff remain the same;
- The products used in vaccination have increased in complexity, yet this is not matched by more competence in management; there is a need for specialized staff;
- The storage and transport system is also challenged. The volume per child immunized has increased more than six times; the number of doses administered have also increased, yet the storage facilities and cold chain have not witnessed commensurate increase over time;
- Waste management and injection safety issues have also increased; and
- There is an increasing risk of programmatic errors in handling more vaccines.

In terms of surveillance, it was noted that the new vaccine surveillance (NVS) network is supporting the existing system. The presentation showed the laboratory network in the region which includes 34 sentinel sites in 30 countries for Paediatric Bacterial Meningitis (PBM); and 25 sentinel sites for Rotavirus in 20 countries.

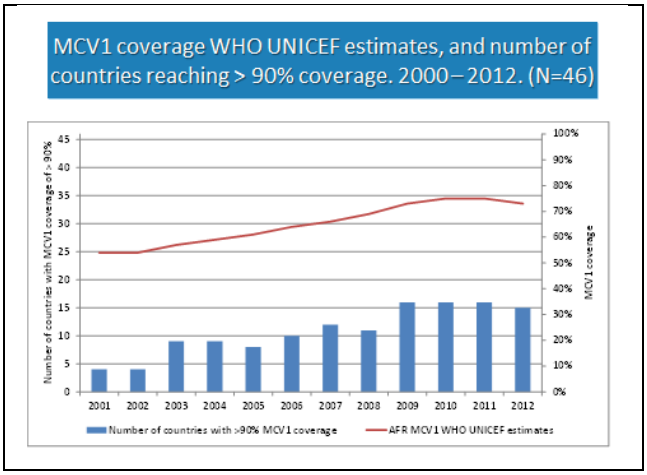
TFI members acknowledged the tremendous success of the introduction of MenAfriVac within the African region and requested that this, and other success stories, be packaged and disseminated broadly to relevant target audiences.

Key issues raised by TFI members included: clearly articulating in future presentations how strengthening routine immunization would help strength the health system; the need for in-depth reflection on the impact of immunization for advocacy purposes; as well as determining how the *Reaching Every District* (RED) approach can be better utilized to enhance health service delivery in general. Furthermore, TFI members requested that the presentation made be updated to accurately reflect the historical narrative of immunization in the Universal Child Immunization (UCI) period.

5.2 Measles & Rubella Elimination

Presenter: Dr Balcha Masresha, Accelerated Immunization Initiatives Programme Areas Coordinator a.i., WHO/AFRO

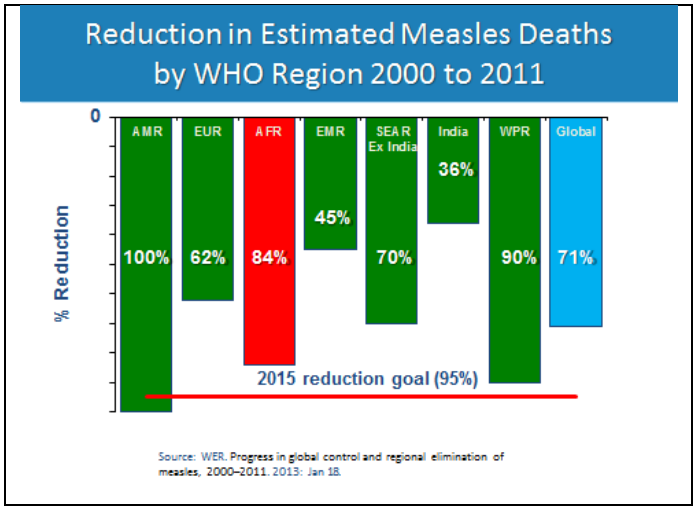
The African regional measles elimination goal with the target of 2020 was introduced. It was highlighted that the target for elimination includes achieving ≥95% MCV1 coverage at national and district level; ≥95% SIAs coverage in all districts and an incidence of <1 case/10^6population/year (excluding imported cases). Meeting participants were informed that programme activities have centred on strategies directed at strengthening routine immunization coverage; provision of second dose of measles vaccine, either through routine immunization or supplementary immunization activities; measles surveillance with laboratory confirmation, among others.



It was demonstrated that, using WHO/UNICEF estimates, the MCV1 coverage has progressively increased until 2010, after which it reached a plateau and a decline in 2012. Only 15 countries (of 47) in the WHO African region maintained a measles coverage of 90% or above for 3 consecutive years. It was reported that, as of December 2013, only 14 countries have introduced the 2nd dose of MCV. However, by 2015 it is estimated that more than 20 countries will have introduced the measles vaccine.

Given there is a current high dropout rate between MCV1 and MCV2, the presenter stressed that demand creation is imperative and that the health system needs to be capable of responding to that demand. Between 2001-2013, measles catch-up and follow-up vaccination campaigns have reached a total of 613.8 million children.

In terms of country ownership, one measure used by the measles partners to gauge country commitments includes the amount of funding raised locally to match external partners' funding. It was reported that in 2011 a total of US$10.3m was raised locally and that only 4 of the 13 targeted countries met the minimum goal of 50% of the operational costs of measles SIAs (i.e. at least US$0.32 per child targeted in the SIAs); in 2012, 10 of the 13 targeted countries successfully raised US$17.3m, thus meeting the target set.



The cumulative effect of measles SIAs and in routine immunization was that the Region witnessed an 84% reduction in measles deaths between 2000 and 2011. However, it was pointed out that the Region is still far from the global target.

The regional measles laboratory network, consisting of 45 laboratories in 43 countries, also supports the yellow fever laboratory diagnosis. Case-based surveillance for measles is in place in 43 countries in the Region supported by the laboratory network. In recent years, the majority of cases reported during measles outbreaks consist of children above 5 years of age, which reflects the gaps in routine immunization and SIAs coverage in the past years, thus causing a shift in the pattern of epidemiological susceptibility to older age groups.

In terms of rubella & CRS, the paper entitled *WHO regional rubella/CRS elimination: a proposed regional strategy option* was briefly presented to TFI members. It was noted that the programme has begun to access GAVI funds for the introduction of rubella into the immunization programme; in 2013, 4 countries accessed GAVI funds and other countries are scheduled to follow in the coming years.

During the discussion session, the debate revolved around the use of measles vaccination coverage as an essential indicator to monitor routine immunization performance. TFI members took note that there is a marked difference between the dropout rate between MCV1 and MCV2, compared to DPT1 and DPT3. Noting that the health system currently uses DPT3 coverage as a proxy indicator for health system delivery, TFI members proposed due consideration be given to using MCV1 along with DPT1 as a proxy to measure immunization services.

5.3 Meningitis A

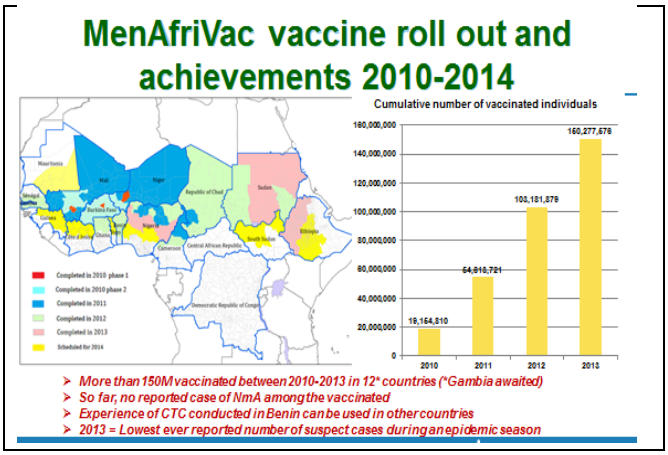
Presenter: Dr Mamoudou Djingarey, Meningitis Vaccine Project Coordinator, WHO/AFRO

A brief overview of the Meningitis Vaccine Project was presented - the goal of which is to eliminate meningitis epidemics as a public health problem in sub-Saharan Africa through the development, testing, licensure and widespread use of affordable conjugate meningococcal vaccines.

The presenter projected the meningitis belt - which incorporates 26 countries in total. He pointed out that meningitis epidemics coincide with the dry season in the Sahelian belt, more than 10% of patients die within 48 hours of onset; and 10-25% of survivors often suffer lifelong disabilities.

The presentation then described in detail the Meningitis A (MenA) conjugate vaccine development model and highlighted the strategies in place for MenA elimination, which include mass vaccination campaigns (1-29 years old); and protecting new birth cohorts by introducing the vaccine into routine immunization. TFI members were informed that every five years mass follow-up campaigns are planned.

Thereafter, the presenter explained how the MenA vaccine came to fruition due to demand generated from African leaders. To date, the project has vaccinated over 150 million persons in 12 countries by December 2013. The plan is to continue vaccinating in all the 26 countries of the meningitis belt.



Since the introduction of Men.A, TFI members were informed that there has been a sharp decrease in both cases and outbreaks. Outbreaks that continue to occur have been restricted to countries that have not introduced the vaccine. The presenter confirmed to TFI members that efforts have been made to strengthen country capacities with respect to strengthening both clinical trials and national ethics committees, and that communities are

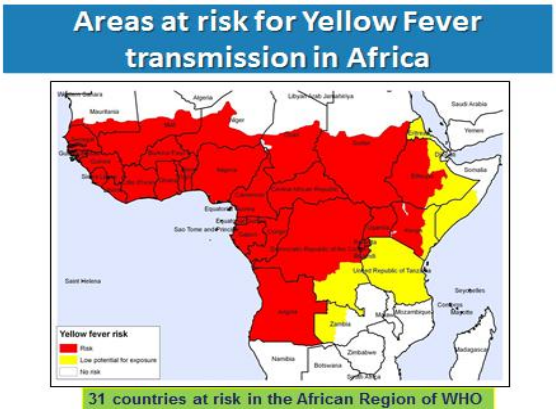
involved in the decision-making process for clinical trials who receive feedback on outcome of trials. Moreover, it was pointed out that capacity for pharmacovigilance was built. It was also pointed out that the vaccine has also shown that it is stable outside the cold chain (40^{o} C) and that it remains affordable. In concluding, the presenter discussed the next steps to include introduction of Men.A to other countries as well as in routine immunization.

Discussions particularly focused around the importance of fully documenting the success of the introduction of Men.A in sub-Saharan Africa and to ensure that when future presentations are made to TFI members that data demonstrates progress made not generalizations.

5.4 Yellow Fever

Presenter: Dr Balcha Masresha, Accelerated Immunization Initiatives Programme Areas Coordinator a.i., WHO/AFRO

TFI members were briefed that there are currently 31 countries at risk of yellow fever transmission in Africa.



They were also informed that a WHO position paper on yellow fever vaccine was recently published stating that one dose of yellow fever vaccine confers life-long protective immunity against yellow fever; thereby a booster dose is no longer necessary. Presenter then described yellow fever control strategies currently in place which include: risk assessments, vaccination in routine immunization, preventive SIAs, laboratory-supported case-based surveillance and outbreak response SIAs.

To date, yellow fever vaccine has been introduced into routine immunization in 23 of the 31 countries at risk. However, coverage has been low as indicated in the 2012 WHO/UNICEF estimates. Since 2006, yellow fever preventive vaccination campaigns have been conducted in 13 countries targeting high risk districts and reaching approximately 69

million people. Outbreak interventions have also been conducted in 12 countries, reaching approximately 13 million people. Risk assessments are on-going to cover at risk countries.

The presentation demonstrated the number of yellow fever cases reported by country over the past two years and highlighted the geographical shift of epidemiology of the disease to different sub-regions which verified the need to intensify control activities in the Central and Eastern Africa sub-regions.

TFI members were then informed of the 2013-2020 Regional Yellow Fever Control Investment Case that was submitted to GAVI for consideration. They were also informed of key programme activities planned to be conducted in the region over the coming months to include: strengthening the laboratory capacity and research on economic burden and socio-cultural aspects of yellow fever; conducting risk assessments, preventive SIAs and case-based surveillance in countries in the East and Central African sub-region; and maintaining a yellow fever vaccine stockpile for outbreak response activities.

4.5 Maternal and Neonatal Tetanus (MNT) Elimination

Presenter: Dr Balcha Masresha, Accelerated Immunization Initiatives Programme Areas Coordinator a.i., WHO/AFRO

Presenter began by informing TFI members of the strategies used to eliminate MNT within the Region and summarized the level of reported TT2+ coverage in countries between 2010 and 2012. WHO/UNICEF coverage estimates demonstrated protection at birth of approximately 75% in all AFR countries as of December 2012. TT SIAs have been conducted in 37 countries between 1999 and 2012, reached over 52 million women with more than two doses of tetanus toxoid. It was reported that between 200 to 400 neonatal tetanus cases are detected annually; however, participants were informed that there is no active surveillance of MNT within the Region and that most of the MNT cases reported occur in rural areas.

Due note was taken of the huge gap in MNT surveillance; thus caution to be adhered to for countries that have been validated to have eliminated MNT. Furthermore, MNT elimination continues to remain low on the priority list of most countries. Other challenges highlighted included: limited funding; weak integration with MNCH and other programmes; and limited access to remote areas.

4.6 Polio Eradication

Presenter: Dr Alex Gasasira, Polio Eradication Programme Area Coordinator, WHO/AFRO

The presentation on the overview of polio eradication in the African region discussed recent global and regional plans/resolutions to interrupt and eradicate polio and enumerated the objectives of 2013-2018 polio eradication and endgame strategic plan to include: polio detection and interruption; improving routine immunization coverage, including IPV introduction with concomitant withdrawal of OPV; polio free certification and WPV containment; as well as legacy planning.

It was highlighted that the African Region had registered progress in reducing the number of infected countries as well as number of confirmed polio cases and that this was a result of improved quality of polio eradication activities, particularly immunization in polio priority countries. Despite the progress registered, there were still challenges faced as manifested by the 2013 explosive polio outbreak in the Horn of Africa and the recent confirmation of WPV1 in Cameroon that had been circulating without detection for close to 3 years. Routine immunization coverage remained sub-optimal in several countries in the region and thereby increased susceptibility to importation and outbreaks.

With respect to immunization strengthening and OPV withdrawal, the presentation showed that all priority countries have elaborated routine immunization strengthening roadmaps which have been implemented in 2013 with close monitoring at all levels. It was pointed out that immunization strengthening is a key component of the work that will be done in the region as part of the introduction of IPV into routine immunization programmes. TFI members were informed that the African Regional Certification Commission was expanded in 2013 and a plan to revive certification activities in the region was finalized.

On legacy planning, the presentation noted that the target is for end-2015. The presenter showed actions that have been undertaken including the WHO Regional Committee for Africa (RC63) consensus on the documentation of lessons learnt, available capacity that could be used elsewhere, and programme assets, among others.

Presenter concluded by saying that the agenda ahead is ambitious. However, progress is being made towards achieving the programme objectives. He listed the opportunities to include high political commitment to polio eradication at the national and sub-national levels, and that there are innovations that countries are identifying to address these issues. He also enumerated the way forward which includes: achieving interruption; implementation of planned activities; documentation of best practices; communication and social mobilization in the high-risk areas; as well as strengthening AFP surveillance.

Issues raised by TFI members included the need to ensure that intensified polio eradication efforts are closely aligned to efforts to improve routine immunization performance, as well as the need to encourage countries to close remaining surveillance gaps using an integrated surveillance approach rather than disease specific surveillance approaches. TFI members further stipulated the need for improved documentation of best practices that countries have implemented to improve access and demand for polio vaccines. Finally, the complementary role of TFI to that played by country and sub-regional polio technical advisory groups (TAGs) was raised, particularly with regard to high-level advocacy.

4.7 Building Demand for Immunization & Development of Regional Immunization Communications Strategy – Progress Report

Presenter: Professor Joseph Okeibunor, Immunization Social Scientist, WHO/AFRO

The presenter recalled the significant progress made in immunization in the African Region and pointed out that, despite some progress made in disease control and introduction of new vaccines, the stagnation of DPT3 coverage around 70% over the past few years raised fears for possible reversal of the epidemiological situation of the vaccines preventable diseases progress. It was explained that one of the factors for this situation is related to gaps in immunization communications which results in inadequate community awareness, insufficient demand for immunization services, and inadequate ownership of immunization - all these gaps are compounded by community ignorance of the benefits of immunization.

It was pointed out that the level of community awareness was insufficient to create demand for immunization and generate community ownership. It was for this reason that the GVAP underscores the need for improved immunization communications. Moreover, a TFI recommendation was made in 2012 for WHO to work with UNICEF to develop an immunization communications strategic framework for the WHO African Region which should provide guidance to countries to reinforce communication for immunization in view of strengthening demand and use of vaccination.

WHO/AFRO and UNICEF/ESARO+WCARO therefore initiated collaboration and developed a two-prong communications strategy development process: a desk review of existing documentation on communication; and anthropological studies to inform an evidence-based communications strategy. Progress to date included the selection of a set of indicators and the definition of the rationale and scope for the strategy. For the literature review, some countries were selected and divided into three sets using the criteria of DPT1 coverage and drop-out rate between DPT1 and DPT3. Using this approach, the study sample was made as follows:

a. DPT1≥ 80% and dropout ≤ 10% : Côte d'Ivoire; Malawi; Rwanda
b. DPT1≥ 80% and dropout > 10% : DRCongo; Ethiopia; Uganda
c. DPT1< 80% and dropout > 10% : Central African Republic; Chad; Nigeria

Analysis of the findings in the three sets of countries showed some strengths, including expression of political will and existence of many planning documents focusing on increasing immunization coverage. However, in most of the countries, the plans were not coordinated and in some cases there was an overlapping of the strategies.

Taking into account the findings, the presenter concluded by stating that the exercise will continue with the aim of publishing a *Regional Immunization Communications Strategy for the African Region.* Some of the next steps of this process will include: working with the Health Promotion department on capacity building for communicators; research to understand the underlining factors on demand creation; community engagement through dialogue; as well as the use of celebrities.

TFI members expressed lack of clarity on the current process and how it would result in the development of the communications strategy. The presenter addressed questions raised by the TFI members and all agreed that there was need to continue the process taking into account the comments and suggestions made by the meeting.

4.8 Immunization Financing

Presenter: Dr Amos Petu, Immunization Financial Sustainability Officer, WHO/IST-ESA

The presenter introduced the current work being undertaken by the WHO Secretariat on immunization financing to include: planning, advocacy, evidence generation, funding data tracking, vaccines pricing and procurement. The presenter noted that country immunization programmes have grown in size, leading to a level of complexity in service delivery and investment requirements. He emphasized that countries and partners were concerned over the issue of sustaining immunization financing. Currently, 46 countries have been supported to develop comprehensive costed multi-year plans with requisite costing and financing plans. These plans are being used to mobilize resources, especially to meet GAVI co-financing requirements in GAVI-eligible countries (which comprises 36 countries in the African Region).

The emphasis of GVAP on: country ownership, responsibility as well as programme sustainability were highlighted and current trends on government financing were analyzed. It was noted that the current levels of governments' spending on vaccines and immunization services were still too low to achieve the GVAP country ownership objective, with a declining trend noted between the period 2010-2012. The presenter noted that in

most countries the level of immunization financing was still below 50% of the requirements with a wide level of variability among countries. It will therefore be necessary to reverse this trend. Some of the priority issues that were identified included: sustainability of government funding for vaccines and immunization; generating evidence on the economic burden of vaccine preventable diseases such as measles outbreaks; cost effectiveness analysis of new vaccine introduction; costing and financing of routine immunization.

In conclusion the presenter sought guidance from TFI members on two issues, including better tracking of country immunization financing data as well as improving advocacy to increase governments' commitment to immunization financing.

TFI members expressed their concern that the presentation was too technical and did not allow the audience to pick up the underlying messages. For example, it was not clear what each country's spending average was. TFI members suggested that all sources of funding be considered in the financing analysis, including at the sub-national levels where more substantial spending are being done. In the same vein, they recommended that the efficiency of the expenditures be also considered in the analysis. In addition, it was indicated that some countries have taken initiatives to establish immunization funds and that such initiatives could also be assessed.

The limitations of data used in the assessment were discussed and the usefulness of the information presented for programme management was not too clear. TFI members reiterated that the GVAP requests countries to increase trends in country allocation to national immunization programmes and that it would be more useful to break the reported information under more specific financing items.

The presenter indicated that most of the data used are from the WHO-UNICEF Joint Reporting Form as provided by the countries with limitation of verification.

Concluding the discussions, the TFI chair recommended refining the information presented in a way to generate a clearer picture on countries spending on immunization. She also recommended the development of a tool for documenting immunization financing that should be shared at the next TFI meeting as well as indicated that TFI would provide support in determining the next steps of the exercise.

4.9 Immunization in Acute Emergencies: A Framework for Decision-Making

Presenter: Professor Helen Rees, TFI Chair

The TFI Chair presented the recently published WHO guidelines entitled: *Vaccination in acute humanitarian emergencies: a framework for decision-making* and explained why such guidance was needed. She indicated that vaccine preventable diseases (VPDs) were major causes of death in refugee populations and that the burden of VPDs increases in emergency situations. The guideline development process was presented which included a wide consultative process via a SAGE working group and external review by stakeholders.

The TFI chair emphasized that the framework would not replace existing guidelines, but was a way of harmonizing implementation of immunization in emergency situations in a more systematic and step wise process.

A brief discussion followed the presentation. Experiences in implementing immunization in current complex emergencies (e.g. Syria, the Philippines, Central African Republic) was discussed. It was indicated that there was a need to align framework procedures for vaccination in acute humanitarian emergency settings with the overall emergency management procedures. The issue of timing for the immunization risk and needs assessment was highlighted. It was noted that in complex emergencies it is not easy to make a decision tree; everything has to be analyzed according to the context and then put the results of the risk analysis in a logical framework for further actions.

Session 4 – Recommendations

No.	Measles Elimination	Responsible	Deadline
1.	WHO/AFRO to consider MCV1 along with DPT1 as a proxy to measure immunization services. This measurement should be considered for inclusion in the 2014-2020 regional strategic plan for immunization (which is currently under development).	WHO/AFRO	Next TFI Meeting
	Meningitis A Elimination		
2.	Acknowledging the tremendous success of the *MenAfriVac* introduction to date within the African region, TFI recommends that this success story be documented & disseminated widely to target audiences.	WHO/AFRO	Next TFI Meeting
	Yellow Fever Elimination		
3.	Noting 31 countries within the WHO African Region are at risk of yellow fever transmission, a well-crafted regional yellow fever surveillance and risk assessment	WHO/AFRO	Next TFI Meeting

	report should be prepared and submitted to TFI for review.		
	Maternal & Neonatal Tetanus Elimination		
4.	WHO/AFRO to explore and optimize the potential programmatic links with the expanding HPV vaccination and school health programmes across the Region, in order to sustain the gains in MNT elimination.	WHO/AFRO	Next TFI Meeting
	Polio Eradication		
5.	WHO/AFRO to propose specific actions for TFI to complement the efforts of country-specific and sub-regional TAGs in guiding countries to implement the 2013-2018 Polio Eradication and Endgame Strategic Plan.	WHO/AFRO	Next TFI Meeting
6.	WHO/AFRO to support countries to better document how experiences, lessons and opportunities from polio eradication are being utilized to support other priority public health programmes.	WHO/AFRO	Ongoing
7.	TFI should play an active role in the preparation of polio eradication legacy plans for the African Region. WHO/AFRO to outline a plan to actively engage TFI in legacy work.	WHO/AFRO	Next TFI Meeting
	Immunization Communications		
8.	To continue the process of development of the Regional Immunization Communication Strategy and address any methodological gaps. Progress report to be shared with TFI members prior to next TFI meeting.	WHO/AFRO	Prior to next TFI Meeting
9.	Appoint TFI members to follow up/support the process of developing the immunization communication strategy via establishing a Working Group.	WHO/AFRO	immediate
	Immunization Financing		
10.	To refine the presentation made on immunization financing to make it more clear for the benefit of using the data generated for advocacy to Governments.	WHO/AFRO	immediate
11.	TFI to work closely with the WHO Secretariat to refine the financial situation analysis and generate a user friendly advocacy document.	TFI	immediate

Session 5 – Discussion Items for TFI's Consideration

5.1 Development of Regional Strategic Plan for Immunization: 2014-2020

Presenter: Professor Daniel Tarantola, TFI Member

The objective of this session was to share information on the progress of development of the 2014-2020 regional strategic plan for immunization as well as request TFI Members' input to further refine the draft plan.

The presenter gave an overview of the process to date in the development of the strategic plan. Key documents and processes that influenced the development of the strategic plan included the Global Immunization Vision and Strategy (GIVS) 2005-2012; the Decade of Vaccine and the subsequent development of the Global Vaccine Action Plan (GVAP) 2012-2020; the 65th World Health Assembly Resolution in May 2012; and the external evaluation report of the regional immunization strategic plan 2009-2013 (conducted in June 2013) which highlighted the strengthens and weaknesses of programme implementation and; the report to the Regional Committee Meeting in 2013.

TFI members were informed that a WHO/AFRO workshop on lessons learned and the formulation of the Regional Strategic Plan took place in October 2013, which provided further guidance for the development of the Regional Strategic Plan for Immunization 2014–2020. Thereafter, an internal working group was established to review the first rough draft of the regional strategic plan and met in N'Djamena, Chad in November 2013 - which resulted in the second draft of the plan that was presented to TFI for review.

It was articulated that the framework guiding the development of the new plan is based on a transition from offer-driven to demand-driven immunization services, with equity in access and use of immunization and responsiveness to informed public demand as its main pillars. Other issues considered include a shift from globally-driven agendas to national ownership, driven by national commitment informed by evidence and growing capacity and; a transition from single-stream programmes to integrated health systems approaches emphasising immunization as the backbone of primary health care based on extensive use of modern technology.

The target readership was also discussed (Member States, NGOs, academia, civil society, ODA agencies, foundations, and private sector) and national actors engaged in the formulation of national strategic plans on immunization viewed as the main target audience. It was pointed out that the draft document will undergo an iterative consultative process prior to its submission to the 2014 Regional committee meeting.

Highlights were given on the issues that are yet to be developed in the draft which include resource implications, the monitoring & evaluation framework and the way forward sections.

In discussion, TFI members opined that the set targets in the draft should as much as possible reflect already existing GVAP targets in order to get the region to move towards such global targets. Inputs from EPI Programme Managers in setting these targets were felt important and could be obtained during the 2014 EPI Managers meetings planned to take place in Q1-2014. It was suggested that there should be definition of terms and concepts so that all readers are of the same understanding to facilitate implementation. The need to translate the regional strategic plan into country operational plans with intermediate milestones was highlighted. Moreover, the need for increased capacity building was also emphasized and it was suggested that this areas of work should be amplified in the plan as it forms a key component for country ownership. It was also articulated that the plan should give a clear guide on how to deal with the issue of demand creation/sustaining demand for immunization and that issues of data and logistics need to be well covered in terms of orientation to countries.

Suggestions were made that CSOs should not be considered solely as implementers but also be part of the decision-making process and a changing force for immunization. This would ensure a movement from Ministry of Health ownership to true national ownership.

The role of ICCs was largely discussed and while they have a key role to play, it was pointed out that countries should have a strategic approach to deal with the increasing complexity of immunization programmes. To further strengthen country ownership, it was iterated that NITAGs be established taking into account the availability of local expertise as well as building on some of the advisory bodies already providing technical guidance on immunization to countries.

For new vaccines introduction, TFI members proposed that provision be made in the strategic plan to cater for future vaccines for malaria, typhoid and possibility for tuberculosis or HIV vaccines. It was discussed that since production of mono-antigen measles vaccines will not be available in the future, to perhaps set a target to get countries to move towards the introduction of MR in their routine immunization system be elaborated.

5.2 NITAGs

Presenter: Dr Philippe Duclos, Senior Immunization Adviser, WHO/HQ

The objective of the presentation was to brief TFI members on the process of developing evidence-based national vaccination policies through National Immunization Technical Advisory Groups (NITAGs).

The presentation provided background on how to derive the best evidence-based national vaccination policies and recommendations that can guide country policies and strategies based on local epidemiology and cost effectiveness, recognizing that immunization is a complex scientific field. It was resolved that this could be handled by well-functioning NITAGs. It was also pointed out that various strategic/technical background documents, such as the WHO/UNICEF GIVS 2006-2015, WHA 61.15 resolution (2008), SAGE recommendations and the Decade of Vaccines GVAP, already supports the establishment of NITAGs as having a technical advisory role for all vaccine preventable diseases and should not serve as an implementing, coordinating or regulatory body.

The presentation emphasized the fact that NITAGs are not ICCs and clarified that NITAGs should not replace the immunization programme, the regulatory authority, the interagency coordinating committee, or the certification commissions. It also emphasized that NITAGs should consist of experts with independent and unbiased expertise which does not necessarily mean independent experts, as most national experts in low-income and lower middle-income countries are paid directly or indirectly by the government. The issue of transparency was highlighted as important and that the declaration of interest of NITAG member is paramount in order to avoid conflict of interest.

In supporting the creation of NITAGs, it was highlighted that the principle of “one size fits all” should not be pursed but rather the adjustment to country specificity was essential and that the process should be tailored to local realities.

TFI members pointed out that countries may not have fully understood the essence of NITAGs and there is a need to sensitize countries. Moreover, the need to be sensitive to the capacity of countries to avoid the danger of “country overload” was highlighted. The importance of countries linking with organizations that already have experience in supporting NITAGs was emphasized. It was also emphasized that in some circumstances, based on the peculiarity of the country, they may already have a structure/organization that does the work of NITAG. What remains important is that the agreed functions of NITAG be carried out in support of decision-making for immunization.

5.3 Ministerial Conference on GVAP Implementation

Presenter: Ms Helena O'Malley, IVE Technical Officer, WHO/AFRO

The objective of this presentation was to brief TFI members on the plan to host a Ministerial conference on GVAP implementation and to seek TFI Members' inputs.

The presentation gave a background to the Ministerial conference, highlighting that it would involve the participation of all countries within the African continent. TFI members were informed that it is proposed is to hold this conference at the African Union headquarters in June 2014 with the theme focusing on country ownership and demand creation. The conference would be co-organized by WHO, the Government of Ethiopia, the African Union, Bill & Melinda Gates Foundation, UNICEF, and GAVI. The overarching goal of the conference would be to obtain Governments' commitment in support of immunization.

TFI Members applauded the WHO Regional Director's initiative to organize such a high-level conference in support of immunization activities on the African continent. However, due caution was raised as organizing such an event would require tremendous planning and coordination with all other immunization stakeholders in the region and that the necessary resources (human, material and financial) need to be allocated for an optimal preparation.

TFI members recognized that the use of social media in publicizing the Ministerial conference would be an important channel and that it should be made clear from the onset what the social media outlet should aim to achieve. The need to have a full-time team to handle all communications issues, including the social media related to the conference was highlighted.

It was noted that given countries present at the Ministerial conference are expected to adopt a declaration in support of immunization in the Africa continent, there would be a need to develop a framework to support the implementation of the Addis Ababa Declaration on immunization. Having the African Union co-organize the conference would facilitate the use of the African Union mechanisms and channels to ensure optimum participation of Ministers especially given Ministers are to be invited not only from the health department but across sectors – education, women's development, youth, etc.

It was proposed that regional professional associations be also considered to be invited to conference to include the Association of Public Health Physicians, as well as the health desk of the sub-regional blocs – i.e. SADEC, ECOWAS, WAHO, COMESA, etc.

5.4 Global Vaccine & Immunization Research Strategy

Presenter: Dr Jean-Marie Okwo-Bele, IVB Director, WHO/HQ

The key objective of this presentation was to brief TFI members on the global strategic directions for vaccine & immunization research and to highlight the areas where WHO could significantly contribute to the global research agenda.

As summarized in Table 1, the presenter informed TFI members of the specific areas of research where WHO could significantly contribute to - namely:

a. Existing vaccines

- Research to minimize barriers and improve coverage of vaccines currently in use;
- Research to improve methods for monitoring of immunization programmes;
- Research to conduct impact evaluation of vaccines in use.

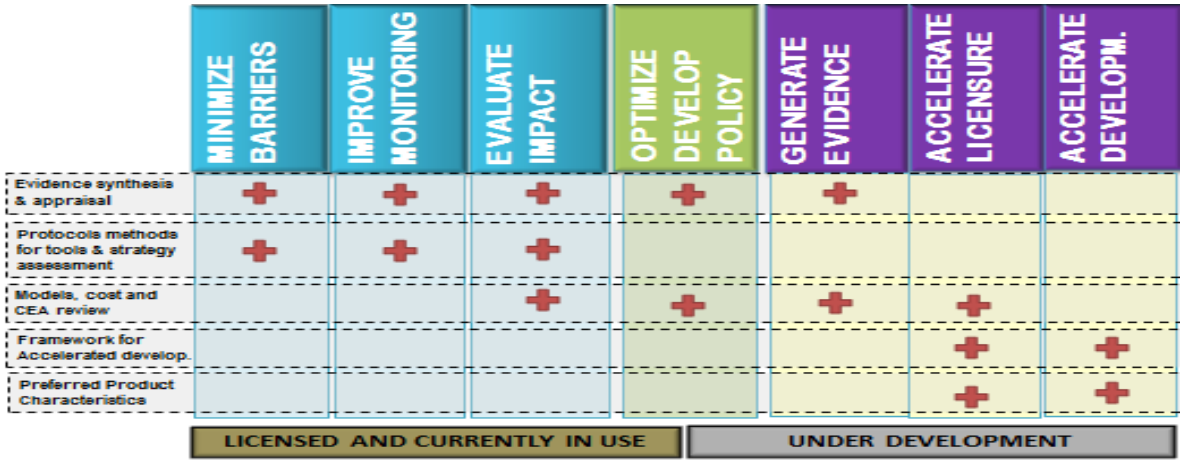
b. Existing & new vaccines

- Research to generate evidence to optimize policy recommendations or develop new ones as appropriate.

c. New vaccines under development

- Research to generate evidence to inform policy recommendations for candidate vaccines at advanced stages of development;
- Research to accelerate licensure of vaccines in earlier phases of clinical development;
- Research to encourage and accelerate the development of vaccines in early development

Table 1: Summary of WHO's proposed areas of research



TFI members were informed that a forum has been established at the global level to monitor research implementation on a regular basis and that WHO, in partnership with the Bill & Melinda Gates Foundation and the National Institutes of Health, are working collectively towards stimulating research to assist effectively implement the Global Vaccine Action Plan.

TFI members raised the issue of the need to build research capacity at the country level as well as the need to raise adequate funding for research particularly on cross-cutting issues such as immunization service delivery. They also requested that WHO/AFRO selects the relevant priority research areas for the African region.

5.5 Current Immunization Research Activities within the WHO African Region

Presenter: Dr Joseph Okeibunor, Immunization Social Scientist, WHO/AFRO

The key objective of this presentation was to inform TFI members on current immunization research activities taking place within the region as well as to obtain their orientation on next steps WHO/AFRO should take in this field.

The presenter began by briefing TFI members on past research recommendations made by TFI in 2011 and 2012 which included requesting WHO/AFRO to support countries to conduct relevant implementation research to address important issues affecting immunization as well as finalize the *implementation research guide for immunization* for final endorsement by TFI members prior to distributing widely to countries. In this light, TFI members were informed that WHO/AFRO has established a regional advisory committee on health research as well has a pre-finalized draft of the *implementation research guide for immunization* ready for TFI members' final review (which will be reviewed by TFI members at its next meeting. Furthermore, TFI members were informed that WHO has hired both a biomedical research scientist and a social scientist to concentrate on immunization research activities to include capacity building at the national level, as well as has hired social scientists in Angola, Chad, DRCongo and Nigeria.

TFI members were also informed that over the past year, capacity building workshops on operational research were held by the WHO Regional Office with the participation of 11 countries and that a number of country study protocols were reviewed. Moreover, TFI members were briefed on the number of country-level operational research studies conducted by WHO over the past year as well as the constraints faced.

TFI members stressed the need for WHO to actively broaden its engagement with the research community, and particularly promote research through research institutions within the African Region. Furthermore, taking note of the research work WHO has

performed to date, TFI members requested WHO to conduct a priority setting exercise to determine key immunization research questions to be addressed as well as review its current research priority setting process which should be amended accordingly to match regional/country needs.

Session 5 – Recommendations

No.	Regional Strategic Plan for Immunization: 2014-2020	Responsible	Deadline
1.	The next draft of the strategic plan should incorporate feedback provided by TFI members (as outlined in section 5.1 of report). Moreover, the next draft should include milestone with timelines to facilitate mid-term review. Furthermore, resource requirements should be elaborated.	WHO/AFRO	Next TFI Meeting
2.	In order to obtain input from EPI Managers on the proposed targets set in the draft regional strategic plan, WHO/AFRO to include a session in the upcoming 2014 EPI Managers' Meetings (scheduled to take place Q1-2014) to gain their insights/feedback.	WHO/AFRO	End Q1-2014
3.	WHO/AFRO to develop a framework for countries to use to develop their operational plan which should be aligned with the strategic plan as well as annexed to plan. Such a framework should take into consideration planning sub-national level operational activities.	WHO/AFRO	Next TFI Meeting
	NITAGs		
4.	Noting that "one size does not fit all", TFI recommends that WHO conducts an assessment by country to determine which strategy/mechanism would be the most appropriate to implement at the country-level to derive the best evidence-based national vaccination policies and recommendations that can guide country policies and strategies based on local epidemiology and cost-effectiveness.	WHO/HQ & WHO/AFRO	Next TFI Meeting
	Ministerial Conference on Immunization		
5.	Noting that adequate planning and resources are required to organize event, TFI recommends that WHO/AFRO hires event organizers to support preparations.	WHO/AFRO	immediate
6.	High-profile participants should be targeted to attend	WHO/AFRO	immediate

	event to include world renowned African leaders. In the event that targeted high-profile participant(s) are unavailable to attend event, WHO/AFRO to consider recording video clips that could be aired at conference.		
	Immunization Research		
7.	WHO/AFRO to develop a framework document on research for TFI's consideration which should take into consideration TFI members' feedback (as outlined in section 5.5).	WHO/AFRO	Next TFI Meeting

Session 6 – Way Forward

The Regional Director joined this final session to be briefed on key outcomes of 3-day event. Before the TFI Chair took the floor to summarize way forward, the Regional Director thanked TFI members for accepting invitation to serve on the African TFI in their personal capacity and stipulated his expectation that this principle advisory group should provide a combination of strategic and technical advice over the coming 3-year period that would assist the Region effectively implement the Global Vaccine Action Plan goals. Moreover, the Regional Director specified that TFI members are to support the development and monitoring of the 2014-2020 regional strategic plan for immunization as well as inform him regularly on major issues/challenges that need to be addressed to effectively implement the regional strategic plan.

Professor Helen Rees, TFI Chair, then took the floor and expressed her commitment to fulfil her role as TFI Chair. She specified that in her role as TFI Chair she would support the region in building strong partnerships and that each TFI member would be ambassadors and advocates for immunization and vaccines in the region.

In terms of *modus operandi*, the TFI Chair informed the Regional Director that the TFI would meet twice yearly with two preparatory phone calls prior to each meeting. Furthermore, for future TFI meetings the Chairs of all immunization TAGs would be invited to participate and present, and a select number of EPI managers, NITAG chairs, academics/experts, donors/partners, NGOs, vaccine manufacturers and immunization technologies associations would be invited to the end-year TFI meeting.

The TFI Chair stipulated that 4 agreed-upon standing agenda items would comprise future TFI agendas in the foreseeable future – namely:

a. Summary briefing on most recent SAGE recommendations;

b. Summary briefing from Chairs of each polio and measles/rubella TAGs;
c. Outcomes from Chairs of established time-limited TFI working groups;
d. Progress in implementing regional/country strategies and attaining set targets.

In terms of immunization priorities identified by the Regional Office over the past 3-days, the TFI prioritized those for which time-limited TFI working groups be established for close follow up – namely:

a. Increasing vaccine coverage including routine immunization
b. Polio eradication
c. Measles elimination/rubella introduction
d. Country ownership (to include NITAGs, financing & sustainability, and capacity building
e. Communication and demand creation
f. Data Quality
g. Research & Development

It was stated that when developing the proposed ToRs for each working group, WHO/AFRO to consider including external experts when required.

Session 6 – Action Points

No.	TFI *Modus Operandi*	Responsible	Deadline
1.	For the 6 TFI working groups proposed, WHO/AFRO to draft ToRs for each working group for submission to the TFI Chair for review. ToRs to include proposed members as well as duration of working group.	WHO/AFRO	End-Jan 2014
2.	Noting there is no archive available which houses past TFI reports/recommendations, WHO/AFRO to develop a composite document identifying previous TFI decisions. Furthermore, TFI to upload to the WHO/AFRO immunization webpage, all past TFI reports.	WHO/AFRO	immediate
3.	For future presentations to be made at TFI, all presenters to utilize a standardized format. This will entail preparing an issue paper (to include a preamble, recommendations and questions section) which is to be presented outlining issues and recommendations; clear conclusions; clear requests to TFI (i.e. information, discussion, recommendation). Furthermore, hard-copies of each presentation should be made available to TFI members	WHO/AFRO	Ongoing

	prior to presentation.		
4.	WHO/AFRO to utilize the meeting planner *Doodle* to set dates for future TFI meetings.	WHO/AFRO	immediate

Having concluded session 6, the Regional Director wished all participants a safe return home and reiterated his high expectations for this principle immunization advisory group.

Summary report

Meeting of the Regional Technical Advisory Group (RTAG) on immunization of the WHO Eastern Mediterranean Region

Amman, Jordan, 21 November 2013

Introduction

The annual Meeting of the Regional Technical Advisory Group (RTAG) on immunization of WHO Eastern Mediterranean Region was held in Amman, Jordan, 21 November 2013. The meeting was attended by members of the RTAG, chairpersons of National Immunization Technical Advisory Groups (NITAGs) of countries of the EMR, representatives from the Centers for Disease Control and Prevention (CDC, Atlanta), Network for Education on Immunization (NESI) and WHO staff from headquarters and EMRO.

The objectives of the meeting were to:

- Review the current situation of measles and rubella elimination and IPV introduction in the Region.
- Review the mandate, internal procedures and Terms of Reference of the proposed Regional Verification Committee (RVC) on Measles elimination
- Review and endorse the regional guidelines for measles and rubella elimination in the countries of the EMR.

Dr Ezzedine Mohsni, coordinator, Immunization and Vaccines, WHO Regional Office for the Eastern Mediterranean (EMRO), opened the meeting and underlined the objectives and expected outcomes of the meeting. Dr Hyam Bashour, RTAG chairperson chaired the meeting.

The meeting started with Moment of Silence in memorial of Dr Ali Jaffer Mohamed, Ex Chairperson of immunization RTAG, EMRO.

Introductory notes were presented for each topic of the agenda, followed by discussion by RTAG members and the recommendations/action points were agreed upon

1. Progress Towards Measles Elimination in the EMR:

Introductory notes were presented by Dr Nadia Teleb, RA/VPI, EMRO. The presentation reflected the current situation of measles in the EMR.

Points raised and discussed

- The region is progressing towards measles elimination despite the challenges:
    - Several countries are close to achieving the elimination target.
    - Even the counties that are now reporting major outbreaks (Pakistan and Sudan), they were able to reduce measles incidence after successful catch up campaigns. It was felt that resurgence occurred because of a delay in implementation of follow up SIAs and that follow-up SIAs were not equal in quality to the catch up campaigns. The initial success indicates that measles elimination is doable even in the challenging countries.
- Funding gap
    - Part of the reason for measles resurgence is inadequate funding for the follow up SIAs resulting in delayed implementation of the campaigns and inadequate funding to support measles/rubella surveillance and response.

  - Partners' and government support is limited to certain countries. GAVI is only supporting Afghanistan and Pakistan for measles SIAs and MRI is supporting the remaining GAVI eligible countries. there is severe shortage of support of the middle income countries, whether for implementation of SIAs or measles/rubella surveillance.
  - The GAVI window of MR campaign is open for all GAVI eligible countries to enhance introduction of rubella vaccine.
  - The current levels of support are not enough to achieve elimination. For example, the target age range supported by GAVI is limited to 9-59 months for measles and 9 months – 14 years for MR.
- Quality of EPI coverage data is a concern
  - There are inconsistencies in coverage data and the epidemiology of measles in several countries, suggesting that there are problems with the quality of administrative coverage data. For example, some countries report high 2 dose vaccination coverage (adequate to achieve elimination) but still experience large outbreaks.
- Need for more government commitment towards measles elimination target.
  - It is important to increase the visibility of measles elimination goal among decision makers, health workers and at the community level.
  - Power of NITAG would be important but only if it is credible. Opportunities like high level meetings and RC should be utilized
- The problem of measles among expatriates in the GCC countries.
  - Countries are encouraged to use the successful strategies of Bahrain and Oman to vaccinate expatriates communities.
- The high number of measles cases among infants< 9 months of age
- The target date of the regional measles elimination (2015):
  - Should it be maintained? Postponing the measles elimination target date might cause government relaxation and losing the momentum. It is important to capitalize on what is available to enhance the elimination activities

Decision/recommendations:

- RTAG members agreed to keep the target date of the regional measles elimination (year 2015) in order to keep the momentum and avoid relaxation.
- The region should proceed with verification of elimination in the countries that are ready to do so.
- Advocacy and communication capacity should be improved at regional and countries levels to increase visibility of Measles elimination among the decision makers, the health workers and the community. Having a well-functioning and supportive NITAG is an important advocacy tool for national health authorities. Opportunities, like high level national meetings and the RC meeting, should also be utilized for advocacy.

2. Scaling up the use of Rubella Vaccine:

Introductory notes were presented by Dr Nadia Teleb, RA/VPI, EMRO. The presentation reflected the current situation of rubella and use of rubella vaccine in the EMR. The points for discussion by the RTAG included the followings:

- With the current situation of measles vaccination coverage and measles outbreaks in some countries of the EMR, should WHO EMRO push for introduction of rubella vaccine in the remaining countries in the EMR?
- Is the region ready for developing regional target for rubella/CRS elimination?

Points raised and discussed

- Providing single measles vaccine is a missed opportunity for combating rubella. The benefit of combining rubella vaccine with measles vaccine is more than the cost of combining. These points will leverage the way to Rubella elimination through integration of efforts.
- The concern was raised about introducing rubella vaccine without attaining high coverage which might result in increasing occurrence of CRS, while the major burden currently might be under 15 years of age.
    - It was clarified that the required coverage for rubella vaccine to achieve elimination is around 80% which is much lower than the 95% required for measles elimination. Therefore, Rubella elimination is easier than Measles elimination due to the lower vaccination coverage needed to achieve elimination. Fifteen countries in the region have already decided to eliminate Rubella.
- Rubella and CRS disease burden
    - For countries lacking rubella disease burden data, there is an abundance of data in other countries to suggest there is significant disease burden in countries that have not introduced rubella vaccine.
    - Country-specific data on CRS is not available to support decision-making on rubella vaccine introduction. The need to set-up CRS surveillance when possible was reiterated
- Introduction of Rubella vaccine in Somalia might be potentially harmful due to the very low coverage of measles vaccine.
- Setting Rubella elimination target for all countries will encourage the remaining countries to introduce the Rubella vaccine and make efforts to achieve the target.
- The current GAVI window for MR campaign constitute and opportunity for introduction of rubella vaccine and consolidating the efforts for measles elimination.

Decision/Recommendations

- Setting a regional target of rubella/CRS elimination by 2020.
- Verification of elimination should be availed for the countries who achieve elimination
- Encouraging the remaining countries to introduce rubella vaccine. GAVI window of MR campaign is an opportunity to introduce rubella vaccine and consolidate efforts for measles elimination
- Somalia should defer introduction of Rubella vaccine due to the potential of the very low vaccination coverage to lead to an increase in CRS.

3. PEI end game strategy: Enhancing introduction of IPV

The subject was introduced by Dr Rudolf Eggers, WHO/HQ.

Points raised and discussed

- The benefit for introducing at least 1 dose of IPV
- The procedure of tOPV-bOPV switch
- Concern of NITAG and RTAG members about the tight time of introduction of IPV, including the tight timeline for GAVI eligible countries and the financial constraints in the MICs.
- The challenge of adding another injectable vaccine and the need for advocacy and communication, especially with the health care providers and the private sector.

Recommendations

- Countries that have not introduced IPV vaccine should develop a plan for implementing objective 2 of the polio endgame strategy, including IPV introduction, with timeline and budget. Planning for IPV introduction should follow same guidelines used for introduction of other new vaccines.
- WHO and partners to provide the necessary guidance and technical support

4. Strengthening the National Immunization Technical Advisory Groups (NITAGs) to support achieving the immunization targets

Dr Philippe Duclos, WHO/HQ, presented on the purpose and functions of NITAGs and their expected roles in achieving immunization targets and IPV introduction. Dr Carine Dochez, NESI, presented on strengthening the NITAGs for supporting EPI to achieve the immunization targets

Points raised and discussed

- The challenge facing the busy secretariat of the NITAG (EPI) in providing the necessary background information and the need for dedicated focal point
- The need for minimizing the number of the TAGs in the country (e.g EPI TAG, polio TAG,..). It was clarified that integration is recommended by EMRO
- There is a need to strengthen NITAG and build the capacity of the NITAG members.
- Engagement of the NITAG with training institutions to build EPI capacity, including members of the academia in the NITAG and ensuring updating the EPI components in the undergraduate and post graduate curricula.
- Focusing on the quality of the NITAG. Meeting the NITAG indicators does not necessarily mean having a fully functioning NITAG. Current NITAG indicators don't reflect how many recommendations of NITAGs are applied and how much government is respecting to NITAG decisions

Recommendations

- Strengthening capacity of the NITAGs with focusing on quality indicators
- Seeking opportunities of sharing information and experience between regional NITAGs and other functioning NITAGs (US, Canada) through exchange of information and/or attending related meetings
- Seeking opportunity of the support of SIVAC and NESI for building the capacity of more NITAGs in the region.

5. The establishment of the Regional Verification Commission and regional guidelines for the Documentation and Verification of Measles and Rubella Elimination

Dr Nadia Teleb, WHO, EMRO, presented the regional guidelines on verification of measles/rubella elimination and the proposal for the establishment of the regional measles-rubella verification commission. The draft guideline (attached) was shared with the RTAG members in advance for review and comments.

Recommendations

The RTAG members expressed their appreciation for the efforts in compiling the guidelines and indicated that the guidelines are well prepared and in a final shape. It was agreed to give the RTAG members two more weeks for providing final comments, if any, after that, the guidelines will be considered endorsed by the RTAG.

The Global Vaccine and Immunization Research Forum

The Global Vaccine and Immunization Research Forum (GVIRF) derives from the Global Vaccine Research Forum (GVRF) that the World Health Organization (WHO) successfully organized for a number of years. Building on that tradition, the meeting has now been expanded and will be co-hosted by the WHO, the National Institute of Allergy and Infectious Diseases, and the Bill & Melinda Gates Foundation. The GVIRF will serve as a forum for the discussion of the Research & Development component of the Global Vaccine Action Plan (GVAP) developed in the framework of the Decade of Vaccines Collaboration and endorsed by the 2012 World Health Assembly.

The objective of the GVIRF is to serve as scientific forum that will:

- review the GVAP R&D agenda progress;
- track progress and discuss obstacles related to priority vaccine research and development;
- identify actions recommended to be taken by the research and development community in the area of vaccines and immunization research, and
- create an opportunity for networking among the vaccine research and immunization community.

As endorsed by the Decade of Vaccines Collaboration Leadership Council and the Strategic Advisory Group of Experts on Immunization in 2012, the GVAP R&D reporting will be done every two years by the GVIRF and will look at:

- expanding capabilities and engagement with end-users,
- enabling development of new vaccines,
- accelerating development, licensing and uptake of vaccines, and
- improving programme efficiencies and increasing coverage.

The first GVIRF was held on 4-6 March 2014 at the Hyatt Regency Hotel in Bethesda, USA.

SIXTY-SEVENTH WORLD HEALTH ASSEMBLY
Provisional agenda item 12.2

A67/12
14 March 2014

Global vaccine action plan

Report by the Secretariat

1. An earlier version of document EB134/13 was considered and noted by the Executive Board at its 134th session.[1] Paragraphs 9, 12 and 15 below have been updated.

ACTION BY THE HEALTH ASSEMBLY

2. The Health Assembly is requested to note the report.

[1] See the summary records of the Executive Board at its 134th session, second meeting, section 1.

World Health Organization

EXECUTIVE BOARD **EB134/13**
134th session **6 December 2013**
Provisional agenda item 6.2

Global vaccine action plan

Report by the Secretariat

1. In May 2012, the Sixty-fifth World Health Assembly endorsed the global vaccine action plan in resolution WHA65.17 and requested the Director-General to monitor progress and report annually, through the Executive Board, to the Health Assembly, until the Seventy-first World Health Assembly, on progress towards achievement of global immunization targets, using the proposed accountability framework to guide discussions and future actions.

2. In May 2013, the Sixty-sixth World Health Assembly noted the Secretariat's report with its proposed framework for monitoring, evaluation and accountability as well as the process for reviewing and reporting progress under the independent oversight of the Strategic Advisory Group of Experts on immunization.[1]

3. An executive summary of the Global Vaccine Action Plan Assessment report[2] of the Strategic Advisory Group of Experts on immunization follows.

EXECUTIVE SUMMARY OF THE REPORT OF THE MEETING

4. Vaccines and immunization have created a healthier world. Progress is being made towards polio eradication. Measles and neonatal tetanus deaths are on the decline and new vaccines are being introduced into the national programmes of low- and middle-income countries with associated reductions in morbidity and mortality. Still, national governments, development partners and international agencies must invest more to meet the Decade of Vaccines' goals of disease eradication or elimination and to reduce mortality and morbidity from vaccine-preventable diseases.

Data quality improvement

5. Accurate immunization coverage and disease surveillance data are critical for making better programmatic decisions, meeting immunization targets and monitoring progress toward disease

[1] See document WHA66/2013/REC/3, summary record of the tenth meeting of Committee A, section 2.

[2] http://www.who.int/immunization/global_vaccine_action_plan/sage_dov_gvap_progress_report_2013.pdf.

reduction. Hence, data quality improvement is selected as the theme for the progress report of the global vaccine action plan in 2013. In many countries, the quality of currently available data are inadequate to inform the proper management of the immunization programmes and often programme managers in these situations lack confidence in the available data for decision-making. High quality data provide the cornerstone for accountability at all levels. National governments must take the responsibility to have the right data available at the right time and at the right places for the effective and efficient implementation of their national programmes by making greater investments for the improvement of data quality as well as enhance data transparency.

6. Improvement of data quality has to become the highest priority for all stakeholders. Priority should be placed on improving immunization coverage and vaccine-preventable disease surveillance data. Development partners and technical agencies must collaborate to establish a step-by-step, country-tailored approach to strengthen data quality at all administrative levels and provide guidance to countries on validating coverage and surveillance data. National Immunization Technical Advisory Groups should play an important role to independently monitor progress and data quality at the national level. Regional Immunization Technical Advisory Groups should support and catalyse activities of the National Immunization Technical Advisory Groups.

7. The availability of new information and communications technologies provide an opportunity for improving the recording, reporting and analysis of immunization data at all administrative levels. National programmes should develop plans to make use of these tools to improve their immunization information systems and improve data quality on vaccine coverage and disease surveillance.

8. In order to improve data quality, the Strategic Advisory Group of Experts on immunization recommends that:

- countries should conduct regular, timely reviews of data, including data quality, at all administrative levels, including the district level, to monitor programme performance;
- all countries should establish systems to monitor subnational data (district level) and report subnational coverage estimates to WHO by 2015;
- technical agencies should promote and provide guidance on the use of new information and communication technologies to improve the recording and reporting of data;
- technical agencies should review, revise and standardize the methodology for collection and analysis of vaccine-coverage survey data, including the use of sero-surveys.

Improving immunization coverage

9. Currently, only 59 (30%) of countries were assessed to be meeting the coverage target of at least 90% nationally and 80% in every district (or similar administrative level) with three doses of diphtheria, tetanus and pertussis-containing vaccines (DTP3) in children ≤12 months of age. Many countries – mainly in the African, South-East Asia and Eastern Mediterranean regions – will not meet routine immunization coverage targets by 2015. Even more worrying is that immunization coverage has remained low, stagnant or even decreasing in several of these countries. These countries should urgently intensify efforts to improve programme performance, utilizing administrative and survey data to direct their corrective actions. Civil society needs to be meaningfully engaged in policy dialogues so that reasons for low coverage are better understood and interventions are tailored to address identified problems. Countries, agencies and all development partners must engage with the vaccine industry to closely monitor the global supply of vaccines and ensure sufficient supply into the future. They should

anticipate and take timely actions to mitigate the risks of vaccine supply shortfalls that contribute to low coverage.

10. In order to improve immunization coverage, the Strategic Advisory Group of Experts on immunization recommends that:

- countries falling short of reaching coverage targets should urgently identify barriers and bottlenecks and implement targeted approaches to increase and sustain coverage based on a systematic review of community and district levels data;
- countries with a DTP1-DTP3 drop-out rate greater than 10% should review programme policies and performance and urgently implement measures to reduce dropout;
- all countries should establish or strengthen capacity for vaccine pharmacovigilance to detect and respond to adverse events to enhance confidence in immunization programmes.

Accelerating efforts to achieve disease eradication or elimination

11. As the world nears the final stages of the polio eradication effort, the challenges to achieve success have increased. It is imperative that all stakeholders now redouble their efforts to complete the job, as failure would represent a failure not only for the immunization community but for public health. Efforts toward meeting this goal should also strengthen immunization programmes and health systems, using the polio eradication initiative's assets and knowledge.

12. All countries are urged to establish national action plans to introduce at least one dose of inactivated poliovirus vaccine (all countries endemic for poliomyelitis should establish such a plan by mid-2014 and other high-risk countries by end-2014) and switch from the use of trivalent oral polio vaccine to bivalent oral polio vaccine once absence of all circulating vaccine-derived poliovirus 2 is confirmed globally for at least six months.

13. Although the Decade of Vaccines' 2012 milestone for neonatal tetanus elimination was met (10 additional countries eliminated neonatal tetanus by 2012, defined as less than one case per 1000 live births in each district), the goal of neonatal tetanus elimination is one that has been long delayed. As this is a relatively easy goal to achieve, it is crucial that all future milestones are met and the verification of elimination in all remaining countries is achieved by 2015.

14. Measles and rubella/congenital rubella syndrome elimination, while long accomplished in the Region of the Americas, is a new challenge for other regions. Currently, in addition to the Region of the Americas, only the Western Pacific Region is on track for reaching the regional measles elimination target; the African, European and Eastern Mediterranean regions are not on track and the South-East Asia Region has only just established an elimination goal and target year. Political commitment at all levels is needed to secure the investments required to achieve measles and rubella/congenital rubella syndrome elimination. Ninety-five per cent coverage with two doses of measles-containing vaccines is required in all districts and nationally (through routine immunization and/or supplementary immunization activities) to achieve measles elimination. Furthermore, it is essential that measles and rubella surveillance is increased to meet verification standards, monitor progress and take timely action.

15. To accelerate progress towards achieving elimination of measles and rubella/congenital rubella syndrome, the Strategic Advisory Group of Experts on immunization recommends that all countries should:

- establish or update their national plans to accelerate measles and rubella/ congenital rubella syndrome elimination. These should include details for strengthening overall health and immunization systems in order to ensure that the 95% vaccination coverage targets nationally and in all districts are met;

- strengthen case-based surveillance for measles and rubella and ensure timely and complete reporting, and establish or strengthen surveillance for congenital rubella syndrome.

Enhancing country ownership of national immunization programmes

16. Optimal performance requires that countries take ownership of their national programmes, establish good governance and invest the required resources. This requires that countries have processes to track immunization expenditures, identify resource gaps and take measures to fill the gaps.

17. The global vaccine action plan calls upon countries to report their national immunization expenditures (on per person basis). However, the data quality on immunization expenditures is inadequate to draw conclusions about expenditure trends.

18. National Immunization Technical Advisory Groups provide a means for national governments and other stakeholders to receive unbiased, critical advice on policy recommendations and for monitoring the successes and failures of the programmes. Even though the number of such Technical Advisory Groups that meet the functionality criteria has increased significantly in recent years, it is noted that many countries are still lagging behind in the establishment of such a body, particularly in the African and Western Pacific regions. The capacities of National Immunization Technical Advisory Groups to use evidence-based approaches need to be further strengthened with the support of all technical agencies and development partners.

19. To improve country ownership, the Strategic Advisory Group of Experts on immunization recommends that countries should: improve processes to track and report immunization expenditures using the System of Health Accounts[1] and establish and/or strengthen National Immunization Technical Advisory Groups and use them to advise on policy recommendations.

ACTION BY THE EXECUTIVE BOARD

20. The Board is invited to take note of the report.

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[1] The System of Health Accounts is a framework developed through collaboration between the Organisation for Economic Co-operation and Development, the European Union and WHO for the systematic description of financial flows related to health care. The aim of the System is to describe the health care system from an expenditure perspective both for international and national purposes (http://www.who.int/nha/sha_revision/en/).

Summary of the November 2013 GAVI Alliance Board Meeting

In November 2013, the GAVI Alliance Board made a number of decisions and recommendations summarised below:

GAVI Vaccine Investment Strategy (VIS)

- Opening of a funding window for Japanese Encephalitis vaccine Inviting country proposals for support in 2014 from all GAVI eligible countries at risk.
- A contribution to the Yellow Fever stockpile for 2014.
- Decided to support new yellow fever vaccine campaigns and request the Secretariat to develop a process for the funding of individual campaigns on the basis of robust risk assessments.
- Approved a contribution to the global cholera stockpile for use in epidemic and endemic settings and noted the opportunity for the GAVI Alliance to generate impact data based on the use of the cholera stockpile in emergency settings.
- Approved an assessment of the feasibility of GAVI support for rabies vaccines (to be evaluated in the next Vaccine Investment Strategy process).
- Noted that based on the current assessment there is a reasonable case for GAVI support for a malaria vaccine, and that the Board will consider opening a window if and when the vaccine is licensed, recommended for use by the joint meeting of the WHO Strategic Advisory Group of Experts and the Malaria Programme Advisory Committee (expected in 2015) and WHO pre-qualified, taking into account updated projections of impact, cost and country demand as reviewed by the Programme and Policy Committee (PPC).
- Noted the potential public health impact of vaccinating pregnant women against seasonal influenza and the need to assess the emerging evidence of impact of vaccination on neonates, but decides not to open a funding window for influenza vaccines at this time.
- Requested the Secretariat to work with Alliance partners to monitor and evaluate investment in stockpiles.

Polio & Routine Immunisation

- Endorsed GAVI's overall objective related to polio eradication to improve immunisation services in accordance with GAVI's mission and goals while supporting polio eradication by harnessing the complementary strengths of GAVI and GPEI in support of countries.
- Opened a funding window for IPV such that the GAVI Secretariat can invite GAVI eligible and graduating countries (the "GAVI IPV Eligible Countries"), in line with the GPEI Endgame Strategy 2013-2018, to submit country proposals for support in accordance with a number of policy arrangements and exceptions.

- Approved, subject to polio-specific additional funds being made available from donors, an initial IPV Funding Envelope from which the Secretariat shall allot funding to IPV programmes until 31 December 2014.

GAVI Engagement with Graduating Countries

- Approved that countries entering the graduation process after 31 December 2013 will be eligible to apply for new support (HSS and vaccine support) until the end of the next calendar year after the date they have been informed of their expected graduation. Vaccine and HSS support may be provided to countries until they graduate.
- However, HSS support will only be available to such countries with a DTP3 coverage below 90%.
- Approved that, to address issues of low immunisation coverage, countries that have entered the graduation process prior to 31 December 2013 and that have a DTP3 coverage below 90% are eligible to apply for HSS support that may be provided until they graduate.
- Requested the Secretariat to conduct analyses and consultations to develop and propose instruments to support access to affordable prices for all Lower Middle Income Countries (LMICs), including graduated countries and non-GAVI LMICs. Options would be brought to the Board for consideration in 2014.
- Approved an amount up to US$ 2 million to be added to the 2014 Business Plan for the GAVI Secretariat and partners to scale-up engagement with graduating countries.
- Noted that the decisions made in relation to support for graduating countries do not pre-empt any decision to be made on graduation support in the 2016-2020 Strategy.

HPV Demonstration Projects

- The Board requested that the Secretariat report on lessons learnt from the HPV demonstration projects and rollouts.

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Global Advisory Committee on Vaccine Safety, 11–12 December 2013

The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body, was established by WHO to provide independent, scientifically rigorous advice on vaccine safety issues of potential global importance.[1] GACVS held its 29th meeting in Geneva, Switzerland, on 11–12 December 2013.[2] The committee reviewed the following topics: the safety profiles of chimeric Japanese encephalitis, inactivated poliovirus, and rotavirus vaccines; allegations related to the safety of human papillomavirus vaccine (HPV); investigations related to increased pyrogenicity of seasonal influenza vaccine; and the development of a global vaccine safety surveillance manual addressing basic concepts for immunization programme managers and regulatory staff.

Safety profile of Japanese encephalitis (JE) chimeric vaccine

During the June 2013 meeting of GACVS the safety profiles of 1 live attenuated and 2 inactivated Japanese encephalitis (JE) vaccines based on the SA 14-14-2 strain were considered, and the committee concluded that there were no significant concerns regarding the safety profile of these vaccines.[3] During the December 2013 meeting GACVS considered the safety profile of a novel chimeric JE vaccine (Imojev). This vaccine is a live vaccine construct using the yellow fever (YF) 17D and

[1] See No. 41, 1999, pp. 337–338.

[2] GACVS invited additional experts to present and discuss evidence related to particular topics. These experts included persons affiliated with: Center for Biologics Evaluation and Research (U.S. F.D.A), Rockville MD, USA; Centers for Disease Control and Prevention, Atlanta GA, USA; CSL, Parkville, Australia; Emory University, Atlanta GA, USA; National Institute of Infectious Diseases, Tokyo, Japan; National Institute for Public Health and the Environment, Bilthoven, The Netherlands; Royal Children's Hospital, Melbourne, Australia; Sanofi Pasteur, Lyon, France; Therapeutic Goods Administration, Symonston, Australia.

[3] See No. 88, 2013, pp. 301–312.

Comité consultatif mondial de la Sécurité vaccinale, 11-12 décembre 2013

Le Comité consultatif mondial de la Sécurité vaccinale (GACVS), composé d'experts cliniques et scientifiques, a été créé par l'OMS pour la conseiller, en toute indépendance et avec la rigueur scientifique voulue, sur des problèmes de sécurité vaccinale pouvant avoir une importance mondiale.[1] Le GACVS a tenu sa vingt-neuvième réunion à Genève (Suisse) les 11 et 12 décembre 2013.[2] Il a examiné les questions suivantes: les profils d'innocuité de 3 vaccins (le vaccin chimère contre l'encéphalite japonaise, le vaccin antipoliomyélitique inactivé et le vaccin antirotavirus); les allégations concernant l'innocuité des vaccins anti-papillomavirus (PVH); les enquêtes relatives à la pyrogénicité accrue du vaccin contre la grippe saisonnière; et l'élaboration d'un manuel pour la surveillance de l'innocuité vaccinale au niveau mondial traitant des concepts essentiels à l'intention des administrateurs de programme de vaccination et du personnel chargé de la réglementation.

Profil d'innocuité du vaccin chimère contre l'encéphalite japonaise (EJ)

Au cours de sa réunion de juin 2013, le GACVS avait examiné les données récentes sur les profils d'innocuité d'un vaccin vivant atténué et de 2 vaccins inactivés contre l'encéphalite japonaise (EJ) préparés à partir de la souche SA-14-14-2, et avait conclu que le profil d'innocuité de ces vaccins ne soulevait aucune préoccupation majeure.[3] Au cours de la réunion de décembre 2013, le GACVS a examiné le profil d'innocuité d'un nouveau vaccin chimère EJ (Imojev). Il s'agit d'un vaccin vivant construit à partir des souches vaccinales 17D du virus de

[1] Voir Nº 41, 1999, pp. 337-338.

[2] Le GACVS a invité d'autres experts pour présenter et discuter les données relatives à des sujets particuliers. Il s'agissait notamment des personnes affiliées aux organismes suivants: Center for Biologics Evaluation and Research (U.S. F.D.A), Rockville MD, États-Unis; Centers for Disease Control and Prevention, Atlanta GA, États-Unis; CSL, Parkville, Australie; Emory University, Atlanta GA, États-Unis; National Institute of Infectious Diseases, Tokyo, Japon; National Institute for Public Health and the Environment, Bilthoven, Pays-Bas; Royal Children's Hospital, Melbourne, Australie; Sanofi Pasteur, Lyon, France; Therapeutic Goods Administration, Symonston, Australie.

[3] Voir Nº 88, 2013, pp. 301-312.

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JE SA-14-14-2 vaccines strains. Construction of the vaccine involves insertion of the nucleic acid sequences encoding the envelope proteins (prM and E) of the JE SA 14-14-2 strain into the YF17D backbone, resulting in a chimeric vaccine virus which is attenuated and lacks neurotropic properties.

Pre-licensure and post-licensure safety and immunogenicity data for Imojev were presented. This vaccine is currently licensed in Australia, Malaysia, the Philippines and Thailand. Pre-licensure data are available for 2486 adults and 2248 children (9–18 months, at first dose). The vaccine is immunogenic and immunogenicity does not appear to be affected by concomitant administration of the measles/mumps/rubella (MMR) vaccine. Short-term safety data for injection site and systemic reactions (reported by >10% of vaccine recipients) were presented and showed that in the adult population, adverse reaction rates were significantly lower with Imojev than with a mouse brain-derived vaccine.[4] There is limited post-licensure safety experience with Imojev, with approximately 49 000 doses administered to date, and a larger safety database will be necessary to evaluate the risk of rare adverse events.

GACVS expressed interest in receiving additional information about potential environmental safety issues relative to the use of a chimeric vaccine. These include the theoretical risk of reversion or genetic reassortment with wild-type JE viruses or other circulating flaviviruses that could result in the vaccine virus acquiring neurotropic and/or infectivity properties, and vaccine virus transmission through mosquito hosts. However the biological plausibility of this is remote, given the short duration of viraemia post vaccination and the limited potential for virus vaccine replication and dissemination within the mosquito.

Post-licensure studies are essential in countries were widespread use of a JE chimeric vaccine is planned or is currently implemented. In particular, post-licensure studies and surveillance should include active surveillance of cases of encephalitis along with a laboratory determination of the aetiology of the encephalitis. Safety data on JE vaccines (including but not limited to the chimeric vaccine) administered to immunocompromised persons and pregnant and lactating women are limited.

Safety of inactivated poliovirus vaccines (IPV)

With several countries on the threshold of adopting the use of IPV, in line with the Global Vaccine Action Plan (GVAP) strategy for polio eradication, the GACVS session on IPV focussed on visiting: i) the safety record of IPV, as determined in controlled clinical trials during development of the currently available stand-alone and IPV-containing combination vaccines; ii) Adverse events following immunization (AEFI) reports related to IPV from the Vaccine Adverse Events Reporting System (VAERS) of the USA; and iii) issues related to the manufacturing process for IPV.

[4] Torresi J, McCarthy K, Feroldi E, et al. Immunogenicity, safety and tolerability in adults of a new single-dose, live-attenuated vaccine against Japanese encephalitis: randomised controlled phase 3 trials. Vaccine. 2010; 28:7993-8000.

la fièvre jaune (FJ) et SA-14-14-2 du virus de l'EJ. La construction du vaccin fait intervenir l'introduction des séquences d'acide nucléique codant pour les protéines d'enveloppe (prM et E) de la souche EJ SA-14-14-2 dans la structure de base YF17D, ce qui donne un virus vaccinal chimère atténué qui ne possède pas de propriétés neurotropiques.

Des données préhomologation et posthomologation relatives à l'innocuité et à l'immunogénicité du vaccin Imojev ont été présentées. Ce vaccin est actuellement homologué en Australie, en Malaisie, aux Philippines et en Thaïlande. Les données préalables à l'homologation sont disponibles pour 2486 adultes et 2248 enfants (âgés de 9 à 18 mois, lors de la première dose). Le vaccin est immunogène et l'immunogénicité ne semble pas atténuée par l'administration concomitante du vaccin rougeole-oreillons-rubéole (ROR). On dispose de données relatives à l'innocuité à court terme concernant les réactions au point d'injection et les réactions systémiques (signalées par >10% des personnes vaccinées) qui démontrent que, dans la population adulte, les taux de réactions indésirables étaient nettement inférieurs avec Imojev qu'avec un vaccin préparé sur cerveau de souris.[4] Les données d'expérience relatives à l'innocuité posthomologation d'Imojev sont limitées, le nombre de doses administrées jusque-là étant approximativement de 49 000; il sera nécessaire de disposer d'une base de données plus importante sur l'innocuité pour évaluer le risque de manifestations indésirables rares.

Le GACVS souhaiterait obtenir davantage d'informations sur les éventuelles questions de sécurité environnementale liées à l'utilisation d'un vaccin chimère. Parmi celles-ci figurent notamment la question du risque théorique de réversion ou de réassortiment génétique avec les virus EJ de type sauvage ou d'autres flavivirus circulants qui aboutirait à l'acquisition par le virus vaccinal de propriétés neurotropiques et/ou infectieuses, et la question de la transmission du virus vaccinal par l'intermédiaire de moustiques hôtes. Toutefois, la plausibilité biologique d'un tel phénomène est toutefois limitée du fait de la faible durée de la virémie postvaccinale et de la capacité limitée du virus vaccinal à se répliquer et se diffuser dans l'organisme du moustique.

Il est essentiel de mener des études posthomologation dans les pays où une large utilisation du vaccin chimère EJ est prévue ou actuellement mise en œuvre. En particulier, les études et la surveillance posthomologation doivent inclure une surveillance active des cas d'encéphalite accompagnée d'une détermination en laboratoire de l'étiologie de l'encéphalite. Les données relatives à l'innocuité des vaccins EJ administrés aux personnes immunodéprimées, aux femmes enceintes et allaitantes restent limitées (y compris mais non seulement pour le vaccin chimère).

Sécurité du vaccin antipoliomyélitique inactivé (VPI)

Plusieurs pays étant sur le point d'adopter le VPI, conformément à la stratégie d'éradication de la poliomyélite définie dans le Plan d'action mondial pour les vaccins, la séance du Comité consacrée au VPI s'est attachée à examiner: i) le bilan du VPI, tel qu'il ressort des essais cliniques contrôlés menés lors de l'élaboration du vaccin existant actuellement administré seul ou des vaccins associés contenant le VPI; ii) les rapports de manifestations postvaccinales indésirables (MAPI) relatifs au VPI provenant du Vaccine Adverse Events Reporting System (Système de notification des manifestations postvaccinales indésirables – VAERS) des États-Unis; et iii) les questions liées au processus de fabrication du VPI.

[4] Torresi J, McCarthy K, Feroldi E, et al. Immunogenicity, safety and tolerability in adults of a new single-dose, live attenuated vaccine against Japanese encephalitis: randomised controlled phase 3 trials. Vaccine. 2010; 28:7993 8000.

The first polio vaccine was developed by Jonas Salk, from formaldehyde-inactivated wild polio viruses. Salk's IPV was tested and proved highly efficacious against paralytic poliomyelitis in a large clinical trial conducted in US schoolchildren in 1954, which was rapidly followed by licensure of the product and implementation of mass vaccination campaigns in children in the USA, Canada and Western Europe. In less than a year, however, this first IPV was the centre of one the most serious vaccine safety events recorded, the Cutter incident, in which inadequate inactivation of the polio viruses during the manufacturing process resulted in 61 cases of vaccine-associated paralytic poliomyelitis (VAPP), 80 family contact cases, 17 community contact cases and 11 deaths. Following this incident, IPV manufacturing techniques were modified to ensure complete inactivation and avoid any potential risk of injecting live polio viruses. This also resulted in a reduction of the immunogenicity of IPV preparations. In the 1970s an enhanced-potency IPV, similar in immunogenicity to the original product, replaced the second generation IPV. Currently IPV is offered as an individual vaccine as well as in vaccine combinations for primary immunization and for boosters. The available data indicate that known adverse events following IPV administered alone are limited to non-serious reactions. Local reactions, as may occur with any inactivated vaccine, are most common. Adverse events due to IPV administered as a combination with other vaccines are difficult to differentiate from those induced by the other vaccines, e.g. diphtheria+ tetanus+ whole cell pertussis (DTwP). Reviews have not documented any serious adverse events causally related to IPV. Further, a dose of IPV administered prior to a course of oral poliovirus vaccine (OPV) reduces the risk of VAPP compared with an exclusively OPV series.

IPV was introduced in the childhood immunization schedule in the USA in 1997, replacing OPV. Currently, there are 4 licensed vaccines of which 1 is IPV standalone vaccine and 3 are in combination with other vaccines. An assessment of AEFI in all ages indicated that most adverse events in VAERS reported from 1 January 1999 to 31 December 2012 were non-serious. Less than 1% of reports were for IPV given alone. The vaccines most commonly co-administered with IPV are pneumococcal conjugate, *Haemophilus influenzae* type b (Hib), hepatitis B, diphtheria+ tetanus+ acellular pertussis (DTaP), and rotavirus vaccines. Although sudden infant death syndrome (SIDS) is the most commonly coded term for deaths in infants for all IPV-containing vaccines, the Institute of Medicine review (2003) rejected a causal relationship between SIDS and multiple vaccines.[5] Based on available data, GACVS is reassured that IPV and IPV-containing vaccines have an excellent safety profile.

Le premier vaccin antipoliomyélitique a été mis au point par Jonas Salk, à partir de virus sauvages de la poliomyélite inactivés par le formaldéhyde. Le vaccin antipoliomyélitique inactivé de Salk a été testé et s'est avéré très efficace contre la poliomyélite paralytique lors d'un gigantesque essai clinique mené chez des enfants d'âge scolaire aux États-Unis en 1954, lequel a été rapidement suivi de l'homologation du produit et de la mise en œuvre de campagnes de vaccination de masse chez les enfants aux États-Unis, au Canada et en Europe occidentale. Toutefois, moins d'une année plus tard, ce premier VPI a été au cœur de l'un des plus graves événements postvaccinaux jamais survenus, le *Cutter incident*, au cours duquel un procédé d'inactivation inapproprié du virus de la poliomyélite au cours du processus de fabrication a abouti à 61 cas de poliomyélite paralytique associée au vaccin (PPAV), 80 cas contacts dans les familles, 17 cas contacts dans la communauté et 11 décès. À la suite de cet accident, les techniques de fabrication du VPI ont été modifiées pour garantir l'inactivation complète du virus et éviter que des virus poliomyélitiques vivants puissent être injectés à la personne vaccinée. Cela s'est également traduit par une réduction de l'immunogénicité des préparations de VPI. Dans les années 1970, un VPI à activité renforcée, semblable par son immunogénicité au produit original, a remplacé la deuxième génération de VPI. Le VPI est actuellement proposé seul ou en association avec d'autres vaccins pour la vaccination primaire ou de rappel. Les données disponibles indiquent que les manifestations indésirables connues du VPI administré seul sont essentiellement des manifestations bénignes. Il s'agit le plus souvent de réactions locales pouvant survenir avec tout vaccin inactivé. Les manifestations indésirables lorsque le VPI est administré en association avec d'autres vaccins sont difficiles à différencier des manifestations indésirables dues à ces autres vaccins (par exemple le vaccin antidiphtérique- anticoquelucheux – antitétanique (DTC) à cellules entières). Les examens n'ont pas permis d'obtenir des informations sur d'éventuelles manifestations indésirables graves liées expressément au VPI. Une première dose de VPI administrée avant le vaccin antipoliomyélitique oral (VPO) réduit également le risque de cas de PPAV par comparaison à une vaccination utilisant exclusivement le VPO.

Le VPI a été introduit dans le programme de vaccination infantile aux États-Unis en 1997 en remplacement du VPO. Il existe actuellement 4 vaccins homologués, l'un est un vaccin VPI administré seul et 3 sont des vaccins associés. Une évaluation des MAPI indépendamment de l'âge a montré que la plupart des manifestations indésirables signalées par le VAERS entre le 1er janvier 1999 et le 31 décembre 2012 n'étaient pas graves. Moins de 1% des notifications concernaient le VPI administré seul. Les vaccins les plus fréquemment administrés conjointement au VPI sont le vaccin antipneumococcique conjugué, le vaccin contre *Haemophilus influenzae* de type b (Hib), les vaccins contre l'hépatite B, la diphtérie, le tétanos, le vaccin anticoquelucheux acellulaire (DTaC) et les vaccins antirotavirus. Bien que le syndrome de mort subite du nourrisson (MSN) soit le terme le plus fréquemment codé pour les décès de nourrissons pour tous les vaccins contenant le VPI, l'examen mené par l'Institute of Medicine des États-Unis (2003) a rejeté tout lien de causalité entre le syndrome de MSN et plusieurs vaccins.[5] Sur la base des données disponibles, le GACVS est convaincu que le VPI et les vaccins contenant le VPI présentent un excellent profil d'innocuité.

[5] Stratton K et al. Immunization safety review: vaccinations and sudden unexpected death in infancy. Institute of Medicine (IOM), 2003.

[5] Stratton K et al. Immunization safety review: vaccinations and sudden unexpected death in infancy. Institute of Medicine, 2003.

GACVS was also presented with an overview of the manufacturing process of IPV by a licensed vaccine manufacturer. The complexities of the manufacturing process were noted, in particular the methods used to ensure virus inactivation and containment to prevent accidental environmental contamination. WHO discussed plans for IPV vaccine technology transfer to emerging country vaccine manufacturers. GACVS noted, given the complexities of the IPV manufacturing process, the importance of ensuring appropriate technical support, training and regulatory oversight to IPV vaccine manufacturers.

Increased occurrence of febrile seizures with a seasonal influenza vaccine

GACVS reviewed progress by the Australian Therapeutic Goods Administration (TGA) and the company that manufactures Fluvax (CSL, Parkville, Victoria, Australia) a trivalent influenza vaccine (TIV) vaccine which, in 2010, was associated with an increased risk of fever and febrile seizures, particularly in children aged <5 years.[6] This resulted in a 3-month suspension of the Australian influenza vaccination programme for children. Subsequent investigations confirmed that no other TIVs were associated with this increased risk. Fluvax is now contraindicated in children aged <5 years and avoided in those aged <9 years.

The manufacturer has conducted several analyses in order to clarify the etiological mechanism of increased pyrogenicity of this specific vaccine product. Initial findings identified several possible contributing factors that may have triggered the reaction to the vaccine. These factors include, in particular, the presence of large RNA fragments, as well as characteristics of the B Brisbane seed virus strain used in seasonal influenza vaccines in 2010 that has a greater ability to maintain RNA fragments during the manufacturing process. GACVS noted that the virus splitting process used by CSL differs from that used by other manufacturers. The company informed GACVS of a planned modification to the vaccine manufacturing process that will be implemented in 2014. It is expected that this modification will lead to a reduction or elimination of the possible contributing factors and therefore a reduction in the additional pyrogenicity.

GACVS recommended that further studies be undertaken in healthy adult (non-pregnant) subjects to ascertain the impact of the new manufacturing process, particularly on safety of the product. Once shown to be safe in this group, the safety of Fluvax in pregnant women will need to be assessed. GACVS concurred with TGA's decision to contraindicate the use of the present CSL vaccine in children aged <5 years. The committee also took note of measures mandated by TGA to reduce inadvertent vaccination, which have included a number of programmatic measures including package labelling. GACVS noted these events illustrate the importance of post-licensure brand-specific safety surveillance which

Un exposé du processus de fabrication du VPI a été présenté au GACVS par le fabricant d'un vaccin homologué. Le Comité a noté la complexité du procédé de fabrication, en particulier des méthodes utilisées pour garantir l'inactivation et l'endiguement du virus afin de prévenir une éventuelle contamination environnementale accidentelle. L'OMS a débattu des projets de transfert de technologie du vaccin VPI aux fabricants de vaccins des pays émergeants. Le GACVS a noté que, compte tenu de la complexité du procédé de fabrication du VPI, il importait de garantir un soutien technique, une formation et une supervision réglementaire appropriés aux fabricants de vaccins antipoliomyélitiques inactivés.

Augmentation des convulsions fébriles après l'administration de vaccins contre la grippe saisonnière

Le GACVS a examiné les progrès réalisés dans l'enquête menée par les autorités de réglementation australiennes (Australian Therapeutic Goods Administration – TGA) et l'entreprise qui fabrique le Fluvax (CSL – Parkville, Victoria, Australie), un vaccin trivalent contre la grippe qui, en 2010, a été associé à un risque accru de fièvre et de convulsions, en particulier chez les enfants âgés de <5 ans.[6] L'Australie avait en conséquence suspendu pour une période de 3 mois le programme de vaccination des enfants contre la grippe. Les enquêtes ultérieures ont confirmé qu'aucun autre vaccin trivalent contre la grippe n'était associé à ce risque accru. Le Fluvax est désormais contre-indiqué chez les enfants âgés de <5 ans et doit être évité chez ceux âgés de <9 ans.

Le fabricant a mené plusieurs analyses afin de préciser le mécanisme étiologique de la pyrogénicité accrue de ce produit vaccinal spécifique. Les conclusions initiales ont décelé plusieurs facteurs ayant pu déclencher la réaction au vaccin. Parmi ces facteurs figurent, notamment, la présence de larges fragments d'ARN, ainsi que les caractéristiques de la souche virale B Brisbane utilisée dans les vaccins contre la grippe saisonnière en 2010 qui présente une plus grande capacité à conserver des fragments d'ARN au cours du procédé de fabrication. Le GACVS a noté que le procédé de fragmentation des virus utilisé par le CSL diffère de celui utilisé par d'autres fabricants. L'entreprise a informé le Comité qu'il était prévu de modifier le procédé de fabrication du vaccin à compter de 2014. On escompte que cette modification conduira à une réduction voire à l'élimination des facteurs supposés contribuer à la pyrogénicité accrue et par conséquent, à une réduction de celle-ci.

Le GACVS a recommandé que des études plus approfondies soient menées chez des sujets adultes (sauf chez les femmes enceintes) en bonne santé afin de confirmer l'impact du nouveau procédé de fabrication et surtout, l'innocuité du produit. Une fois que l'innocuité du produit aura été avérée pour ce groupe, il sera nécessaire d'évaluer l'innocuité du Fluvax chez les femmes enceintes. Le GACVS a approuvé la décision des autorités australiennes concernant la contre-indication de l'utilisation de l'actuel vaccin de CSL chez les enfants âgés de <5 ans. Le Comité a également pris note des mesures prescrites par les TGA afin de réduire la vaccination par inadvertance, parmi lesquelles figurent un certain nombre de mesures programmatiques dont l'étiquetage des emballages. Le GACVS

[6] See No. 29, 2013, pp. 301–312.

[6] Voir N° 29, 2013, pp. 301-312.

presents particular challenges with seasonal influenza vaccines.

Update on intussusception following rotavirus vaccine administration

GACVS last reviewed the safety profile of Rotateq and Rotarix vaccines during its December 2011 meeting.[7] At that time, the committee concluded that both vaccines had a good safety profile, but that they may be associated with an increased (up to 6-fold) risk of intussusception after the first dose of vaccine in some populations. During the current meeting, new data from Australia and the USA were reviewed in order to update the assessment of intussusception risk related to both vaccines.

In Australia, a recently published study of intussusception cases identified from national hospitalization databases, supplemented by active hospital-based surveillance from July 2007 through June 2010, was reviewed.[8] As both vaccines are available in the country, the study allowed estimation of product-specific risks of intussusception. Findings were similar for both vaccines, suggesting that a significant risk of intussusception exists after the first and second dose of both vaccines. The average vaccine-attributable risk for intussusception, based on the estimated relative incidence in the 1–21 days after dose 1 and the 1–7 days after dose 2, was estimated to be 5.6 additional cases per 100 000 vaccinated infants.

In the USA, data are available from the spontaneous reporting system for vaccine safety (VAERS), as well as from 2 distinct vaccine safety monitoring systems that allow for cohort study designs: the Vaccine Safety Datalink (VSD) and the Post-licensure Rapid Immunization Safety Monitoring system (PRISM). VSD is a network of linked databases, involving 9 integrated healthcare delivery institutions, whilst PRISM is a sentinel-like system using claims data from national health insurance companies. VAERS data showed that for Rotateq, from 2006 to 2012, 584 confirmed cases of intussusception were reported for 47 million doses distributed. A cluster of cases was observed between days 3 and 6 after doses 1 and 2. For Rotarix, 66 confirmed intussusception cases were reported for 7.4 million doses distributed. The VSD analyses identified a small cluster of cases following Rotarix, with 6 cases of intussusception for 200 000 doses administered. In contrast, no such cluster was found with Rotateq, with 8 intussusception cases identified (4 each after dose 1 and dose 3) for 1.3 million doses administered. The PRISM data suggest that Rotateq is also associated with clusters of intussusception cases with an attributable risk of approximately 1 case per 100 000 doses whilst the number of cases is currently too small to allow calculation of an attributable risk for Rotarix.

GACVS acknowledged that the findings from both countries tend to confirm a risk of intussusception following

[7] See No. 6, 2012, pp. 54–56.

[8] Carlin JB et al. Clin Infect Dis. 2013; 57:1427-34.

a noté que ces manifestations illustrent l'importance de la surveillance de la sécurité spécifique aux marques après l'homologation, qui pose des défis particuliers lorsqu'il s'agit des vaccins saisonniers contre la grippe.

Actualisation des données sur l'invagination après l'administration d'un vaccin antirotavirus

Le GACVS a procédé pour la dernière fois à l'examen du profil d'innocuité des vaccins Rotateq et Rotarix au cours de la réunion de décembre 2011.[7] Le Comité avait alors conclu que les 2 vaccins avaient un bon profil d'innocuité, mais pouvaient être associés à un risque accru (pouvant être multiplié par 6) d'invagination après la première dose de vaccin dans certaines populations. Au cours de la présente réunion, de nouvelles données en provenance d'Australie et des États-Unis ont été examinées afin d'actualiser l'évaluation du risque d'invagination lié aux 2 vaccins.

Pour l'Australie, l'étude examinée[8] est l'étude publiée récemment sur les cas d'invagination recensés à partir des bases de données d'hospitalisation au niveau national, qui a été complétée par une surveillance active dans les établissements hospitaliers, menée de juillet 2007 à juin 2010. Étant donné que les 2 vaccins sont disponibles dans le pays, l'étude a permis une estimation des risques d'invagination spécifiques au produit. Les conclusions ont été semblables pour les 2 vaccins, suggérant qu'un risque significatif d'invagination existe après la première et la deuxième dose des 2 vaccins. On estime que le risque moyen d'invagination attribuable au vaccin, basé sur l'estimation de l'incidence relative entre les premier et 21e jours après la dose 1 et les premier et septième jours après la dose 2, est de 5,6 cas supplémentaires pour 100 000 nourrissons vaccinés.

Aux États-Unis, les données sont issues du système de notification des manifestations postvaccinales indésirables (VAERS), ainsi que de 2 systèmes de suivi de la sécurité vaccinale distincts qui permettent de réaliser des études de cohorte: le Vaccine Safety Datalink (VSD) et le Post-licensure Rapid Immunization Safety Monitoring system (PRISM). VSD est un réseau de bases de données reliées entre elles, auquel participent 9 établissements de prestation de soins intégrés, tandis que PRISM est un système de type sentinelle utilisant les compagnies d'assurance maladie nationales qui fournissent des données relatives aux demandes d'indemnisation. Les données du VAERS montraient que, pour le Rotateq, de 2006 à 2012, 584 cas confirmés d'invagination ont été signalés sur un total de 47 millions de doses distribuées. On observe une grappe de cas entre les troisième et sixième jours après les doses 1 et 2. Pour le Rotarix, 66 cas confirmés d'invagination ont été notifiés sur un total de 7,4 millions de doses distribuées. Les analyses menées par VSD ont recensé une grappe de cas survenus après l'administration du Rotarix, sur un petit nombre limité à 6 cas d'invagination pour 200 000 doses administrées. À l'inverse, aucune grappe de cas de ce type n'a pu être constatée avec le Rotateq sur les 8 cas d'invagination recensés (4 après la dose 1 et la dose 3) pour 1,3 million de doses administrées. Les données de PRISM suggèrent que le Rotateq est également associé à des grappes de cas d'invagination avec un risque attribuable d'environ 1 cas pour 100 000 doses, tandis que le nombre de cas est actuellement trop faible pour permettre un calcul du risque attribuable par le Rotarix.

Le GACVS a pris note des conclusions des 2 pays qui tendent à confirmer un risque d'invagination suite à l'administration

[7] Voir No 6, 2012, pp. 54-56.

[8] Carlin JB et al. Clin Infect Dis. 2013; 57:1427-34.

administration of both vaccines, in particular during the first 7 days following a first dose. The committee noted that attributable risk estimates vary across studies. This might reflect differences in the background rate of intussusception (estimated to be double in Australia compared to the USA) but could also reflect sampling uncertainty in all available estimates and limitations of the surveillance systems that lead to some uncontrolled biases (e.g. differences in diagnostic tests and case definitions in different settings). Overall, the findings remain reassuring that the risk of intussusception following current rotavirus vaccines remains small compared to the benefits of preventing the impact of severe diarrhoea. Given possible population differences in risk of intussusception, it is important that rotavirus vaccine introduction in other parts of the world be accompanied by similar active intussusception surveillance studies together with rotaviral disease surveillance so that the benefits and risks can be ascertained with relevant evidence.

Human papillomavirus vaccines safety (HPV)

GACVS reviewed evidence related to autoimmune disease and the HPV, with a focus on multiple sclerosis (MS). The last review was conducted in June 2013, when the Committee reviewed updated data from the USA, Australia, Japan, and the manufacturers of Cervarix (GlaxoSmithKline) and Gardasil (Merck). With >175 million doses distributed worldwide and more countries offering the vaccine through national immunization programmes, the Committee continued to be reassured by the safety profile of the available products. Serious adverse events that have been reported as potential signals have been investigated in more detail and were not confirmed, including Guillain-Barré syndrome, seizures, stroke, venous thromboembolism, anaphylaxis and other allergic reactions. Surveillance of pregnancy outcomes among women inadvertently vaccinated during pregnancy through spontaneous reports and registries has not detected any adverse outcomes above expected rates.

While surveillance data and epidemiologic studies on HPV vaccine have remained reassuring, allegations have continued to surface in the media and elsewhere about the safety of the vaccine. Epidemiologic studies before and after licensure showed no increased risk of autoimmune disease, including MS. Since the introduction of HPV vaccines, such diseases have been under particularly careful investigation given their correspondingly high age-specific background incidence.[9, 10, 11]

des 2 vaccins, en particulier au cours des 7 premiers jours suivant une première dose vaccinale. Le Comité note que les estimations relatives au risque attribuable varient d'une étude à l'autre. Ces variations peuvent être le reflet de différences dans le taux d'invagination de référence (2 fois plus élevé en Australie qu'aux États-Unis), mais peuvent aussi refléter des incertitudes liées à l'échantillonnage pour l'ensemble des estimations disponibles ainsi que les limites des systèmes de surveillance qui conduisent à certains biais non maîtrisés (par exemple des différences dans les tests de diagnostic et les définitions des cas d'un lieu à l'autre). D'une manière générale, les conclusions restent rassurantes, confirmant que le risque d'invagination dû aux vaccins antirotavirus actuels reste faible par comparaison aux avantages de la prévention de la diarrhée sévère et de ses conséquences. Compte tenu des différences possibles dans le risque d'invagination au sein des populations, il est important que l'introduction du vaccin antirotavirus dans d'autres parties du monde soit accompagnée d'études semblables de surveillance active de l'invagination et d'une surveillance des maladies à rotavirus de façon à ce que des éléments probants permettent d'évaluer les avantages et les risques.

Innocuité des vaccins contre le papillomavirus humain (PVH)

Le GACVS a examiné les données factuelles liées aux maladies auto-immunes et à la vaccination par le vaccin contre le PVH. Le dernier examen de ces vaccins avait été effectué en juin 2013, lorsque le Comité avait examiné les données actualisées provenant des États-Unis, de l'Australie, du Japon et des fabricants du Cervarix (GlaxoSmithKline) et du Gardasil (Merck). Avec >175 millions de doses distribuées dans le monde et davantage de pays proposant la vaccination par l'intermédiaire des programmes de vaccination nationaux, le Comité continue à se montrer satisfait du profil d'innocuité des produits disponibles. Les manifestations indésirables graves qui ont été notifiées en tant que signes d'alerte potentiels ont fait l'objet d'enquêtes plus approfondies et n'ont pas été confirmées, qu'il s'agisse du syndrome de Guillain-Barré, de convulsions, d'AVC, de thrombo-embolie veineuse, d'anaphylaxie ou d'autres réactions allergiques. La surveillance des issues de la grossesse chez les femmes vaccinées par inadvertance, qui a été effectuée par une notification spontanée ou examen des registres, n'a pas permis de recenser des issues défavorables allant au-delà des taux escomptés.

Bien que les données de surveillance et les études épidémiologiques concernant le vaccin anti-papillomavirus restent rassurantes, des allégations mettant en doute l'innocuité du vaccin continuent à être relayées par les médias notamment. Les études épidémiologiques menées avant et après l'homologation n'ont montré aucun risque accru de maladie auto-immune, y compris de sclérose en plaques. Cependant, depuis l'introduction du vaccin contre le PVH, ces maladies font l'objet d'enquêtes particulièrement approfondies compte tenu de leur incidence de fond élevée dans la tranche d'âge correspondante.[9, 10, 11]

[9] Siegrist CA. Autoimmune diseases after adolescent or adult immunization: what should we expect? CMAJ. 2007 Nov 20;177(11):1352-4.

[10] Siegrist CA, Lewis EM, Eskola J, Evans SJ, Black SB. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be mistaken for adverse reactions. Pediatr Infect Dis J. 2007 Nov;26(11):979-84.

[11] Callréus T, et al. Human papillomavirus immunisation of adolescent girls and anticipated reporting of immune-mediated adverse events. Vaccine. 2009 May 14;27(22):2954-8.

[9] Siegrist CA. Autoimmune diseases after adolescent or adult immunization: what should we expect? CMAJ. 2007 Nov 20; 177(11):1352-4.

[10] Siegrist CA, Lewis EM, Eskola J, Evans SJ, Black SB. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be mistaken for adverse reactions. Pediatr Infect Dis J. 2007 Nov; 6(11):979-84.

[11] Callréus T, et al. Human papillomavirus immunisation of adolescent girls and anticipated reporting of immune-mediated adverse events. Vaccine. 2009 May 14; 27(22):2954-8.

Examples of such studies include a register-based cohort study in Sweden and Finland that included almost 1 million girls aged 10–17 years, among whom almost 300 000 were vaccinated against HPV.[12] The study investigated whether vaccination was associated with an increased risk of autoimmune, neurological or thromboembolic events. The study results did not show evidence of any association between exposure to HPV vaccine and autoimmune, neurological, and venous thromboembolic adverse events.

In the USA, an observational study involving almost 200 000 girls and young women who had received at least 1 dose of HPV vaccine found no increased incidence of 16 investigated autoimmune diseases in the vaccinated compared to the non-vaccinated group.[13] The incidence of MS in the vaccinated cohort, for example, was not significantly higher than the non-vaccinated cohort (incidence rate ratio 1.37, 95% confidence interval 0.74–3.20). In a third study, a pooled analysis of data from 11 clinical trials involving nearly 30 000 participants aged >10 years, of which 16 142 received at least 1 dose of Cervarix and 13 811 received either a placebo containing aluminium hydroxide or 1 of 2 different hepatitis A vaccines. No increased risk for the onset of autoimmune diseases after administration of Cervarix was observed in comparison to the control group.[14]

The committee was provided with an overview of cases that were the subject of concern in France. These included one case of MS that had been ajudicated by a French Regional Commission for Conciliation and Compensation. Another 14 cases of MS were reported through regional pharmacovigilance centres and/or the manufacturers to the European Medicines Agency. All 15 cases had been classified as being of "doubtful" causality, according to the French grading system. In addition, the overview from France included results of a cohort study involving 2 million girls aged 12–16 showing a lack of increase in hospitalization rates for autoimmune diseases among those who received the HPV vaccine (2.1/10 000 patients/year) compared to those who did not (2.09/10 000 patients/year).

In summary, GACVS was presented with a series of cases of adverse events following administration of the HPV vaccine. Multiple studies have demonstrated no increase in risk of autoimmune diseases, including MS, among girls who have received HPV vaccine compared to those who have not. The Committee remains reassured by the safety profile of the vaccine, but noted the importance of continued surveillance and epidemiological investigation with an emphasis on the collection of high quality data; such data are essential for interpretion of any adverse events which may occur following vaccination. Alle-

Parmi les exemples de ces études figure une étude de cohorte basée sur les registres menée en Suède et en Finlande, qui a porté sur près de 1 million de jeunes filles âgées de 10 à 17 ans, chez lesquelles presque 300 000 ont été vaccinées contre le PVH.[12] L'étude a recherché si la vaccination était associée à un risque accru de manifestations auto-immunes, neurologiques ou thrombo emboliques. Les résultats de l'étude n'ont apporté aucun élément probant à l'appui de l'association entre l'exposition au vaccin anti-PVH et les manifestations indésirables prenant la forme de maladies auto-immunes, neurologiques ou thrombo emboliques veineuses.

Aux États-Unis, une étude d'observation impliquant près de 200 000 jeunes filles et jeunes femmes qui avaient reçu au moins 1 dose de vaccin anti-PVH n'a constaté aucune augmentation de l'incidence des 16 maladies auto-immunes recherchées chez les personnes vaccinées par comparaison au groupe des personnes non vaccinées.[13] L'incidence de la sclérose en plaques dans la cohorte vaccinée, par exemple, n'était pas nettement plus importante que dans la cohorte non vaccinée (ratio du taux d'incidence: 1,37, intervalle de confiance de 95%: 0,74 à 3,20). Dans une troisième étude, une méta-analyse de données provenant de 11 essais cliniques incluant près de 30 000 participants âgés de >10 ans, dont 16 142 avaient reçu au moins une dose du Cervarix et 13 811 avaient reçu soit un placebo contenant un hydroxyde d'aluminium soit 1 des 2 différents vaccins contre l'hépatite A, aucun risque accru d'apparition d'une maladie auto immune après l'administration du Cervarix n'a été observé par comparaison au groupe contrôle.[14]

Un exposé des cas qui ont soulevé des craintes en France a été présenté au Comité. Parmi ceux-ci figurait un cas de sclérose en plaques qui a fait l'objet d'une décision d'une commission régionale française de conciliation et d'indemnisation. Quatorze autres cas de sclérose en plaques ont été signalés par l'intermédiaire des centres régionaux de pharmacovigilance et/ou des fabricants à l'Agence européenne des Médicaments. Les 15 cas avaient été classés comme présentant un lien de causalité «douteux» selon le système de classement français. En outre, la synthèse présentée par la France comprenait les résultats d'une étude de cohorte portant sur 2 millions de jeunes filles âgées de 12 à 16 ans, montrant l'absence d'augmentation des taux d'hospitalisation pour les maladies auto-immunes parmi celles qui avaient reçu le vaccin anti-papillomavirus (2,1/10 000 patientes par an) par comparaison à celles qui n'avaient pas reçu de vaccin (2,09/10 000 patientes par an).

En résumé, une série de cas de manifestations indésirables suite l'administration du PVH a été présentée au Comité. De multiples études n'ont démontré aucune augmentation du risque de maladies auto immunes, y compris de sclérose en plaques, parmi les jeunes filles ayant reçu le vaccin contre le PVH humain par comparaison à celles qui ne l'avaient pas reçu. Le Comité continue à être satisfait du profil d'innocuité du vaccin, mais note qu'il est important de poursuivre la surveillance et les enquêtes épidémiologiques en mettant l'accent sur la collecte de données de grande qualité; de telles données sont indispensables pour interpréter les manifestations indésirables qui se produisent à la suite de la vaccination. Les allégations de dommages dus

[12] Arnheim-Dahlström L, 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 Oct 9; 347.

[13] Chao C et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med. 2012 Feb;271(2):193-203.

[14] Descamps D, et al. Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. Hum Vaccin. 2009 May;5(5):332-40.

[12] Arnheim-Dahlström L, 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 Oct 9; 347.

[13] Chao C et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med. 2012 Feb; 271(2):193-203.

[14] Descamps D, et al. Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. Hum Vaccin. 2009 May; 5(5):332-40.

gations of harm due to vaccination based on incomplete information may lead to unnecessary harm when effective vaccines are not used.

Vaccine safety monitoring manual

There is a need for a global manual that addresses the basic concepts of vaccine safety surveillance. GACVS reviewed a draft document based on a recent publication[15] by the WHO Regional Office for the Western Pacific. GACVS advised that the global version should be designed primarily for immunization programme managers (at all levels) and for regulatory authority staff. Such a manual should focus on the general principles of immunization, AEFI detection, reporting, investigation, analysis and follow-up activities. It is essential to provide guidance on the systems and functions required of AEFI surveillance, and the channels of communication of safety data, as well as including sample forms that can be adapted by individual countries.

It is important to note that the manual should not be exhaustive with respect to all vaccine safety monitoring principles and methods. It should, however, provide links to the appropriate references and materials. For example, the new causality assessment classification endorsed by GACVS is described in another manual[16] that, although designed as a reference for expert review committee members, can serve to supplement the chapter in the general document. The new manual should, therefore, limit its content to an explanation of the need for and basic principles of causality assessment and what is the purpose, general principles and outcomes of causality assessment, without advanced technical discussion. Links to periodically updated e-documents such as the AEFI rate sheets[17] will be more helpful than incorporating them into the main text of the manual which could quickly become outdated.

The committee also advised on some important aspects to be addressed in the manual. It should describe the general structure of an AEFI surveillance system. This includes in particular a focus on relationships between immunization programmes and regulatory agencies. It should also stress the importance of vaccine safety communication to the community, to decision makers and to all levels of immunization services. With respect to clinical interventions or recommended diagnostic methods for specific AEFI, GACVS advised that the manual should focus on general principles, given the diversity of current clinical practices and health-care resources. However, the manual should include generic forms for use in surveillance of vaccine safety and investigation of serious AEFI. Likewise, it should provide access to the content of the aide-memoires on AEFI investigation[18] and causality assessment.[19] ■

[15] Immunization safety surveillance guidelines for immunization programme managers on surveillance of adverse events following immunization (Second Edition). World Health Organization, Western Pacific Region, 2013.

[16] See http://www.who.int/vaccine_safety/publications/gvs_aefi/en/index.html

[17] See http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html

[18] See http://www.who.int/vaccine_safety/publications/AEFI_Investigation_Aide_Memoire.pdf

[19] See http://www.who.int/vaccine_safety/publications/AEFI_aide_memoire.pdf

à la vaccination reposant sur des informations incomplètes peuvent conduire à des dommages inutiles lorsque des vaccins efficaces ne sont pas utilisés.

Manuel de suivi de l'innocuité des vaccins

Il est nécessaire de disposer, au niveau mondial, d'un manuel qui traite des principes essentiels de la surveillance de l'innocuité vaccinale. Le GACVS a examiné un projet de document basé sur une publication récente[15] du Bureau régional OMS du Pacifique occidental. Le Comité a recommandé que la version mondiale soit conçue en premier lieu pour les administrateurs de programme de vaccination (à tous les niveaux) et pour les autorités chargées de la réglementation. Un tel manuel doit être axé sur les principes généraux de la vaccination, le dépistage des MAPI, la notification, les enquêtes, l'analyse et les activités de suivi. Il est indispensable de fournir des orientations sur les fonctions et systèmes requis pour la surveillance des MAPI, et les circuits de communication des données relatives à l'innocuité, ainsi que de fournir des formulaires types qui puissent être adaptés par les différents pays.

Il est important de noter que le manuel ne doit pas être exhaustif s'agissant de l'ensemble des principes et méthodes de suivi de l'innocuité vaccinale. Il doit toutefois fournir des liens vers les outils de référence et documents appropriés. Ainsi, le nouveau classement d'évaluation de la causalité approuvé par le GACVS est décrit dans un autre manuel[16] qui, bien que conçu comme un outil de référence pour les membres du Comité d'experts, peut permettre de compléter ce chapitre du document général. Le nouveau manuel doit par conséquent se limiter dans son contenu à une explication de la nécessité et des principes de base de l'évaluation de la causalité, ainsi que de son but, ses principes généraux et ses résultats, pour laisser de côté les discussions techniques plus poussées. Il sera plus utile de fournir des liens vers des documents électroniques tels que les fiches d'information sur les taux de MAPI[17] qui seront périodiquement mises à jour plutôt que de les intégrer dans le corps du manuel, au risque qu'elles soient rapidement obsolètes.

Le Comité a également donné des conseils sur certains aspects importants qui devront être abordés dans le manuel. Il devra ainsi décrire la structure générale d'un système de surveillance des MAPI. Il convient ainsi de mettre l'accent sur les liens entre les programmes de vaccination et les organismes de réglementation. Il doit également souligner l'importance de la communication sur l'innocuité vaccinale auprès de la communauté, des responsables politiques et à tous les niveaux des services de vaccination. S'agissant des interventions cliniques ou des méthodes de diagnostic recommandées pour des MAPI spécifiques, le GACVS a recommandé que le manuel n'aborde que des principes généraux compte tenu de la diversité des pratiques cliniques actuelles et des ressources en matière de soins. Le manuel doit toutefois inclure des formulaires types pour la surveillance de l'innocuité vaccinale et les enquêtes sur les manifestations indésirables graves. De même, il doit donner un accès au contenu des aide-mémoire sur les enquêtes sur les MAPI[18] et l'évaluation de la causalité.[19] ■

[15] Immunization safety surveillance guidelines for immunization programme managers on surveillance of adverse events following immunization (Second Edition). Région du Pacifique occidental de l'Organisation mondiale de la Santé, 2013.

[16] Voir http://www.who.int/vaccine_safety/publications/gvs_aefi/en/index.html.

[17] Voir http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html.

[18] Voir http://www.who.int/vaccine_safety/publications/AEFI_Investigation_Aide_Memoire.pdf.

[19] Voir http://www.who.int/vaccine_safety/publications/AEFI_aide_memoire.pdf.

Immunization Supply Chain and Logistics: a neglected but essential system for national immunization programmes

*A **Call-to-Action** for national programmes and the global community by the WHO Immunization Practices Advisory Committee*

Geneva, Switzerland – March 2014

We, the IPAC members, call on national immunization programmes and the global community to review and renew investment in their Immunization Supply Chain and Logistics (ISCL) systems; otherwise the benefits of immunization programmes will be jeopardized by obstacles limiting access to and use of effective vaccines.

Call-to-Action

The Immunization Supply Chain and Logistics (ISCL) systems designed in the 1980s have supported the achievement of acceptable vaccination coverage using coping mechanisms to overcome enduring challenges in vaccine storage, distribution, and management. The dedication, intelligence, and creativity of health workers acting within outdated ISCL systems have substituted for needed assets and capital. Despite many efforts, national immunization programmes already struggling to meet the demands of routine immunization and supplemental campaigns may not be in the best position to respond to the introduction of all new vaccines.

A widening variety of new vaccines and immunization schedules, a diversity of service delivery strategies, an expanding target population, increased cold chain infrastructure requirements, and insufficient funding are just a few of the new realities that will further stress ISCL systems, initially designed to manage fewer, less expensive, and less bulky vaccines and related supplies. Existing systems cannot keep pace with the changing landscape of national immunization programmes, resulting in stock-outs, potential administration of ineffective vaccines, avoidable wastage, and inadequate cold chain capacity, all of which have considerable coverage, performance, and cost implications. These inefficiencies not only hinder the ability to provide much-needed immunizations; they also yield a lower return in health outcomes for those investing in the research, production, procurement, and delivery of vaccines, threatening the dependability of future funding sources.

The growth in complexity of immunization programmes is occurring at the same time as the development and application of innovative supply chain strategies and technology, especially in the private sector. In the public sector, national immunization programmes and the global community that supports them have an opportunity to improve their performance; and a mandate to provide the right vaccines, in the right quantities, in the right condition, at the right time, in the right place, at the right supply chain cost.

Recommendations

National Immunization Programmes

- ***Measure and monitor the health of the ISCL system***
  Apply the Effective Vaccine Management (EVM) tool and process to assess the state of the ISCL system, identifying strengths and weaknesses to prioritize improvements. Emphasize routine programme monitoring and performance improvement.
- ***Plan and implement improvements***
  Prepare and implement improvement plans that address system weaknesses with pragmatic responses, introducing supply chain innovations that produce increased visibility and flexibility to manage future changes in ISCL systems.

Global Community of Partners

- ***Increase awareness and investment***
  Call attention to the complexities of ISCL systems. Increase funding to recruit, train, and incentivize people and prioritize the collection and analysis of data, needed to run national immunization programmes.
- ***Address ISCL in immunization recommendations***
  Place implementation issues and evidence of ISCL impacts into the core of immunization recommendations and decision-making.
- ***Harmonize ISCL systems***
  Take more deliberate advantage of new vaccination initiatives to build upon and strengthen an integrated ISCL system across programmes.
- ***Resolve knowledge gaps to accelerate learning***
  Highlight ISCL knowledge gaps, identify what is working, create learning opportunities, and accelerate the spread of proven approaches.

Table of Contents

Acronyms

ACRONYM	DEFINITION
EVM	Effective Vaccine Management
HIV	Human Immunodeficiency Virus
HSS	Health Systems Strengthening
IPAC	Immunization Practices Advisory Committee
ISCL	Immunization Supply Chain and Logistics
KPI	Key Performance Indicator
LMIS	Logistics Management Information System
MDVP	Multi-Dose Vial Policy
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VMI	Vendor Managed Inventory
VVM	Vaccine Vial Monitor
WHO	World Health Organization

Terms

TERM	DEFINITION
Avoidable Wastage	Also known as unopened vial wastage, vaccine wastage due to being lost, stolen, broken, expired, or any other cause to make the vaccine unusable prior to being opened.
Cold Chain Capacity	The total volume of functional temperature-controlled storage, including fridges, cold rooms, carriers, or other temperature controlled storage equipment.
Cold Chain Inventory	A record of the quantities and types of temperature-controlled storage and transport equipment, including refrigerators, freezers, cold rooms, cold boxes, and vaccine carriers.
Direct Delivery	The movement of inventory directly from a vendor to a buyer. Also, the movement of inventory directly from a national storage warehouse to a district warehouse or health facility.
Immunization Supply Chain and Logistics System	The people, data, assets, and processes that manage the data collection, forecasting, ordering, distribution, storage, and delivery of vaccines and other supplies.
Inventory Holding Point	A location where inventory is stored, which could be a warehouse, a health facility, or transport equipment.
Inventory Service Level	A measurement of the performance of inventory replenishment policies, taking into consideration the amount of safety stock, the speed of use, and the number of stock-outs.
Order Response Time	The amount of time between a product being ordered (requested), and the product arriving at the destination.
Stock-out	When a product is not available.
Third Party Logistics Provider	A firm that provides outsourced (or "third party") logistics services for part, or all of the supply chain management functions.
Transportation Sourcing	The process of establishing a contractual relationship with transportation providers.
Vaccine Availability	A measurement of the amount of time that a vaccine is available for shipment from a warehouse or available for use at a health facility.
Warehouse Efficiency	A measurement of how efficiently a warehouse stores and moves product in terms of cost, human resources, and space utilization.
Wastage Rate	A measurement of the amount of vaccine that is not administered (due to both open and unopened vial wastage), compared to the amount of vaccine issued.

Supporting Evidence

ISCL Challenges

The introduction of new vaccines and higher coverage targets has increased demands on ISCL systems. Comparing the requirements of ISCL systems in the 1980's to the present, it is clear that the landscape has grown inherently more complicated, as national immunization programmes prepare to:

- Provide protection against 2.5 times as many diseases[a]
- Increase age ranges from infants to adults[b]
- Administer 3 times as many doses per person[c]
- Store and transport 4 times more vaccine volume per fully immunized person[d]
- Increase 6-fold the spending on vaccines to fully immunize one person[e]
- Serve a global target population size that has doubled[f]

[a] Varies by national immunization schedule; represents maximum. In 1980, standard vaccines included Diphtheria, Pertussis, Tetanus, Measles, Polio, and Tuberculosis. In 2010, additional vaccines include Pneumococcal conjugate, Rotavirus, Hepatitis B, Haemophilus influenzae Type B, Yellow Fever, Rubella, Japanese Encephalitis, and Meningitis A.

[b] Generally, vaccinations for the first 30 years focused on infants and women of reproductive age. The current mix of vaccines is provided for infants, children (Measles), pre-teens (Human Papillomavirus), and adults (Meningitis A and Tetanus/Diphtheria).

[c] Represents maximum, assuming the maximum number of doses as above. In 1980, this included 1 Bacillus Calmette-Guerin, 3 Diphtheria, Pertussis, and Tetanus, 3 Oral Polio vaccine, 1 Measles. In 2010, the total number is based on 2012 WHO immunization position papers.

[d] Based on projected volume per fully immunized child for 20 countries according to introduction plans. This compares 2001 volumes for traditional vaccines with 2020 expected volumes, where growth is driven by Pentavalent, Pneumococcal conjugate, Rubella, and Human Papillomavirus. Additional surge capacity is required for mass campaigns.

[e] Based on 2008 projections. WHO Bulletin, 62 (5):729 -736 (1984); Optimize Vaccine Supply Chains, Optimize (2009); State of the world's vaccines and immunization, WHO (2009); Vaccine volume calculator, S. Kone, WHO (2011); Immunization position papers, WHO (2012). Historical analysis of cMYPs in GAVI-eligible countries, L. Brenzel and C. Politi (2012)

[f] United Nations Population Division, World Population Prospects: The 2010 Revision, medium variant (2011)

ISCL systems originally designed to manage fewer and less expensive vaccines are not keeping pace with the changing landscape of immunization programmes. As a result, countries are experiencing inventory unpredictability, inadequate cold chain capacity, and insufficient funding, as exemplified in Table 1.

Table 1 – Examples of ISCL Challenges

Inventory Unpredictability	Inadequate Cold Chain Capacity	Insufficient Funding
• Ethiopia 2012: Average of 5 levels of inventory holding points[1] • Nigeria 2012: In one month, 30% of states had no syringes, and 20% of states experienced vaccine stock-outs[2] • 2011: 50% of GAVI-eligible countries reported a vaccine wastage rate in excess of WHO recommendations[3]	• 2011: 2.8 million vaccine doses lost in 5 countries due to cold chain failures[4] • Nigeria 2011: 41% of fridges were non-functional[5] • Turkey 2008: New vaccine introduction increased required storage capacity 20-fold[6]	• Ethiopia 2012: Lack of maintenance leading to 30% of cold chain equipment being non-functional[7] • Tanzania 2006: Operating at 25% of required staffing levels[8] • Ukraine 2012: Funding only sufficient for 60% of forecasted vaccine needs. Reported DTP3[g] coverage in 2011 was 46%[9] • 2013: Less than 10% of countries meet WHO recommendations for effective vaccine management practices[10]

Effective Vaccine Management (EVM), launched by WHO and UNICEF in 2010, is a quality improvement process for ISCL systems to compare their effectiveness against best-practice benchmarks. It is both a consultation and survey tool designed to identify the strengths and weaknesses of immunization programmes. By periodically repeating the process, programme managers can measure their programme's health, chart a course for improvement, and measure progress against their improvement plans.

EVM measures a wide spectrum of programmatic activities, including the following:

- **Vaccine arrival**
  All pre-shipment and arrival procedures ensure that every international shipment of vaccines from a manufacturer reaches its first destination in a country (a primary vaccine store or central medical store) in satisfactory condition (no breaks in the cold chain and no damaged vaccines) accompanied with all recommended paperwork.

[g] Third dose of the DTP-containing vaccine used in Ukraine, which consists of Diphtheria, Pertussis, and Tetanus, Haemophilus influenzae Type B, and Inactivated Polio Vaccine.

- **Temperature control**
  All vaccines and their diluents are stored and distributed within a cold chain system that maintains at all times the WHO-recommended temperatures ranges for all types of vaccines.

- **Storage capacity**
  The national supply chain system has sufficient and quality cold storage, dry storage, and transport storage capacity to accommodate all vaccines, diluents and injection supplies needed for the national immunization programme.

- **Infrastructure**
  The status and the layout of storage buildings, cold chain equipment, and vehicles enable the supply chain system to function effectively.

- **Maintenance**
  Preventive and curative maintenance systems are standard and operational for storage buildings, cold chain equipment, and vehicles used to distribute vaccines.

- **Stock management**
  Systems and procedures for managing the stocks of vaccines are effective in terms of vaccine handling, physical inventory, stock control systems, adequate stock-level policy, good warehousing practice, and disposal procedures for damaged and expired vaccines.

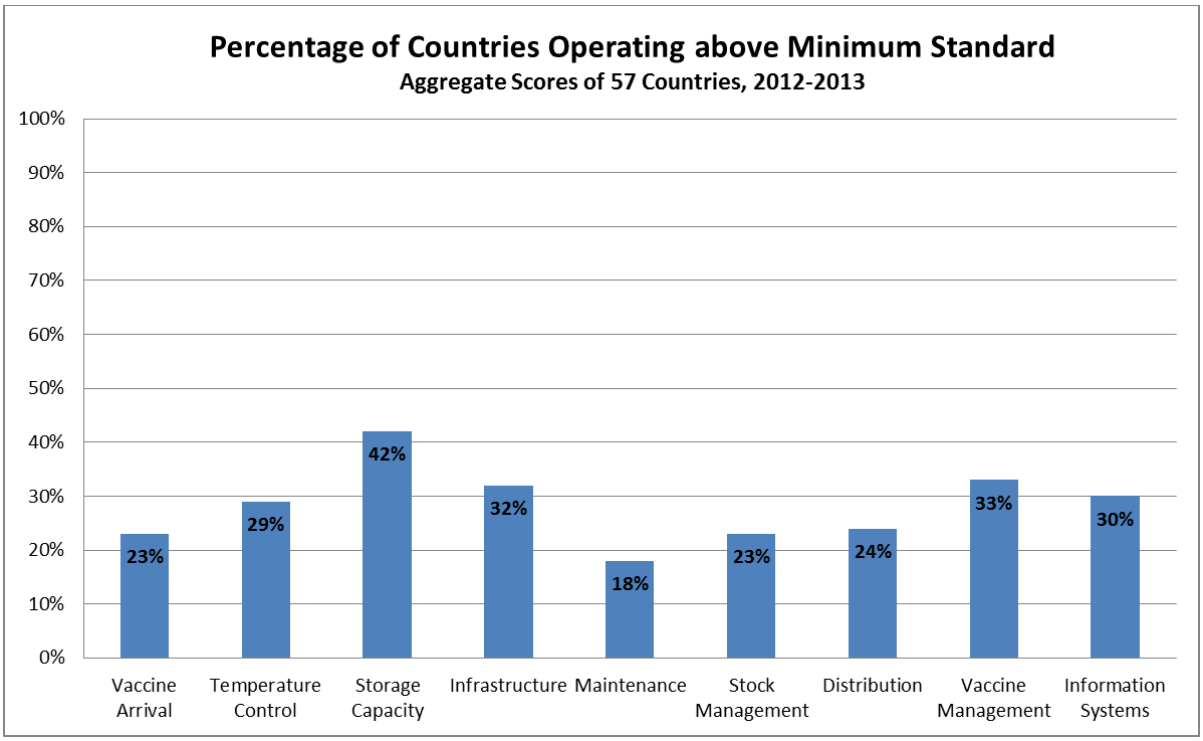
- **Distribution**
  The transport of vaccine between each level in the supply chain is effective, including the correct use of passive containers (cold boxes), packing practices with coolant packs (conditioned ice-packs or cool water packs), temperature indicators, and maintaining transport contingency plans.

- **Vaccine management**
  All recommended policies for vaccine management are adopted and implemented including the use of vaccine vial monitors (VVMs), the shake-test, the multi-dose vial policy (MDVP), the use of diluents, and the monitoring of vaccine wastage rates.

- **Information systems**
  Logistics management information systems (LMIS) and supportive management functions are effective, including standard operating procedures and vaccine-needs forecasting.

While this Call-to-Action applies to all countries, a recent study[11] of 57 GAVI-eligible countries shows that a vast majority of country ISCL's are underperforming. Analyzing the average EVM scores per criterion, as depicted in Figure 1, reveals that less than 25% of countries are operating at even a minimum standard within the criteria of Maintenance, Stock Management, and Distribution. Furthermore, only 29% of countries are meeting minimum standards for Temperature Control.

Figure 1 - Percentage of GAVI-eligible countries with ISCL operating above minimum standards, based on EVM assessments, 2012-2013[12]



Clearly, current processes and coping mechanisms are not adequately keeping pace with the changing vaccine landscape. To be able to continue to serve their populations, it is essential that national immunization programmes analyze their supply chains as a means to improve availability of potent vaccines and related supplies and reduce avoidable wastage without compromising the goals of increasing vaccination coverage.

Recommendations

Recommendations for National Immunization Programmes

Recognizing that improved ISCL practices during this Decade of Vaccines could alleviate the current strain on national programmes and protect more individuals against more diseases with better quality and at lower cost, we call on countries to

1. ***Measure, monitor, and evaluate the health of the ISCL system***
   Measure, monitor, and evaluate performance for availability, quality, and cost. Apply the Effective Vaccine Management (EVM) tool and process to assess the state of ISCL systems, identifying strengths and weaknesses in order to prioritize improvements.

2. ***Plan and implement improvements***
   Based on EVM assessments, prepare and implement costed improvement plans that address system weaknesses with pragmatic responses, as well as introducing supply chain innovations that produce increased visibility and flexibility to manage future changes in ISCL systems.

1 – Measure, Monitor, and Evaluate the Health of the ISCL System

To properly assess a country's ability to effectively forecast, store, supply and deliver vaccines, programme and logistics managers need to know what to measure and must establish the tools and processes to enable the timely and complete collection of routine, regular, and reliable data.

Effective Vaccine Management is a continuous quality improvement process for ISCL systems to compare their effectiveness against best-practice benchmarks. It is both a consultation and survey tool designed to identify the strengths and weaknesses of national immunization programmes. By periodically repeating the process, programme managers can assess their performance, chart a course for improvement, and measure progress. The World Health Organization (WHO) and UNICEF have published a Joint Statement calling on countries to embrace the EVM initiative. For more information on the EVM process, please refer to the WHO UNICEF Joint Statement on Effective Vaccine Management[13].

To fully measure the health of an ISCL system, one must gather supply chain data, analyze the data to identify strengths and weaknesses, and continuously monitor performance.

A. **Gather data:** Data are the essential first step to measure the ISCL system's capabilities. Developing the data sets with which to assess the programme can be the first signal that information systems may be a weakness at the national or sub-national levels. This is not a trivial task. While data are the key building blocks for managing and measuring a programme's effectiveness, they are often not readily available. They may be lost, not recorded on paper or digitally, or geographically dispersed. Establishing a baseline dataset of assets, commodities, and transactions is key to guiding future decision-making.

B. **Analyze data:** Using the gathered data, programmes can analyze their ISCL system's effectiveness to identify and prioritize what requires attention and improvement. The EVM analysis measures the ISCL system against nine key criteria:
    - Vaccine arrival
    - Temperature control
    - Storage capacity
    - Infrastructure
    - Maintenance
    - Stock management
    - Distribution
    - Vaccine management
    - Information systems

C. **Continuously monitor:** In order to determine if the ISCL system is functioning properly on a continuous basis, programme managers must establish a monitoring system using Key Performance Indicators (KPIs) to track performance. The reality of any supply chain is that the world presents a more chaotic series of events than the planned process is built to support. To allow decision-makers to remain informed, and to help reduce the number of decisions made solely on instinct, managers can use KPIs as an objective means to gauge the health of the supply chain. While the supply chain community has a wealth of KPIs for monitoring everything from warehouse efficiency to transportation sourcing, the ISCL system can best capture the six rights (product, quantity, condition, time, place, and cost) using the following metrics:
    - Availability or access, which measures stock-outs and over-stocking at storage depots
    - Quality or suitability, which measures temperature exposure and cold chain equipment performance
    - Cost, which measures the cost per fully immunized person, dose delivered, or volume delivered

In summary, to properly measure the health of the ISCL system, one must

1. Regularly monitor its ability to store, supply, and deliver vaccines and related commodities against established benchmarks to identify strengths, weaknesses, and opportunities for improvement.
2. Continuously track its performance against metrics to understand the system's productivity and efficiency.

2 - Plan and Implement Improvements

After measuring the health of the ISCL system, the EVM assessment provides effectiveness scores against nine ISCL criteria. Programme and logistics managers can use this knowledge as the foundation for improvement planning. The improvement plan identifies and addresses the key challenges with strategies to achieve measurable improvement.

A. **Consider tomorrow:** During this planning stage, it is important to emphasize not only the existing ISCL system, but also to plan against future needs, such as new vaccine

introductions; design for uncertainties, such as flexibility to respond to epidemics or an influx of refugees; and build in resiliency to respond to natural disasters or conflicts. An improvement plan that fares well only in the best conditions will not succeed. Therefore, national immunization programmes should consider the EVM improvement plan as an opportunity to fix the challenges of today and prepare for the unknowns of the future.

B. **Introduce supply chain innovations:** Planning and implementing EVM improvement plans is an opportune time for countries to address large-scale ISCL changes, think about solutions differently, take advantage of new knowledge and technology, and support both proven and novel approaches. While impactful evidence of various innovations is limited, national immunization programmes are applying new technologies, processes, and incentives to respond to their challenges. The examples below highlight some supply chain innovations. Note that this is a summary and does not represent a complete report of all projects or improvement plans.

- **Supply Chain Redesign** is the economic and logistical analysis and reconfiguration of ISCL processes, such as changing warehouse locations, moving from an inventory push to an inventory pull system, or increasing the frequency of shipments between warehouses and health clinics. In 2008, the Ministry of Health in the Cabo Delgado province of Northern Mozambique measured the impact of redesigning their supply chain, in which they removed inventory levels, invested in technology to improve information flow, consolidated tasks into a small group of workers focused full-time on supply chain operations, and provided reliable sources of energy to clinics. They found that their efforts dramatically increased vaccination coverage from 69% to approximately 95% of children, reduced stock-outs to less than 1% of health centers, and improved the cold chain by ensuring that 93% of health facilities had reliable refrigeration.[14]
- **Supply Chain Modelling** predicts the impact of changes to supply chain processes, such as supply chain redesign, modifying inventory safety stock levels, or integrating health commodities. In 2010, the Ministry of Health in Tanzania modeled the impacts of various supply chain decisions on their distribution network to assess supply chain changes needed for their future growth, including studying the use of a new Direct Delivery model. Through Supply Chain Modelling, they discovered that there would not be enough warehouse or transport capacity to manage the growth of programmes without significantly affecting availability. They also found the expected costs for Direct Delivery were much higher than budgeted, suggesting that changes in network structure or outsourcing to a third-party logistics provider, in addition to increased investment, must be considered.[15]
- **Vendor Managed Inventory (VMI)** is the process by which the buyer of a product provides information to the vendor of a product, and the vendor takes full responsibility for maintaining agreed upon service levels for the inventory. The buyer benefits from better service, and the vendor benefits from more control of their product's demand. In 2011, the Ministry of Health in Thailand outsourced the distribution and inventory management functions to a third-party, resulting in overall supply chain costs that were 20% less than their in-house supply chain costs,

driven mostly from the lower number of procured vaccines required in the VMI model.[16]

- **Outsourcing** is the practice of sourcing processes from third-parties to fulfil various roles in the supply chain, such as transportation, warehousing, or information technology. In 2012, the Ministry of Health in The Gambia outsourced the management of their transportation fleet to a third-party, which fulfilled vehicle maintenance and driver training roles for the Ministry of Health. As a result, the health programme increased their frequency of visits three-fold, could visit three times more villages, and was able to improve vaccination coverage by almost 20 percentage points.[17]
- **Logistics Management Information Systems (LMIS)** are software tools to improve information, such as stock-on-hand, received, administered, or wasted, flowing between partners, such as health workers and logistics managers. In 2013, the Karnataka (India) Department of Health and Family Welfare implemented a LMIS across 133 sites and 151 health commodities. After recording over 200,000 transactions in 12 months, the programme has improved order response times 10 fold in times of emergency or stock-outs, and the system has contributed to vaccine service levels above 95%.[18]
- **Incentive Pay** is the payment to an employee based on performance. The incentive can be a bonus, part of the standard payment structure, or be a nonmonetary reward. In 2011, the Rwandan Ministry of Health studied the impact of Pay-for-Performance incentives on healthcare delivery in mother and child healthcare service. They found that institutional deliveries increased by 23% and preventive care visits increased between 56% and 132%, depending on the age of the baby.[19]
- **Worker Training** is the professional development of staff for personal development, career advancement, and the routine implementation of new processes and technology. While worker training appears to be an obvious requirement of national immunization programmes, it is rarely viewed as an innovative investment. In 2009, Nepal's Ministry of Health measured the impact of training on their new LMIS. They learned that sharing training duties between the implementing technology partner and the Ministry of Health, as well as educating users on the value of the LMIS, helped the programme realize a 50% reduction in stock-outs.[20]

C. **Link Implementation Plans:** To ensure that improvement plans have the support of leadership and the foundation for long-term success, it is critical that the plan be linked to broader immunization strategic plans or health sector plans, such as a comprehensive multi-year plan. Tying the improvement plans to other programmatic objectives helps to raise the visibility of the resources required to implement the tasks, such as the addition of people or technology. However, the added visibility may not produce sufficient funding to support the improvement plan activities, and proactive programme managers could consider using GAVI Health Systems Strengthening (HSS) funding, and other funding sources, to fill the budgetary gaps.

D. **Use resources:** In addition to the examples above, information about various supply chain innovations exists in online resources that provide valuable reference materials, technology

reviews, and collaborative forums. Prominent ISCL and global health resources are cited below:

- Project Optimize[21]: A library of ISCL improvements covering topics such as technology, packaging, policy, and process, summarized in the document, *Achieving the Global 2020 Vision for Future Immunization Supply and Logistics Systems*[22].
- Technet-21[23]: A collaborative forum for experts in the field of immunization technology, cold chain, injection safety, and health logistics to share their experiences, coordinate activities, and discuss major global policy issues.
- USAID | DELIVER PROJECT[24]: A library of tools, studies, and policies that support improved commodity security and logistics management for a variety of global health programmes.
- International Association of Public Health Logisticians[25]: A collaborative forum to support knowledge transfer and professionalization for supply chain managers working in public health logistics for a variety of global health programmes.

Recommendations for the Global Community of Partners

The organization and functioning of national ISCL systems are often heavily influenced by global forces beyond individual borders. For national ISCL systems to be successful, the global community of partners must address common issues that hinder progress. This Call to Action recommends that the global community of partners:

1. ***Increase awareness and investment***
   Call attention to the complexities of immunization supply chains, culminating in the need to support ISCL systems with increased funding to invest in the vital elements of all national immunization programmes: people and data.

2. ***Address ISCL when formulating immunization recommendations***
   Factor in the best available field evidence on implementation and ISCL system performance when formulating policy recommendations.

3. ***Harmonize ISCL systems***
   In the context of a broader Health System, take more deliberate advantage of new vaccination initiatives to build upon and strengthen an integrated ISCL system across programmes.

4. ***Identify and resolve knowledge gaps to accelerate learning and spread solutions***
   There is need for further evidence on effectiveness of supply chain innovations. The global community of partners must highlight ISCL knowledge gaps, identify what is working, create learning opportunities, and accelerate the spread of proven approaches.

1 - Increase Awareness and Investment

In order to organize and respond, the global community needs a clear and convincing picture of the urgent needs of ISCL systems. The key ISCL challenges, such as those presented in this paper, must be shared through forums, conferences, and publications. Naturally, increased awareness is a necessary component for increasing investment.

Immunization programmes require people, data, and funding, in addition to other important considerations such as population acceptance, to achieve high coverage and prevent disease. Based on the high proportion of countries operating below the EVM minimum standards, it is clear that change is required at both the national level, to identify and communicate needs, and the global level, to reply in kind with necessary strategies and investment.

A. **People:** Human resources, such as logisticians, managers, data managers, drivers, and warehouse workers, are the backbone of ISCL systems. Investment is needed to train, incentivize, and reward their dedication, creativity, and enthusiasm.

B. **Data:** Just as national ISCL systems must prioritize data gathering for continuous monitoring and analysis, the global community must facilitate the process of generating actionable, complete, and timely data at all levels to identify needs and track performance. Until

information systems are treated as a necessary and expected budgetary line item, data will continue to be assumed, anecdotal, or missing, thereby preventing meaningful and essential ISCL improvements.

2 - Address ISCL when Formulating Immunization Recommendations

Recommended immunization policies generated by expert committees have a direct impact on national ISCL systems. For example, before a Minister of Health decides to introduce a new vaccine into the national immunization programme, an assessment should be conducted to ascertain if the ISCL system will have enough cold storage capacity to hold the new vaccine, enough transport vehicles to carry the vaccine, and enough trained staff to competently deliver the new vaccine. Implementation issues such as these can jeopardise the deployment and uptake of new and otherwise effective interventions.

Evidence regarding burden of disease and vaccine immunogenicity, efficacy, effectiveness, and safety alone is insufficient to meaningfully issue recommendations on courses of action in health care. Evidence on implementation issues, such as costs, opportunity costs, equity, and logistics need to be considered alongside evidence on effectiveness. Technical strategies need to be crafted with an eye towards if and how they can be operationalized. Expert committees must adopt or refine procedures to incorporate operational implications in immunization recommendations.

3 - Harmonize ISCL Systems

Various vaccine preventable disease control and elimination initiatives, such as measles, meningococcal disease, and yellow fever among others, have been planned and organized with a focus on their immediate ISCL needs. By concentrating on individual ISCL needs, the resulting operations have tended to create parallel systems for financing, procurement, distribution, transport, training, communication, and reporting. The focus on individual initiatives, instead of strengthening and integrating existing ISCL systems and building their links to other health initiatives, presents a missed opportunity and is not an optimal use of resources.

When planning new initiatives, or re-planning existing initiatives, the ISCL system should be rationalized by consolidating the existing system(s) under uniform processes and control. For example, incorporating data capture on a reduced number of standardized forms and eventually moving to electronic data capture at all levels will reduce long-term overhead costs and data errors, resulting in better data quality, analysis, and decision-making. Likewise, a new initiative presents the opportunity to re-examine the cold chain, transport, and maintenance capacity and needs. Better harmonization of ISCL components will produce economies of scale, efficiencies, and more unified public health policies.

Further, immunization systems should be considered in the context of broader health systems and their reforms. For example, a Ministry of Health may be seeking investment in the cold chain to support a new pediatric HIV programme, where HIV test kits and pediatric anti-retrovirals require storage between 2 and 8 degrees Celsius. Such scenarios present an opportunity to engage health managers to assess cold chain inventories and seek mutually beneficial storage and transportation strategies.

4 - Identify and Resolve Knowledge Gaps to Accelerate Learning and Spread Solutions

There is little published evidence of successful ISCL practices and innovations along with their impacts on national vaccination systems. Knowledge gaps and new opportunities must be brought to the top of the research and policy agenda. For example, can removing an inventory level in the supply chain reduce the amount of time to re-supply vaccines? If so, how does this impact transportation costs, reporting, and decision-making? More importantly, does this improve vaccine availability, reduce avoidable wastage, or increase coverage? Academics, health workers, and global partners can work together through forums and expert committees to highlight areas of research, subjecting studies to the same rigorous conditions that are routinely employed in vaccine, drug, and medical trials.

Finally, it is critical that researchers document and publish the evidence on effectiveness and cost as a result of good or innovative ISCL practices, to accelerate learning about what is working and what needs improvement. Knowledge of successful ISCL innovations must be broadcast through forums, journals, expert committees, regional conferences, and within countries to support the adoption of promising practices more rapidly and enable national immunization programmes to adapt and respond to the complexities of the changing immunization landscape.

Endorsement

Existing ISCL systems are not keeping pace with the rapidly changing vaccination landscape as a result of new vaccine introductions and immunization schedules, a diversity of service delivery strategies, a growing target population, and increased cold chain infrastructure requirements. In response to these challenges, national ISCL systems and the global community must rethink their ISCL systems in order to provide the right vaccines, in the right quantities, in the right condition, at the right time, in the right place, and at the right supply chain cost.

We call on national immunization programmes to measure, monitor, and invest in their ISCL systems, and to plan and implement improvements. Additionally, we call on the global community of partners to increase awareness and investment, harmonize ISCL silos, address ISCL when formulating immunization recommendations, and to identify and resolve knowledge gaps.

Immunization Practices and Advisory Committee
Endorsed by unanimous vote
March 2014
Geneva, Switzerland

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EVM - setting a standard for the vaccine supply chain

WHO & UNICEF
Joint Statement
DRAFT VERSION

Effective Vaccine Management

World Health Organization

unicef

The Context

In the early days of EPI since its launch 40 years ago at the World Health Assembly (in May 1974), vaccines were the only essential commodity that required their own specific supply chain system – with vaccines needing to be kept in a 2-8°C cold chain unlike any other essential medicines at the time. Subsequently, the Universal Childhood Immunization (UCI) launched by UNICEF in the 1980s, and the abundance of external funding that flowed for this initiative, saw the rise of in-country immunization supply chain systems as the backbone of routine immunization. Both EPI and UCI were significant forces from both WHO and UNICEF that drew attention and resources to the global immunization push of the 1980s and early 1990s.

When the UCI goals were reached and the world claimed success of achieved global immunization coverage rates of 80% or more, donor priorities shifted away from routine immunization towards support the next priority – eradicating Polio. After UCI, few national governments were able to continue funding the upkeep and improvements of the supply chain infrastructure upon which the success of UCI was built. Although some elements of in-country immunization supply chain system were sustained and improved with support of the Polio Eradication Initiative (PEI), little attention and funding has been provided since the mid-90s. This has led to its gradual downfall.

Today, and many decades later, in-country immunization supply chains continue to be government-run and severely underfunded. In 2010 and 2011 WHO and UNICEF have supported 65 countries in the implementation of Effective Vaccine Management (EVM) assessments. Key findings from these assessments highlighted to what extent countries are failing to reach the minimum WHO recommended target level of 80% for each of the nine criteria that is measured under the EVM. As a consequence, countries have not been able to adapt, innovate and change to meet the demands of today's immunization programme needs.

Figure 1: Supply chain performance in 65 low and lower-middle income countries (2010-2013)

Source: WHO analysis based on 65 EVM assessments

Key findings highlight that in 65 low and lower-middle income countries:

- Adequate temperature control for vaccines is achieved in 26% of countries,
- Sufficient storage capacity for vaccines and supplies is available in 38% of countries,
- Functional vaccine stock management is attained in 20% of countries,
- Effective distribution of vaccines is compliant in 20% of countries, and
- Adherence to vaccine management policies and practices are reached in 28% of countries

"Of the 65 low and lower-middle income countries assessed on effective vaccine management, none has met the recommended WHO standard."

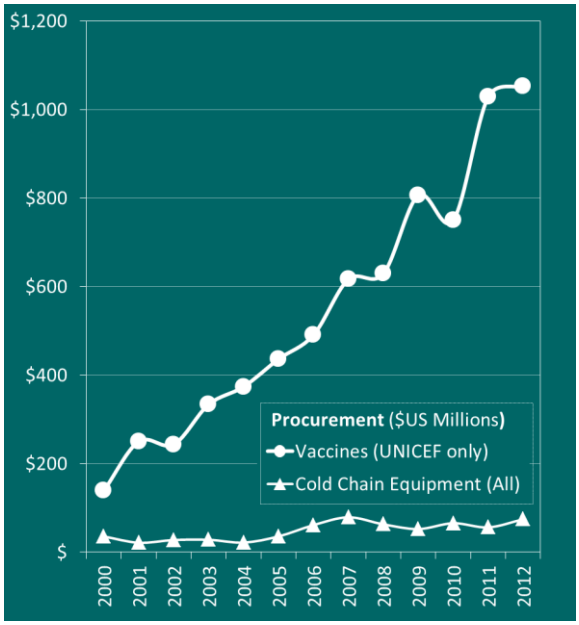
In addition to the persistent challenges in the storage, distribution, handling, management and stock control of vaccines and supplies, new challenges are putting additional pressure on currently fragile and strained systems that have,

up to now, shown extreme resilience by resorting to coping mechanisms. However, these coping mechanisms are ad-hoc and unsustainable approaches to dealing with the growing challenges. There is growing evidence that these immunization supply chain systems developed over 35 years ago have outgrown their ability to manage the priorities of introducing new vaccines, vaccinating age groups beyond infancy, and addressing the equity gaps in access to all vaccines at the last mile.

"Global procurement of vaccines has risen tenfold in the last 10 years, while procurement for cold chain equipment to protect the potency of vaccines has remained relatively constant"

Ignoring these challenges is no longer possible given the significant growth in the volume and financial investment in vaccines – respectively a four and ten-fold increase from the year 2000. In contrast, investments in protecting vaccines in the cold chain have remained relatively constant. This gap in funding for cold chain equipment is indicative of the inattention given to in-country immunization supply chains systems.

Figure 2: Vaccine and cold chain procurement (2000-2012)



Without fundamental and transformational changes in the way the immunization supply chains are designed and managed, the aspirations delineated in the *Global Vaccine Action Plan* (GVAP) will not be achieved and the ability for this decade to become a successful *Decade of Vaccines* will be compromised.

Box 1: Key context messages

1. **Today, immunization supply chains in developing countries are fragile, strained to keep up with the demands for today's immunization priorities, and continue to suffer from enduring problems of vaccine storage, transport and stock management.**
2. **Without a better alignment between the investments in vaccines and those to protect them in the cold chain, in-country supply chains will soon become a bottleneck to achieving future immunization goals and the aspiration delineated in the Global Vaccine Action Plan will not be achieved.**
3. **Estimates suggest that investing up-to 10% of the value of vaccines being procured will ensure that in-country immunization supply chain systems facilitate the equitable access and availability of effective vaccines at service delivery over the next decades; and ultimately support immunization programmes to reach the estimated 22 million children in developing countries each year.**

"Better supply and logistics systems, international cooperation and funding are essential to reach the estimated 22 million children annually in developing countries."

The EVM Initiative

In 2010, WHO and UNICEF launched the EVM initiative to help low and lower-middle income countries upgrade their immunization supply chains, and in doing so, strengthen their ability to manage today's, tomorrow's and future priorities. This includes introducing new vaccines, vaccinating age groups beyond infancy, and addressing the equity gaps in access to all vaccines at the last mile. The EVM initiative began by establishing a process to help countries evaluate the current performance of their immunization supply chain, and benchmark this performance against best-practice standards. For this exercise, an EVM assessment tool was developed by WHO and UINCEF that is used to thoroughly review their immunization supply chain at all relevant levels of the system – from national to service levels.

The EVM assessment tool sets standards in nine areas (criteria) of vaccine management based on well-established principles and standards for quality management that are applied throughout the industrialized world (for example the ISO 9000 series of standards). The EVM criteria are described as follows.

1. **Vaccine arrival**: to assess that pre-shipment and arrival procedures ensure that every shipment from the vaccine manufacturer reaches the receiving store in satisfactory condition and with correct paperwork
2. **Temperature control**: to assess that vaccines and diluents are stored within the WHO recommended temperature ranges in the cold chain system.
3. **Storage capacity**: to assess that cold storage, dry storage and transport capacity is sufficient to accommodate all vaccines and supplies needed for the programme.
4. **Infrastructure**: to assess whether the state of the storage buildings, the cold chain equipment and the fleet of vehicles for distributing vaccines and supplies is acceptable.
5. **Maintenance**: to assess that the maintenance systems for the storage buildings, the cold chain equipment and vehicles is satisfactory.
6. **Stock management:** to assess that effective stock management systems and procedures are in place.
7. **Distribution**: to assess that vaccines are distributed between each level in the supply chain in an effective manner.
8. **Vaccine management**: to assess that appropriate vaccine management policies are adopted and implemented at all levels of the immunization supply chain.
9. **Information systems**: to assess that relevant information systems and supportive management functions are satisfactory.

Once completed with the necessary information, the EVM assessment tool generates an overall score in percent, for each criterion at each level of the supply chain assessed. The minimum recommended standard score for each criterion at each level of the supply chain is set at 80%.

"WHO and UNICEF recommend that countries should strive to reach and exceed the minimum requirement for EVM. The minimum EVM score for each of the nine criteria and for each level of the national supply chain system should be 80%or higher".

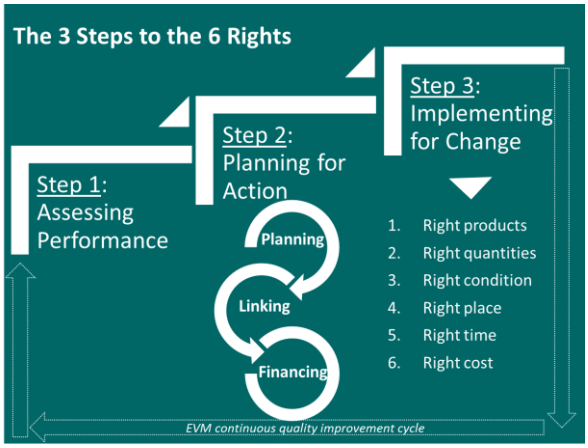
The Improvement Process

The EVM is first and foremost a continuous quality improvement process. The ultimate objectives are for countries to have immunization supply chains that ensure the **availability** of the needed vaccines and supplies up to service delivery levels; with vaccines that have not lost their **potency** from temperature damage in the cold chain; and with increased supply chain **efficiency** achievable within the reach of each country specific setting.

These three objectives are captured within the six rights of an effective immunization supply chain system to ensure that the right vaccines are delivered in the right quantities, in the right condition, at the right place, in the right time at the right cost.

Reaching these objectives cannot rely on conducting an EVM assessment alone. It will rest on putting in motion a comprehensive continuous quality improvement process at country level coined the **3 steps to achieving the 6 rights** of an effective supply chain. The cyclical nature of the process is aimed to help countries define an achievable target for each iteration; within what is achievable in a cycle; and to benchmark that targets have been met or exceeded this during the next cycle.

Figure 3: The EVM continuous quality improvement cycle



Source: WHO and UNICEF

Step 1: Assessing Performance

The objective of this first step is to assess the current performance of the immunization supply chain using the EVM assessment tool in order to identify key strengths, weaknesses and bottlenecks. Given that an EVM assessment is conducted in a representative sample of storage facilities in the country, it is worth collecting additional data during this process to complement certain aspects of the immunization supply chain not covered in the EVM assessment tool. This is particularly encouraged for countries wanting to conduct a cold chain inventory or a supply chain network optimization modelling exercise and gain a deeper understanding of certain aspects related to human resources for logistics or their logistics management information systems (LMIS).

Step 2: Planning for Action

The objective of this second step is to use the findings and recommendations from the assessment results from step 1 and translate these into a comprehensive plan of action, identifying interventions and activities to address both current and future challenges. The planning for action step is a critical one in the EVM improvement process and is best described through three inter-related sub-steps as follows:

2.1 – Comprehensive Improvement Planning

A comprehensive improvement plan should include all prioritized strategies, tactics, and implementable activities to address each of the identified deficiencies from the EVM assessment in a successful and sustainable way. It is strongly encouraged that the improvement planning process be taken as an opportunity to plan for supply chain strengthening beyond the nine vaccine management criteria covered in the EVM assessment tool. Many relevant assessment tools and methods exist for activities such as vaccine forecasting or cold chain equipment planning for the future. As such, the comprehensive improvement planning process should try to include recommendations, activities and strategies from other relevant assessments to:

- Address both current and future anticipated supply chain challenges, especially those linked with new vaccine introduction, and
- Explore the adoption of innovative solutions and promising approaches around immunization supply chain optimization (see box 2).

Box 2: Immunization supply chain optimization – key attribution for comprehensive improvement planning

- **Immunization supply chain networks should be designed to maximize efficiency, effectiveness, agility and responsiveness to the needs of the immunization programme.**
- **Immunization supply chain systems should continually improve by monitoring performance with key indicators that are track through a strong logistics management information systems based on point of service data.**
- **Immunization supply chain systems for heat tolerant products should be optimized at all levels, including through the adoption of a controlled temperature chain (CTC) strategy.**
- **Human resources for immunization logistics should be in sufficient numbers, competent, motivated, and empowered by professionalizing supply chain management.**
- **Immunization supply chain systems should introduce innovative technologies in the field of cold chain equipment, temperature monitoring, and more efficient, reliable, and durable equipment choices for storing and transporting vaccines.**
- **Immunization supply chain systems should be integrated with wider health commodity supply systems when appropriate and leverage synergies with the private sector where feasible.**

2.2– Linking for Visibility and Ownership

While it is important to develop a comprehensive improvement plan, government ownership and commitments is critical from the onset. No matter how strong the improvement plan is, it will have little chance of implementation if there is no national buy-in from all stakeholders in the Ministry of Health; no strong ownership within the national immunization programme; and limited visibility within the broader strategic immunization or the health sector planning processes. Given that the comprehensive multi-year plan (cMYP) is the basis for formulating the national immunization budget, the improvement plan for strengthening the in-country immunization supply chain should be linked to an existing cMYP and/or be an integral piece during the elaboration of a new one. This will ensure that activities, strategies and resource requirements are included in the broader strategic plan for immunization and contribute to linking for visibility and national ownership.

Box 3: Guiding principles for developing a comprehensive improvement plan

1. **Government ownership and commitment**
2. **Review and endorsed by the national inter-agency coordinating committee (ICC)**
3. **Improvement plan addresses:**
   - ***EVM Assessment recommendations***
   - ***Recommendations of other related assessments***
   - ***Future new vaccine introduction needs***
4. **Improvement plan outlines steps towards immunization supply chain optimization**
5. **Improvement plan includes realistic activities, responsibilities, budget, and timeline**
6. **Improvement plan includes a system to monitor implementation**

2.3– Financing for Improvements

The last sub-step is to ensure that opportunities to mobilize resources and financing are leveraged. Linking the comprehensive improvement plan to the broader strategic plan for immunization and reflecting activities and resource requirements in the cMYP will help raise the visibility for needed resources – particularly from national domestic sources. However, this is no guarantee that funds will be made available. Financing for Improvement will first require increased awareness-raising efforts of the issues at stake and the consequences of not investing the immunization supply chain. Advocacy efforts should be targeted at decision makers within the Ministry of Health, the interagency coordinating committee (ICC) and, if present in country, the national immunization technical advisory committee (NITAC) or any other forum and in-country mechanism for planning, budgeting and financing. Secondly, every funding opportunity needs to be leveraged. For instance, in countries eligible for Global Alliance for Vaccines and Immunization (GAVI), Health Systems Strengthening (HSS) funding is potentially an important source of financing for the improvement plan. If a country is planning to submit an HSS application or discuss the reprogramming of existing HSS funds, this is an ideal opportunity to ensure that elements of the improvement plan are featured in the HSS application or reprogramming discussions.

Step 3: Implementing for Change

The objective of this third step is to implement the comprehensive plan of action developed in step 2 and put in place a mechanism for reviewing progress against planned activities on an annual basis, and monitor implementation using defined process indicators.

The ending of an implementation cycle for the improvement plan will mark the end of an iteration in the three steps. The results of this iteration are used as the starting point for the next. The process begins again with step 1 and each iteration aims to further approach a desired goal and performance targets on the nine EVM criteria for an effective vaccine supply chain management system.

The Resources

For this EVM initiative, WHO and UNICEF have developed several tools, guidance materials and e-learning courses to assist countries and many produced in several languages.

- The EVM assessment package and guidance materials are available on the WHO website for EVM
- The EVM technical assistance and training course is available on the EVM e-learning site
- The EVM assessments conducted and the reports are available on the EVM database site (registration is required)

The Recommendations

The adoption and long-term success of the EVM initiative ultimately depends on the benefits it brings. Countries need to embrace the EVM process for system-wide improvements of their immunization supply chain systems. In addition, WHO, UNICEF and global partners recognize the importance of providing necessary long-term support to strengthen country supply chain systems for immunization.

In order to achieve these aims, **the EVM initiative embodies key recommendations as follows:**

WHO-UNICEF recommends that countries:

- Adopt the 3 step approach of assessing, planning and implementing change and within the national immunization programme budgeting, planning and financing cycle.
- Ensure that the 3 step approach to EVM addresses today's, tomorrows' and future anticipated supply chain challenges, especially those linked with new vaccine introduction.
- Make every effort towards achieving an effective vaccine management system that meets the minimum recommended standard for each criteria and each level of the in-country supply chain.
- Implement steps towards immunization supply chain optimization
- Continually adapt to the changing context with innovative approaches and technologies.
- Continuously monitor the performance of their in-country immunization supply chain with defined metrics and key performance indicators measuring the objective of availability, potency and efficiency.
- Commit the necessary human and financial resources to address existing and anticipated challenges of immunization supply chain and logistics systems.

WHO-UNICEF commits to:

- Support countries with the EVM initiative and adopting the 3 step approach of assessing, planning and implementing change for in-country immunization supply chain strengthening.
- Ensure that guidance and policies on immunization supply systems keep pace with country needs and that tools, methods and training materials are continually updated.
- Provide training and local capacity building opportunities as it relates to the EVM initiative.
- Provide enhanced technical assistance and strategic support to countries by training WHO and UNICEF staff, in addition to a cadre of consultants that can be deployed to support countries on any, or all recommended steps in the EVM process.
- Continue to generate knowledge and evidence on supply chain performance and experiences in countries to support fund-raising efforts for national immunization supply systems.

WHO-UNICEF signatories

TBD
World Health Organization (WHO)

TBD
Programme Division
UNICEF

TBD
Supply Division
UNICEF

Photo credit: Cover (GAVI Alliance): Two health workers covering the last mile logistics in Zanzibar to reach every child.

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Copies of this statement and further information may be requested from

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Why is the GAVI Alliance developing an immunization supply chain strategy?

The rapid expansion of immunization programs in GAVI-eligible countries over the last ten years has already resulted in tremendous improvements in health in the world's poorest countries. Since 2000, GAVI-eligible countries have collectively completed 343 new and underused vaccine program introductions. In the next two years alone, they will make 228 more vaccine program introductions, including inactivated polio vaccine, and vaccines that protect against human Papillomavirus, Japanese encephalitis, rubella, meningitis A, rotavirus, and pneumococcal disease. Many of the newer vaccines being introduced are highly temperature sensitive and some must reach larger target populations with different strategies and at contact times different from the traditional EPI schedule.

From 2000 to 2020, the overall volume of vaccines to be stored and transported is expected to quadruple, and the number of doses to be administered is expected to increase six-fold. Photo: S. Sipursky

Most immunization supply chains were established 30 years ago, when immunization programs were quite small and static. The expansion and evolution of today's immunization programs is requiring significant operational and structural changes in national immunization supply chains to achieve better performance. Results from Effective Vaccine Management (EVM) assessments in 57 countries since 2010 indicate that no country has met the WHO recommended 80% score across all nine categories of vaccine supply chain management. Only 23% of countries achieved adequate temperature control for vaccines; 23% of countries have functional vaccine stock management systems; and 24% of countries have effective vaccine transport systems.

Until supply chains are improved, stock-outs, avoidable wastage, inadequate cold chain capacity, and potential administration of compromised or expired vaccines will increasingly threaten coverage, equity, and cost-effectiveness of immunization programs.

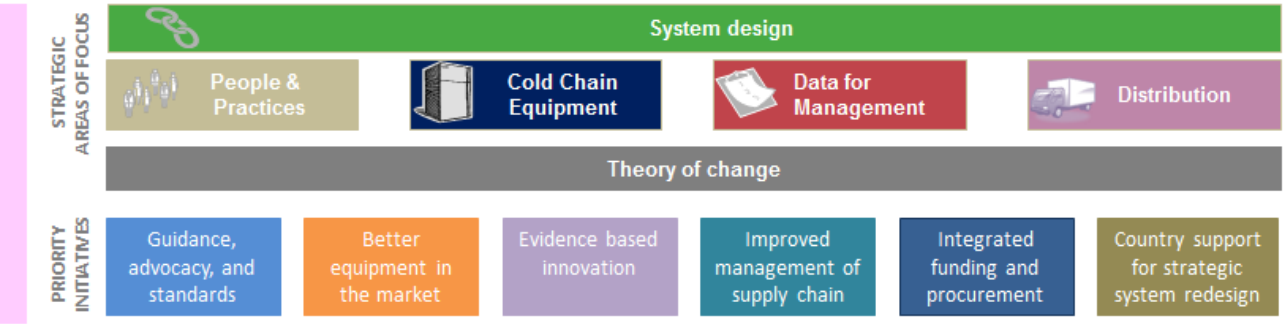
Who is working on it?

In 2013, the GAVI Secretariat convened a task force made up of four core Alliance partners: the GAVI Secretariat, WHO, UNICEF (both supply and program divisions), and the Bill & Melinda Gates Foundation. Their role has been to lead the development of an immunization supply chain strategy that leverages the core capabilities and strengths of each organization to support and influence meaningful, measurable improvements in national immunization supply chains.

Under the leadership of this group and building from the 2020 Vision for Vaccine Supply and Logistics Systems that was initiated by Project Optimize, immunization partners at international, regional, and national levels have engaged in the development of a detailed strategy to achieve a vision in which all countries provide safe and potent vaccines efficiently to all who need them.

What will it look like?

The goal of the GAVI Alliance immunization supply chain strategy is to have evidence, by 2020, that all GAVI-eligible countries *measure* and *meet* minimum international and WHO standards for supply chain performance (currently measured by the Effective Vaccine Management assessment tool) and *show continuous improvement* of indicators for vaccine potency, safety, availability and program efficiency.



PRIORITY AREAS FOR INTERVENTION

To achieve this goal, Alliance members have identified five priority areas of immunization supply chains that are considered to have the greatest impact on in-country supply chain performance:

People and practices: involves establishing human resource policies, education programs, and training and supervision systems to ensure that leaders and professionals with strong supply chain management capabilities are in place to manage distribution and supply chain performance.

Data for management: addresses definition of standards, collection and use of high quality, timely, and relevant data for routine (e.g., avoiding a stock-out when a delivery is delayed) and strategic (e.g., procuring the right equipment based on an up-to-date inventory) decision-making.

Distribution systems: involves the procurement, allocation, proper use, fueling, and maintenance of vehicles and transport systems; decisions about delivery routes and frequencies; and proper vaccine handling during transport.

Cold chain equipment: addresses the development, selection, deployment, installation, proper use, and maintenance of refrigerators, freezers, cold boxes, cold rooms, temperature monitoring devices, and other equipment used to keep vaccines at proper temperatures.

Supply chain design and structure [cross-cutting]: involves looking holistically at the design of the system, and finding opportunities to improve network structures and their efficiency, which could include: reducing the number of intermediate storage levels in a supply chain; outsourcing specific functions, such as fleet management or cold chain equipment leasing to private or parastatal organizations; and shifting from collection to distribution systems with efficient supply routes. It also includes efforts to integrate specific supply chain functions with other health commodity supply chains or merge data collection and management systems.

GROUPS OF PRIORITY INITIATIVES

Recognizing that supply chains are primarily the responsibility of national governments, and that each supply chain has a different set of capabilities, opportunities, and challenges, immunization partners agree that a country-specific approach is required. The GAVI Alliance supply chain strategy leverages the policy-making, convening power, and standards-setting abilities of WHO and UNICEF and the advocacy, proposal review, and funding abilities of GAVI itself to establish a powerful enabling environment for supply chain improvement within countries. Incentives for purposeful and meaningful investments in supply chains will be provided along with guidance and technical assistance to countries as they embark on this change process. Priority initiatives within the strategy are organized in the following groups:

Guidance, advocacy, and standards: Priority initiatives under this theme establish norms and offer general knowledge and guidance to countries as they make improvements to their immunization supply chains. Examples include global guidance and recommendations for in-country information systems; knowledge-sharing platforms for cold chain equipment (including a buyers' guide, equipment field performance reports); and standard operating procedures for equipment commissioning, operation, maintenance, and disposal.

Availability of improved cold chain equipment: Priority initiatives under this theme are directed toward improving the quality and choice of cold chain and temperature monitoring equipment. Examples include investing in early-design-stage field-testing of equipment that meets desirable specifications defined by countries and the GAVI Alliance, and promoting timely feedback on post-market product performance.

Evidence-based innovation: Priority initiatives under this theme are designed to encourage innovation in education and training, cold chain equipment, information systems, distribution strategies, and forecasting approaches.

Improved management of supply chain: Priority initiatives under this theme are designed to build capacity among supply chain managers through education and training, the development of tools and processes, and the provision of direct assistance to countries. Examples include supporting the establishment of a Supply Chain Manager position in every GAVI country, and providing technical assistance to help countries build and actively manage cold chain equipment.

Integrated funding and procurement: Priority initiatives under this theme are designed to reduce the cost of supply chains and improve efficiency. They include integrating forecasting of equipment volumes across countries, advocating with global supply chain donors to adopt standards from the GAVI supply chain strategy, and coordinated procurement as well as supplier interaction on cold chain equipment as much as possible.

Country support for supply chain system design: Priority initiatives under this theme are directed toward helping countries redesign their immunization supply chain systems. Examples include encouraging and supporting countries to engage in redesign of their supply chain network by reducing levels or changing distribution models, and helping support integration with other health supply chains where countries express interest.

How does the WHO/UNICEF immunization supply chain Hub fit with the strategy?

The GAVI immunisation supply chain task force conducted a landscape of new and ongoing supply chain activities and prioritized critical activity areas that were likely to provide the strongest support the GAVI Alliance's objectives. Building on recent WHO/UNICEF activities focusing on the immunization supply chain Hub, WHO and UNICEF have assumed responsibility for a set of activities that are now well-coordinated with the emerging GAVI strategy:

- Providing global guidance on the supply chain through the establishment of a policy change mechanism at global, regional and country levels using SAGE, Immunization Practices Advisory Committee, regional Technical Advisory Groups, EPI managers' meetings, etc.
- Developing an in-country change mechanism with support from WHO and UNICEF regional and country offices (i.e., establishing sub-groups of the ICC dedicated to planning and implementing supply chain change).
- Supporting the implementation of a comprehensive EVM approach (as defined in the WHO/UNICEF EVM Joint Statement) to guide further development and improvement of immunization supply chains.

In addition, WHO and UNICEF will maintain their traditional roles associated with immunization supply chains, including UNICEF's vaccines and cold chain market shaping and procurement functions, the WHO Performance, Quality, and Safety (PQS) process for qualifying cold chain equipment, the Vaccine Presentation and Packaging Advisory Group for suggesting improvements to vaccine products and packaging, global monitoring and evaluation activities, and the ongoing development of guidelines and policies.

How is the broader immunization community involved in the strategy development?

The supply chain strategy task force has involved the broader immunization community through interaction with key stakeholders in working groups, as well as individual interviews and feedback cycles with country managers.

- Each priority topic area has been elaborated by working groups made up of representatives from organizations active in immunization, including PATH, Clinton Health Access Initiative, John Snow Inc, USAID, VillageReach, Bioforce, Agénce de Medecine Preventive, OpenLMIS, consultants, universities and others. These groups have reviewed potential initiatives in person, engaged in regular discussions, and participated in moderated online discussions.
- In November 2013, the task force distributed a web-based survey to logisticians, EPI managers, civil society organizations, UN agency staff, consultants, and international nongovernmental organizations asking them to describe the supply chain challenges they are facing. Approximately 150 individuals responded, about half of whom work at the national or sub-national level. Currently, the task force is surveying participants of EPI manager meetings in various regions of AFRO to collect further feedback on specific strategic elements. The task force also continues to consult with individuals that represent specific constituencies, including donors, civil society, and international NGOs.

These stakeholders will continue to participate in discussions and decisions as the strategy is finalized and the implementation stage begins.

When will implementation begin?

Several key initiatives are already underway with funding from GAVI business plan and other sources. These include technical assistance to specific countries; the development of target product profiles for solar direct-drive refrigerators; investment in new supply chain innovations such as bar codes on packaging to improve stock management of vaccines; and, passive-cooling for vaccine storage.

The supply chain task force is planning to begin broader implementation during the second half of 2014.

What are the next steps?

The strategy will be presented to the GAVI Programme and Policy Committee (PPC) on 5-6 May. The GAVI board will review the supply chain strategy on 18-19 June, where they will be asked to provide guidance on direction and decide on a few relevant policy and funding decisions.

5 - 6 Feb | 2014

8th Meeting of the SAGE Polio Working Group

Conclusions and recommendations

Note for the Record

World Health Organization

DRAFT AS OF 3/17/14

Executive Summary

Since the inception of the Global Polio Eradication Initiative (GPEI) in 1988, the number of paralytic cases dropped from an estimated 350,000 in 1988 to 403 reported in 2013, and wild polioviruses currently remain endemic in only three countries (Afghanistan, Nigeria, and Pakistan). However, as long as polioviruses circulate anywhere, they can be exported to polio-free countries. Between 2004 and 2013, for example, exportations caused 179 outbreak events in previously polio-free countries, which resulted in more than 3,500 paralytic cases. The GPEI has expended over $1.1 Billion in international funds alone, for outbreak response following wild poliovirus importations over the last 10 years (2004-2013). This estimate does not include the indirect costs of diverting public health experts and health workers from other public health work or the opportunity costs associated with using vaccine for outbreak response instead of for intensified eradication activities during times of restricted supplies.

Following the polio outbreaks of 2013 in the Middle East and the Horn of Africa due to international spread of poliovirus, and the threat such events pose to the eradication of poliomyelitis globally, during the World Health Organization (WHO) Executive Board meeting in January 2014, Member States requested that the WHO Director General (DG) convene an Emergency Committee under the International Health Regulations (IHR) to review as a matter of urgency the potential need for additional measures for reducing the risk of international spread of polio within the IHR mechanism for public health emergencies of international concern (i.e. PHEIC). Several WHO Member States (e.g. Saudi Arabia, India, Syria, and Brunei) had already introduced polio vaccination requirements for travellers arriving from polio-infected countries, and some Member States requested additional WHO guidance in this regard.

Given the availability of new information on the impact of polio vaccines on humoral and intestinal immunity, on the role of adults in international spread of the virus, and on the duration of intestinal immunity to poliovirus, the WHO Director-General requested that the Strategic Advisory Group of Experts on immunization (SAGE) review this evidence and, if appropriate, provide advice to WHO for updating its technical recommendations concerning the vaccination of travellers from polio-infected countries.

The SAGE Polio Working Group (WG) convened an extraordinary session on 5 and 6 February 2014 in Geneva, Switzerland to review WHO's technical recommendations on polio vaccination for travellers from polio-infected countries and propose an update for consideration by SAGE at its April 2014 meeting. The WG also discussed potential challenges and practical considerations that might be encountered in implementing such recommendations. Representatives of the governments of Nigeria, Pakistan, Israel, Saudi Arabia, and from the International Civil Aviation Organization (ICAO) and the International Air Transport Association (IATA) were invited to share their perspectives with the WG.

Noting that all polio-free countries remain at risk of importations as long as poliovirus circulation continues anywhere, the WG concluded that vaccination of international travellers from polio-infected countries would help to mitigate the risk of international spread of the virus, especially to polio-free countries with vulnerable populations and at high-risk of importations. The WG also reinforced the importance of all countries ensuring high immunization coverage, especially in high risk and vulnerable populations, and maintaining sensitive surveillance to rapidly detect circulating poliovirus. The WG emphasized that the best way to reduce and eliminate the exportation of wild polioviruses (WPV) and circulating vaccine-derived polioviruses (cVDPVs) was to stop all remaining virus transmission in polio-infected countries. Efforts to reduce spread of polioviruses from infected countries through travellers should complement and not detract from the critical work of terminating transmission in polio infected countries.

RECOMMENDATIONS

The WG reviewed new evidence on the efficacy of polio vaccines and the epidemiology of polio, and recommended that the current advice for international travellers in the WHO document *International Travel and Health (ITH) 2013* should be updated as follows:

Definition of "polio-infected" countries

- The WG reaffirmed the following definitions used by WHO to identify countries with active poliovirus transmission (i.e. 'polio-infected countries'):
    - **Endemic WPV transmission**: continued transmission of an indigenous WPV which by definition has never been interrupted. Endemic WPV transmission is considered to be interrupted, when all indigenous WPVs have not been detected for > 12 months from any source (e.g. Acute Flaccid paralysis (AFP) cases, their contacts, environmental samples, stool surveys). As of February 2014, three countries were considered endemic (Pakistan, Nigeria, Afghanistan);
    - **Re-established wild poliovirus transmission**: persistence of WPV of non-indigenous origin for > 12 months in a previously polio-free country. Re-established WPV transmission is considered to be interrupted, when the imported strain of WPV has not been detected for > 12 months from any source (e.g. AFP cases, their contacts, environmental samples, stool surveys);
    - **Re-infection with wild poliovirus** : a) at least one AFP case with isolation of WPV in a person who has not travelled outside the country during the two months prior to onset of paralysis *or* b) detection of 2 or more genetically related WPVs in environmental samples and/or other non-AFP sources (e.g. stool surveys). WPV is considered to be interrupted, when there is no detection of the imported strain of WPV for > 6 months from any source (e.g. AFP cases, their contacts, environmental samples, stool surveys);
    - **Re-infection with a cVDPV**: detection of a genetically related cVDPV in 2 or more AFP cases in a country, or detection of a genetically related cVDPV in 2 or more environmental samples or samples from other sources. Re-infection with cVDPV is considered to be interrupted when there has been no detection of the cVDPV for > 6 months.

- The WG also reaffirmed that an isolated "WPV or cVDPV importation event", wherein a country detects a WPV or cVDPV in (a) a single AFP case who had proven exposure and/or paralysis onset outside the country, or (b) in a single environmental sample or sample from another source, is not considered evidence of active poliovirus transmission.

Recommended population for vaccination ("Recommended population")

- Vaccination recommendations for travellers from polio-infected countries should apply to all residents and long-term visitors (i.e. non-residents who spend more than 4 weeks in the country) of all ages;
- Polio vaccination recommendations for travellers from polio-infected countries would not apply to short-term visitors (e.g. those who visit the polio-infected country for periods of ≤4 weeks duration) or travellers in transit through an infected country, as they would pose a low risk of poliovirus infection and international spread;

Recommended vaccinations

Travellers from infected countries (those who meet the definition of "recommended population" above)

- All such travellers from polio-infected countries should have received one documented, additional dose of OPV or IPV at least 4 weeks and at most 12 months before departure;
- In addition, all such children travelling from polio-infected countries should have completed their age-appropriate primary series for polio vaccination according to the national immunization schedule (e.g. children too young to have received at least 3 doses of a polio vaccine according to the national schedule should be up-to-date for their age);

- Such travellers from polio-infected countries embarking on last minute/urgent (i.e. less than 2 weeks) travel that cannot be postponed should receive one dose of OPV or IPV before departure if they have not received a documented dose of polio vaccine within 12 months before the date of travel.

Travellers to infected countries

- Per the current WHO *International Travel and Health (ITH) 2013,* travellers to polio-infected countries are advised to have completed the age-appropriate polio vaccine series recommended in their national immunization schedule; adult travellers should have a one-time booster dose of OPV or IPV prior to travel to polio-infected countries

CONSIDERATIONS FOR IMPLEMENTING POLIO VACCINATION RECOMMENDATIONS FOR TRAVELLERS

The WG discussed a number of operational issues related to the implementation of vaccination recommendations and/or requirements for travellers (e.g. for yellow fever, polio) that should be considered in applying such measures.

Documentation of vaccination

- To facilitate international travel, each polio-infected country would need to ensure its travellers have access to a standardized certificate that would be accepted internationally as proof of appropriate polio vaccination;
- The WHO vaccination and prophylaxis 'Yellow Book or Booklet'[1] (preferably), and the 1-page IHR model International Certificate of Vaccination or Prophylaxis in Annex 6 of the IHR (2005) (which is also part of the Yellow Book), are two internationally acceptable documents for proof of vaccination that could be used for this purpose;
- To facilitate international acceptance of any nationally-issued vaccination certificates, authorities should ensure that such documents contain the information included in the above IHR model International Certificate and Annex 6;
- To reinforce the authenticity of the certificates of vaccination, countries should be encouraged to make efforts to ensure the validity, accuracy, and integrity of the certificates they issue (e.g. producing certificates with features that resist falsification). The WG noted that at least 1 country has included a security feature within its vaccine certificate for yellow fever to reduce this problem;

Role of countries of departure (polio-infected countries)

- The WG recognized that exit screening of vaccination certificates is not currently recommended or implemented for any vaccine-preventable disease risk. However, this might be a consideration for polio in some settings given the small number of polio-infected countries;
- At ground-crossing points with a high volume of travellers, and limited capacity for screening (e.g. an uncontrolled land border), implementation of special measures could be considered to boost population immunity in that area (e.g. expanded age group campaigns or vaccination/documentation at the border).

Role of countries of arrival

- Countries receiving travellers within the recommended population for vaccination from polio-infected countries may need to:
    - Validate at border crossings proof of appropriate polio vaccination of such travellers arriving from these countries (including at airport, seaport and ground crossing-points);

[1] The Yellow Book is available as a pdf download on the WHO website. See WHO International Certificate of Vaccination or Prophylaxis: International Health Regulations (2005), at http://www.who.int/ihr/ports_airports/icvp/en/.

- Establish a process for managing such travellers who are not able to produce a valid certificate of vaccination. Options for managing such travellers may include vaccination on arrival, refusal of entry, and/or quarantine, depending on the assessed risk of importation in accordance with any relevant IHR and national and international obligations regarding such measures;
- Establish options for managing such arriving travellers who are not able to produce a valid certification of vaccination and refuse vaccination on arrival;
- Explore the potential value of linking proof of polio vaccination to the issuance of entry visas for such travellers to minimize the number of travellers arriving without proper documentation of polio vaccination.

Acceptable vaccines

- WHO pre-qualified polio vaccines should be considered acceptable for the purposes of vaccinating travellers from polio-infected countries; nationally-licenced polio vaccines, but which have not been submitted for WHO prequalification, may also be considered acceptable for this purpose.

Administrative and financial issues

- Governments of both departure and arrival countries will need to reinforce their capacity to vaccinate, issue certificates, communicate to the public, and, potentially, screen at border points in order to assess the polio vaccination status of travellers within the recommended populations and to manage any health measures applied to them as appropriate;
- The financial and human resources needed to implement polio vaccination recommendations and/or national requirements for travellers, and the potential opportunity costs associated with undertaking these measures, should be assessed for planning purposes so that polio-infected countries can act accordingly;
- To mitigate the financial and administrative impact of any potential polio vaccination requirements for travellers, consideration might be given to a phased introduction, beginning with populations and/or areas at highest risk for transmission of virus to other countries (e.g. guest workers leaving a polio-infected country for another country).

Communication and public education

- Careful planning and communications in polio-infected countries, and also for relevant personnel in countries of arrival, will be important to ensure effectiveness and facilitate implementation of any polio vaccination recommendations or national requirements;
- Although airline companies may play a role in helping to inform passengers about vaccination requirements, such companies should neither be responsible for exit/arrival screening of vaccination certificates nor required to bear expenses related to a failure of passengers to comply with any such requirements, including the transport of Individuals who are not granted entry back to the country of origin

Annex-1: Key WG recommendations and supporting evidence

Current recommendations (ITH 2013)	Proposed Recommendations	Key Evidence
Population recommended for vaccination • Individuals living in areas where polio cases area still occurring	• Population recommended for vaccination should include residents of all ages of polio-infected countries*, as well as long-term visitors (>4 weeks)	• Excretion of WPVs has been detected among individuals of all ages, Persons of all ages who excreted WPVs were detected in many areas of active WPV circulation; • Some recent outbreaks (4 of 22) showed most paralytic cases occurred among adolescents and adults • Several documented cases of international spread of WPVs involved transmission from adults (people > 15 yrs); • Short-term travelers likely assume a low risk of community exposure to poliovirus (e.g. staying in hotels), while longer term travellers may assume a much higher risk of household poliovirus exposure (e.g. staying with families).

* "Polio-infected countries include all countries with transmission of indigenous or re-established WPV within the past 12 months and/or transmission of an imported WPV or cVDPV within the past 6 months). The evidence of ongoing poliovirus transmission can come from cases of AFP, environmental samples, and other sources such as stool surveys

Current recommendations (ITH 2013)	Proposed Recommendations	Key Evidence
Vaccination recommendation for travellers from polio infected countries • Travellers should have completed a full course of vaccination against polio, preferably with OPV • Travellers from infected areas should receive an additional dose of OPV at least 6 weeks before each international journey	• If the last documented dose of polio vaccine was received more than 12 months before departure, the traveller within the recommended population should receive at least one additional dose of OPV or IPV at least 4 weeks before departure • All children (within the recommended population) from polio-infected countries should have completed age-appropriate primary polio vaccination before departure • For last minute and urgent travel that cannot be postponed, the traveller within the recommended population should receive a dose of OPV or IPV, prior to departure.	• Data from polio-infected areas suggest that intestinal immunity wanes within 12 months of the previous vaccination with OPV • More than 90% of those who will seroconvert will have done so by 4 weeks (either by OPV or IPV). • Most poliovirus excretion (wild and vaccine related viruses) is cleared within 4 weeks, especially in OPV-vaccinated populations and areas of endemic transmission • Two randomized controlled trials indicate that IPV can boost intestinal immunity among individuals previously-vaccinated with OPV.
Vaccination recommendation for travellers to polio infected countries • These travellers should ensure that they have completed the age-appropriate polio vaccine series as recommended in their national immunization schedule. • Travellers to polio-infected areas who have previously received three or more doses of OPV or IPV should also be given another dose of polio vaccine before departure.	• The WG recommended keeping the current ITH language (2013) that recommends a one-time polio vaccine booster for travellers from polio-free countries who have completed a primary series	• Studies have shown that one dose of IPV or OPV after the primary series is sufficient to boost humoral immunity. In persons previously vaccinated with OPV. Both IPV and OPV also boost intestinal immunity.

Draft: 14 March 2014

CONSIDERATIONS FOR VACCINATION RECOMMENDATIONS FOR TRAVELLERS FROM POLIO-INFECTED COUNTRIES

INTRODUCTION

Following the discussion at the World Health Organization (WHO) Executive Board meeting in January 2014, the WHO Director-General requested that the Strategic Advisory Group of Experts on Immunization (SAGE) review the scientific evidence regarding polio vaccination recommendations for travellers arriving from polio-infected countries. This communication summarizes the key elements and the supporting scientific data for the vaccination recommendations, including a) the recommended population for vaccination, and b) the recommended vaccinations.

Considerations for the recommended target population to be vaccinated prior to travel from polio-infected countries

Role of older age groups in international spread of poliovirus:

Poliovirus importation into polio-free areas is assumed to occur frequently. However, most of these importation events are silent (i.e., not leading to paralytic cases) and the transmission is self-limiting because of high population immunity. Occasionally these events are detected and reported (i.e., Paris, Strasbourg, Geneva, etc.).

A subset of these importations may lead to establishment of circulation that manifest as outbreaks. Between 2004 and 2013, 179 importation events resulted in more than reported 3,500 paralytic cases. Of these, 27 (15%) were associated with long-distance travel (i.e., transmission between non-contiguous countries or across oceans) where adult travellers would be expected to much more likely to be involved[1,2,3,4], although no definitive information about the transmission path and specific individuals who imported virus were available.

Furthermore, there are several lines of evidence that support the potential importance of adult travellers in harbouring and propagating poliovirus infection, including: 1) stool surveys demonstrate that adults can be infected and excrete poliovirus: 2) duration and titre of poliovirus excretion among adults is similar to that of children because mucosal immunity wanes relatively rapidly (i.e., <12 months); and 3) adults travellers constitute the vast majority of international travel and occasionally infected adult travellers are identified[5].

[1] Afif H., Sutter R.W., Kew O.M., et al.: Outbreak of poliomyelitis in Gizan, Saudi Arabia: co-circulation of wild type 1 polioviruses from three separate origins. J Infect Dis. 175 (suppl 1):S71-S75 1997

[2] Kidd S, et al. 2011 Poliomyelitis outbreaks in Angola genetically linked to India: risk factors and implications for prevention of outbreaks due to wild poliovirus importations. Vaccine 29, 3760–3766

[3] Smorodintsev A.A., Davidenkova E. F., Drobyshevskaya Y.A. et al. Results of a study of the reactogenic and immunogenic properties of live anti-poliomyelitis vaccine. Bull World Health Organ. 1959;20:1053–1074.

[4] Yakovenko M et al Euro Surveill. 2014 Feb 20;19(7)

[5] Kubli D., Steffen R., Schar M. (1987) Importation of poliomyelitis to industrialised nations between 1975 and 1984: evaluation and conclusion for vaccination reccomendations. Br. Med. J. 295:169–171.

There is epidemiological evidence that older persons (those over 15 years of age) have participated in poliovirus transmission. In 2009, two investigations conducted in UP and Bihar in India on the prevalence of asymptomatic WPV infection found that 60% of silent transmission (measured by excretion of wild poliovirus in stool) was among those over 5 years of age[6]. In addition, a stool survey conducted in Southern Israel in July 2013 among a convenience sample of ~2,000 individuals found an excretion rate of 3.3% among children 0-18 years, with a higher rate of excretion in cohorts not given tOPV in the past (0-9 years age band). An excretion rate of 0.5% was documented among adults >18 years, and 1.4% (2 out of 147) among >45 years[7]. Numerous studies found that older children and adults can become infected and excrete poliovirus if challenged with an OPV virus or if in contact with children who excrete poliovirus[8]. For example, the 1965 Virus Watch studies by Fox and associates that investigated OPV virus introductions from the community into families also demonstrated that adults can not only become infected but also infect others (e.g., of the introducers, 66% were <5, 11% were older children, and 22% were adult parents[9]. Also in Israel, an OPV challenge study in 2007 indicated that 1.1% of 99 mothers of OPV- challenged children excreted virus on day 7 after challenge of their children. Similarly, 2.1% of 145 siblings of challenged children excreted by day 7, declining to 1.4% and 0.7% by days 14 and 21, respectively, after challenge. This illustrates the potential for adults, even those previously vaccinated or exposed such that they benefit from lifelong protection from paralysis, to become infected in the course of poliovirus transmission among children[10].

There is some scientific evidence to show that there is no significant difference in the duration of poliovirus excretion between adults and infants. The stool study in Bihar suggested similar titres of poliovirus found in stool in children and adults[11]. A more recent study in Moradabad, India also demonstrated that the titter and duration of poliovirus excretion after the OPV challenge is similar across age groups (6-11 months, 5-6 years and 10-11 years)[12].

Lastly, there have been several documented cases of adult poliovirus excretors travelling long distances. WHO and other public health authority records indicated that 175 cases of poliomyelitis were imported to industrialized countries between 1975 and 1984, including 34 travellers above 20 years old[13]. There are more recent documented cases of adults, who are travelling long distance with wild poliovirus excretion (e.g. three cases from Mexico, Nepal, and Zaire to the U.S. between 1980 and 1989[14], one case from Pakistan to Australia in 2007[15], and one case from Xinxiang to

[6] Mach O et al. Prevalence of Asymptomatic Poliovirus Infection in Older Children and Adults in Northern India: Analysis of Contact and Community Enhanced Surveillance, 2009. Journal of Infectious Diseases. In press.
[7] Unpublished data
[8] Duintjer Tebbens RJ, Pallansch MA, Chumakov KM, Halsey NA, Hovi T, Minor PD, Modlin JF, Patriarca PA, Sutter RW, Wright PF, Wassilak SGF, Cochi SL, Kim J-H, Thompson KM. Expert review on poliovirus immunity and transmission. Risk Analysis 2013;33(4):544-605
[9] Fox JP, Hall CE, Viruses in Families, PSG Publishing Co, Inc, Littleton, Massachusetts, 1980, page 194.
[10] Schwartz et al. Intestinal immunity following a combined enhanced inactivated polio vaccine/oral polio vaccine programme in Israel. Vaccine. 2007.
[11] Mach O et al., ibid.
[12] Jafari H et al. in prep (WHO Moradabad study)
[13] Kubli D et al., ibid.
[14] Strebel Pm, Sutter Rw, Cochi Sl, et al. Epidemiology of poliomyelitis in the United States one decade after the last reported case of indigenous wild virus-associated disease. Clin Infect Dis 1992; 14: 568-579
[15] Stewardson AJ, Roberts JA, Beckett CL, Prime HT, Loh PS, Thorley BR, Daffy JR: Imported case of poliomyelitis, Melbourne, Australia, 2007.Emerg Infect Dis 2009, 15(1):63-65

Beijing in 2011[16]). These data suggest the high likelihood that older individuals participate in the international importation of poliovirus.

Considerations for the recommended vaccinations for travellers from polio-infected countries

There are a number of general considerations that may influence policy decisions for the recommended vaccinations for travellers from polio-infected countries.

Rapidity of humoral and intestinal immunity induced by IPV and OPV: Analysis of kinetics of antibody response has shown that the majority of naïve individuals develop serum IgG within 4 weeks of vaccination with IPV or OPV[17]. An early study in the USSR in 1959 with 70 seronegative children demonstrated almost all the children responded to OPV by day 21 with a significant increase in antibody titre (i.e. average GMT of 130.0-306.4)[18]. There are several studies demonstrating that OPV or IPV-primed individuals given a supplementary dose of either vaccine show an increase in antibody titres in as early as 7 days: Studies in both Oman[19] and Cuba[20] showed a peak boosting response with IPV within 7 days among OPV or IPV-primed individuals. Another more recent study in Cuba in 2013[21] showed that among individuals who had an immune response by 21 days, antibodies rose in 5-10% of individuals within 3 days and in more than 90% within 7 days after administration of the boosting dose of IPV. The kinetics analysis also suggested that induction of intestinal immunity is quicker (i.e. one to two weeks after vaccination)[22] although the available evidence from clinical research on the rapidity of mucosal immunity is limited. A study in Japan with four naive subjects who received tOPV in 2001 showed that secretory IgA (sIgA) appeared in naive infants as early as 7 days after administration of either the first dose or second dose of tOPV[23]. Another study from the Netherlands (1999) also demonstrated the rise of sIgA within 7 days after a booster dose of IPV among adults previously immunised with OPV[24].

Frequency and duration of poliovirus excretion: A review of cross-sectional and longitudinal studies of wild or Sabin poliovirus excretion concluded that live polioviruses are excreted by a majority of previously unvaccinated infants and young children for 3-4 weeks following the onset of paralysis (i.e. 4-6 weeks after exposure). The duration of excretion data among the studies was consistent despite numerous differences in design, and the cumulative excretion rates for Sabin strains were similar to those for wild type. However, it should be noted that studies for WPV were measured relative to onset of paralysis and the ones for Sabin were measured relative to the time of challenge. This

[16] Luo, H. M. et al. Identification and control of a poliomyelitis outbreak in Xinjiang, China. N. Engl. J. Med.2013; 369, 1981–1990

[17] Ogra PL, Karzon DT, Righthand F, MacGillivray M. Immunoglobulin response in serum and secretions after immunization with live and inactivated poliovaccine and natural infection. N Engl J Med 1968; 279: 893–90

[18] Smorodintsev A.A., Davidenkova E. F., Drobyshevskaya Y.A. et al. Results of a study of the reactogenic and immunogenic properties of live anti-poliomyelitis vaccine. Bull World Health Organ. 1959;20:1053–1074.

[19] Sutter RW, Suleiman AJ, Malankar P *et al.* Trial of a supplemental dose of four poliovirus vaccines. N Engl J Med 2000;343:767–73.

[20] Resik S , Tejeda A, Sutter RW, Diaz M, et al. Priming after a fractional dose of inactivated poliovirus vaccine. N Engl J Med. 2013;368:416-24.

[21] Unpublished data

[22] Ogra PL et al. Viral vaccination via the mucosal routes. Reviews of infectious disease, 1980, 2:352-369.

[23] Morimoto N. The relationship between poliovirus multiplication, the sIgA antibody response and the serum neutralizing antibody titers after trivalent oral polio vaccination. Kansenshogaku Zasshi 2001;75:1030-9.

[24] Herremans TM, Reimerink JH, Buisman AM, Kimman TG, Koopmans MP (1999) Induction of mucosal immunity by inactivated poliovirus vaccine is dependent on previous mucosal contact with live virus. J Immunol 162: 5011–5018

would suggest longer excretion for WPV than Sabin. However, there is no study that provides a direct comparison of Sabin vs. WPV[25].

The frequency and duration of viral shedding appears reduced among infants with high levels of serum neutralizing antibody due to prior OPV, IPV or natural infection[26]. Numerous studies found that the duration of faecal excretion of poliovirus by infants who have recently received OPV is less than that of infants who have received IPV, suggesting a significant role of local immunity in reducing intestinal replication of poliovirus[27,28].

Duration of intestinal immunity: Intestinal immunity against poliovirus induced by OPV wanes as early as 12 months after vaccination. Two OPV challenge studies indicated that children and adults previously exposed to live poliovirus (OPV or WPV) frequently shed poliovirus following OPV administration more than 10 years after the last vaccination[29,30]. However, the time frame for most challenge studies is such that OPV is provided either more than 10 years after the last vaccination (for older children or adults), or 1-3 months after the last vaccination for younger children (under 18 months); few studies have examined shedding in relation to the time since last vaccination[31]. A retrospective analysis of AFP surveillance data in India showed that the odds of excreting virus increased significantly (1.5-2.0 times) in the group which received a challenge dose of OPV more than six months (average time 9-15 months depending on serotype) following the last exposure to the OPV[32]. Shedding of poliovirus after OPV challenge was found to increase with age in a recent study in India in a manner consistent with waning of immunity after leaving the age group eligible for supplementary immunisation activities (shedding among 10 year old children > 5 year old children > 6-11 months old infants) (Jafari et al.)

Ability of IPV/OPV to boost intestinal immunity among those previously vaccinated with OPV: Two randomized controlled studies indicated that IPV has a greater effect than OPV in boosting intestinal immunity among OPV-primed individuals. A study in Moradabad, India demonstrated that a single dose of IPV administered to infants and children (aged 6-11 months, 5-6 years and 10-11 years) with a history of multiple OPV doses significantly boosts intestinal immunity, and reduces prevalence of excretion after a bivalent OPV challenge. The relative reduction in excretion between IPV and control group were remarkably consistent across the age groups. For poliovirus type 1 the decrease in excretion in any stool sample after challenge in the IPV group compared to the control group was 38.8% (14.4% vs 8.8%) in the 6-11-month, 65.6% (24.1% v 8.3%) in the 5-year, and 74.2% (52.4% vs 13.5%) in the 10-year age group; the corresponding decreases for poliovirus type 3 were 71.1% (13.5% vs 3.9%) in the 6-11-month, 52.4% (25.0% vs 11.9%) in the 5-year, and 75.7% (51.4% vs 12.5%) in the

[25] Duintjer Tebbens RJ, ibid.
[26] Alexander, J. P., Jr., H. E. Gary, Jr., and M. A. Pallansch. 1997. Duration of poliovirus excretion and its implications for acute flaccid paralysis surveillance: a review of the literature. J. Infect. Dis. 175(Suppl. 1):S176-S182.
[27] Duintjer Tebbens RJ, ibid.
[28] Onorato IM, Modlin JF, McBean AM, Thoms ML, Losonsky GA, Bernier RH. Mucosal immunity induced by enhance-potency inactivated and oral polio vaccines. J Infect Dis. 1991 Jan;163(1):1–6
[29] Smith JWG, Lee JA, Morris CA, Parker DA, Yetts R, Magreth DI, Perkins FT. The responses to oral poliovaccine in persons aged 16-18 years. J Hyg 1976;76:235-247
[30] Abbink F, et al. 2005. Poliovirus-specific memory immunity in seronegative elderly people does not protect against virus excretion. J. Infect. Dis. 191:990–999.
[31] Hird TR and Grassly NC. Systematic review of mucosal immunity induced by oral and inactivated poliovirus vaccines against virus shedding following oral poliovirus challenge. PLoS Pathog 2012; 8 (4)
[32] Grassly NC, Jafari H, Bahl S, Sethi R, Deshpande JM, Wolff C, Sutter RW and Aylward RB (2012). Waning intestinal immunity following vaccination with oral poliovirus vaccines in India. J Infect Dis 205: 1554-1561

10-year age group[33]. It also reduced overall viral titre shed (4.1 vs. 3.6 in log10 CCID 50 in type 1, and 4.1 vs. 3.4 in type 3) and length of overall excretion (8.7 vs. 7 days in type 1 and 12.9 vs. 10.5 days in type 3). This reduction effect is largest in children aged 10-11 years and is considerably larger than that of a supplemental dose of bOPV (which reduced excretion prevalence by 51.7% and 48.8% against types 1 and 3 respectively in the 10-11 year old group). Also, a recent study in South India demonstrated that IPV can boost both intestinal and humoral immunity better than bivalent OPV among 1-4 year-olds who last received OPV 7-10 months previously[34]. However, there is insufficient information as to whether the intestinal immunity boosted by IPV lasts as long as or longer than for OPV.

Conclusion

The evidence reviewed in this paper reaffirms the scientific basis for the current advice on polio vaccination for international travellers, as outlined in the WHO document *International Travel and Health (ITH) 2013* , as well as the updated recommendations on the vaccines of choice for, and timing of, additional doses. This evidence and its implications for vaccination recommendations for travellers is summarized as follows (key changes highlighted):

– Epidemiological and observational evidence indicate that older children and adults have participated in poliovirus transmission and the international spread of poliovirus. Therefore, travellers of all ages within the recommended population (i.e. residents of polio-infected countries and long-term visitors) should be vaccinated before travelling from polio-infected countries.

– The risk of poliovirus exportation through excretion is reduced among individuals 4 weeks after receiving a supplementary dose of IPV or OPV, so travellers from the recommended populations should receive at least one additional dose of OPV or IPV at least 4 weeks before departure:

    - By 4 weeks following administration of IPV or OPV, most naive individuals will have developed sufficient serum and mucosal antibodies (in case of OPV) to protect against shedding and transmission of infection. A boosting dose of IPV/OPV can induce humoral and intestinal immunity as early as 7 days post vaccination.

    - Even if a traveller is infected with wild poliovirus or a cVDPV at the time of vaccination, most poliovirus excretion from natural infection is over in 3-4 weeks.

– A recent analysis using data from the polio endemic country indicates that the Intestinal mucosal immunity appears to wane within 12 months after the vaccination with OPV. This suggests that a traveller should be vaccinated within 12 months before departure to ensure adequate intestinal immunity.

– In children whose intestinal mucosal immunity has waned, one dose of polio vaccine (OPV or IPV) will decrease prevalence of poliovirus excretion (50-75%), decrease viral titre and shorten duration of excretion. This suggests that additional vaccination with OPV or IPV should decrease the risk of travellers importing poliovirus into polio-free areas.

[33] Jafari H et al., ibid.
[34] John J et al in prep (CMC IPV study)

Independent **Monitoring Board**

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POLIO GLOBAL ERADICATION INITIATIVE

26 February 2014

Dr Margaret Chan
Director-General
World Health Organization
Avenue Appia 20
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Switzerland

Dear Dr Chan

The IMB met with senior representatives of the GPEI's five core partner agencies on 18 February in Washington DC, to hear the program's response to our October 2013 report and to discuss the current global situation. The presentations and discussion were of very high quality. In the face of great challenge, the partnership leaders are clearly determined and seem more cohesive as a group than we have ever previously observed.

I write to summarise the IMB's main findings.

Polio virus circulation

The current situation in Pakistan is a powder keg that could ignite widespread polio transmission. The number of cases in this country is going in the wrong direction. The new government has been slow to grasp the fundamental seriousness of the situation. If the current trend continues, Pakistan will be the last place on earth in which polio exists. The most serious situation is in the north-west, where the virus is enjoying unencumbered circulation at great human cost. We welcome the firm and intelligently designed initiative underway in Peshawar, but such innovation must be sustained in this region and be promoted elsewhere in the country. The adequacy of the government's plans will be in full public view at our May meeting, and at the subsequent World Health Assembly.

We will also meet in May with the government of Nigeria. This is a crucial year for Nigeria. Many are hoping that polio transmission can be stopped in 2014. In our view, this is potentially feasible but far from certain. We welcome the country's determination to succeed this year but elections are looming, and the country has previously achieved periods of forward momentum that have not been sustained. Nigeria desperately needs continuity and unwavering commitment in the face of election-related distraction. When we meet, we will particularly examine the situation in Kano and Borno states, where performance is critical to wiping polio from Nigeria, and so from Africa and the world. The governors of Kano and Borno are vital figures in global polio eradication. They should be strongly supported and encouraged to apply their unique power and influence at this critical time.

At our suggestion, the program has identified a Red List of the countries most vulnerable to a polio outbreak. In the IMB's view, when a country is placed on the Red List, all possible means must be used to get it out of this precarious position as swiftly as possible. As the ongoing outbreak in the Horn of Africa demonstrates, the program softens its focus on such countries at its peril. Decisions about the required vaccination campaigns must be based on need. To be swayed by a shortage of funds is false economy. Campaign coverage is abysmal in many of these countries. Some would let this continue, and rely on being able to respond to the inevitable outbreak. There is no place for such a defeatist mentality. It is not worthy of this ambitious global program. The number of campaigns is important, but urgent attention must also be given to improving the quality of campaigns in outbreak-vulnerable countries, and to other measures that can increase immunity or decrease the risk of importation. We are deeply worried about the present situation in Ukraine, which was very vulnerable even before the recent civil conflict, and recommend that the country be included in the program's Red List.

Since our October 2013 meeting, a new outbreak has emerged in Syria. The program has done a commendable job of responding to this outbreak, within the constraints of major conflict. There can be no place for polio in the modern world, in peace or in conflict. Protecting children from this scourge should be part of a core humanitarian response. We suggest that when humanitarian emergencies occur in countries where the reintroduction (or export) of poliovirus is possible, the GPEI seek to work with the United Nations Office for the Coordination of Humanitarian Affairs (OCHA) as a key partner, and that OCHA be asked to include polio vaccination as a priority of the health clusters established under the Humanitarian Reform system.

Lastly, the circulation of virus in Israel and West Bank and the Gaza Strip continues to concern us. It is still entirely possible that Israel may become an epicentre for outbreaks started by travellers from its country to parts of the world currently free of polio. The risks of this disastrous situation would be greatly reduced if the Israeli government conducted further vaccination rounds, to finish off the job that they started. The WHO has rightly highlighted this problem through its Global Alert and Response system (we note the posting on 20 September 2013). We are concerned that this, and similar, information may not always reach doctors and travel clinics advising those intending to travel to the affected area of the importance of pre-travel vaccination. We would recommend that the polio team in Geneva strengthen these communication channels.

Other key program considerations

We particularly convened last week's meeting to hear the program's response to our most recent recommendations. These recommendations were based on the significant concerns presented in our October 2013 report. I must commend the program's response. The IMB's recommendations have always been taken seriously, but we were particularly impressed by the comprehensive response to this most recent report.

I know that you and your Polio Oversight Board colleagues are giving serious attention to our analysis of the program's management dysfunctions, and are considering how best to commission the comprehensive management review that we recommended. The rumour mill is alive with talk that this review may be conducted by people from within the partner agencies, or by people already close to the program. To succeed, it needs an objective, external perspective, with expertise in the management of complex organisations being more important than expertise in polio or even global health. The IMB asks to review details of who will conduct the review and their brief before these decisions are finalized.

The IMB greatly welcomes your decision to convene an Emergency Committee under the International Health Regulations. Given that the 2012 World Health Assembly declared polio eradication to be a programmatic emergency for global public health, it seems vital that all possible measures to impede the virus' international spread be given serious consideration. The introduction of the controls we recommended seems long overdue.

There is confusion about whether the program has set a deadline for interrupting transmission, and what it is. The 2013-18 Strategic Plan presents a goal of end-2014. Other statements have hinted at greater flexibility, focusing on 2018 as the ultimate deadline. Given the program's history of failing to meet deadlines, we think it is vital that a common and consistent line is taken on this. Whether this is setting the goal as a fixed point in time, or as a window, or on a country-by-country basis, the important thing is clarity.

Finally, the IMB is concerned by the persistent shortfall in funds available to the program, seemingly due to significant delays in some donors following through on their pledges. We will examine this issue more fully at our next meeting.

The next full meeting of the IMB is 6-7 May 2014. I will write again after this meeting, to send you our full report. In the meantime, please allow me to reiterate the crucial importance of your leadership and to thank you, on behalf of those spared from polio paralysis, for all that you are doing.

Yours sincerely

SIR LIAM DONALDSON
CHAIR

Presentation	Supplier Name	Inactivated Polio vaccine																	
		2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014**	2015**	2016**	2017**	2018**
Inactivated Polio Vaccine (trivalent) in a single dose liquid presentation	Bilthoven Biologicals												$3.30	$3.30	$2.80	$2.80	$2.80	$2.80	
Inactivated Polio Vaccine (trivalent) in a five dose liquid presentation	Bilthoven Biologicals/Serum Institute of India														$1.90	$1.90	$1.90	$1.90	$1.50-$1.90
Inactivated Polio Vaccine (trivalent) in a ten dose liquid presentation	Sanofi Pasteur (73 GAVI supported countries)														€ 0.75	€ 0.75	€ 0.75	€ 0.75	€ 0.75
	Sanofi Pasteur (tier 1)*														€ 1.49	€ 1.49	€ 1.49	€ 1.49	€ 1.49
	Sanofi Pasteur (tier 2)*														€ 1.93	€ 1.93	€ 1.93	€ 1.93	€ 1.93
	Sanofi Pasteur (tier 3)*														€ 2.40	€ 2.40	€ 2.40	€ 2.40	€ 2.40

Data shows awarded price per dose (in US$ or EUR) per product per supplier per calendar year, based on supply agreements.
For products priced in EURO, the actual price to countries will be in US$ based on the UN exchange rate US$/EURO on the date of payment of supplier's invoice.
Prices displayed are in response to tenders with FCA incoterms.

***Pricing tiers:**
The pricing tiers offered by the supplier are based on GNI per capita as well as considering each country's overall level of development by adjusting the GNI per capita to account for inequities in wealth distribution within each country.
Tier 1 countries: Cape Verde, Egypt, Morocco, Palestine, Philippines, Samoa, Swaziland, Vanuatu
Tier 2 countries: Albania, Algeria, Fiji, Iran, Macedonia, Maldives, Namibia, Serbia, Thailand, Tonga, Tunisia, Turkmenistan
Tier 3 countries: Botswana, Gabon, Lebanon, Mauritius, Seychelles, Tuvalu
Pricing tiers applicable to other Middle Income Countries would need to be confirmed by supplier on a country-by-country basis.

**Special terms apply except for a single dose liquid presentation.

Last updated 4 March 2014

Background Paper on Varicella Vaccine

SAGE Working Group on Varicella and Herpes Zoster Vaccines

Contents

Introduction

Varicella or chickenpox is an acute, highly contagious viral disease with worldwide distribution. It is characterized by a generalized, pruritic maculopapular vesicular rash that appears in successive crops and that rapidly progresses to develop crusts and scabs [1]. Although varicella is usually a self-limited illness of childhood, it can cause significant morbidity and mortality in otherwise healthy children and adults and may assume greater relative importance in preventable disease burden as other diseases are prevented through vaccination. Morbidity and mortality are higher in immunocompetent infants and adults as well as in immunocompromised persons compared to healthy children[1]. Nonetheless, due the ubiquitous nature of varicella infection, the majority of severe disease burden occurs in healthy persons, primarily children[2, 3]. Varicella is the manifestation of the primary infection caused by the varicella-zoster virus (VZV). Following the primary infection, the virus remains latent in neural and intestinal ganglia and may reactivate years or decades later to cause herpes zoster (HZ) or shingles[4]. HZ develops primarily in healthy adults after the age of 50 and in immunocompromised persons of all ages. In its full clinical expression, HZ causes pain which is followed by a pruritic vesicular rash usually restricted to one or more dermatomes that closely overlap the segmental distribution of the nerve cells in which latent VZV resided[4]. Rash can disseminate beyond the initial dermatome in immunocompromised patients.

Varicella can be treated with antiviral drugs[5]. However, considering the minimal clinical benefit in healthy persons and the cost of the treatment, antiviral treatment is recommended for persons at high risk for severe varicella. Varicella-zoster immune globulins are effective as post-exposure prophylaxis to reduce disease severity in persons at high risk for severe varicella but they are also costly and not widely available worldwide[5]. Control of varicella can be achieved only by vaccination. A varicella vaccine based on attenuated live VZV virus (Oka strain) was developed approximately four decades ago and some countries started introducing vaccination into the childhood immunization programs after more widespread global licensure that followed licensure in the United States in 1995. Currently there are several formulations of live attenuated varicella vaccines. While these vaccines are licensed and available throughout the world they are recommended for routine use only in a small number of countries, primarily industrialized countries (i.e., Unites States, Canada, Australia, Germany, Greece, Latvia, Israel, Uruguay, Costa Rica, United Arab Emirates, Saudi Arabia, Quatar, Taiwan, various regions in Spain and Italy). Where high coverage rates have been attained, vaccination has resulted in important declines in varicella-related incidence, morbidity and mortality[6-9].

Objectives

The SAGE Working group on varicella and herpes zoster vaccines (established in May 2012) was tasked with reviewing the evidence, identifying information gaps, and guiding the work to formulate proposed

recommendations related to the use of varicella vaccine to update the 1998 varicella vaccine WHO position paper for SAGE review. This report reviews the evidence related to the main topics considered by the working group, including:

1. Varicella epidemiology: the global incidence and burden of disease caused by varicella according to country development status
2. Safety and effectiveness profile of varicella vaccine and duration of protection following immunization, including those of combination vaccines such as MMRV
3. Country experiences with introduction and use of varicella vaccines
4. Changes in the epidemiology of varicella with the introduction of the childhood varicella vaccination
    a. In population groups who received the vaccine
    b. Potential for shift in the age at infection and increase burden of varicella
5. Changes in the epidemiology of herpes zoster with the introduction of the childhood varicella vaccination
    a. In population groups who received the vaccine
    b. Potential impact of the varicella vaccination program to increase the incidence of herpes zoster
6. Evidence on the cost-effectiveness of varicella vaccination, in particular in low and low-middle income countries
7. Varicella disease and vaccination in immunocompromised individuals

Methods

To update the 1998 WHO position paper on varicella vaccine, the SAGE working group for varicella and herpes zoster vaccination considered several key issues (outlined above). To address these issues and review available data on varicella disease and varicella vaccines, the working group first met in June 2012 conducted monthly teleconferences through February 2014 and had a face-to-face meeting in June 2013. Published, peer-reviewed studies were the primary source of data used. They were identified by leading experts in the field of varicella and varicella vaccines based on their expertise and by literature search in preparation for the presentations during teleconferences. In addition, a systematic review of literature available in the electronic databases (the Cochrane Library and Pubmed) was performed by the WHO secretariat on varicella vaccine effectiveness, duration of protection and safety from the beginning of each candidate database through November, 2013. Included were studies reporting on vaccination with varicella vaccine alone, MMR and varicella, or MMRV. The electronic search was completed by a manual search examining bibliographies of relevant previous reviews and the reference lists of selected articles to identify studies not identified through the databases listed above. The summary of the reviews is included in the present document and the detailed reports are posted on the web for SAGE members. The working group discussed the quality of evidence (study design, risk of bias, results) and the results were summarized by WHO secretariat in GRADE tables. The Global Advisory Committee on Vaccine Safety reviewed the varicella vaccine safety data during a dedicated call.

Because published data are sparse on the burden of varicella disease in low and middle income countries, and especially from the African continent for which only one seroprevalence study was identified[10], WHO funded two studies to inform discussions:

- a serologic study to test specimens from one African country to gain insight on VZV serology and distribution of varicella by age groups
- a modeling study to assess the potential impact of one dose varicella vaccination on shifts in the age at infection and morbidity in low and middle income countries

Results

Pathogen and transmission

The causal agent of varicella and zoster is varicella-zoster virus (VZV), a double-stranded DNA virus belonging to the herpesvirus family[11] that naturally infects only humans. VZV is transmitted from person to person by direct contact with rash, inhalation of aerosols from vesicular fluid of skin lesions of patients with varicella or herpes zoster, or from infected respiratory tract secretions of patients with varicella that might also be aerosolized. The virus enters the host through the upper-respiratory tract or the conjunctiva. After primary infection as varicella, the virus remains dormant in the sensory-nerve ganglia and can reactivate at a later time, causing herpes zoster. The period of communicability of infected varicella patients is estimated to begin 1-2 days before the onset of rash and to end when all lesions are crusted, typically 5-6 days after rash onset in immunocompetent people, but this period may be longer in immunocompromised people[1]. Herpes zoster patients are less contagious than patients with varicella and are considered infectious while they have active lesions (usually 7–10 days). In utero infection can occur during the first two trimesters of gestation as a result of transplacental passage of virus during maternal varicella infection. Varicella infection usually confers immunity for life; second attacks of varicella are rare in immunocompetent persons but have been documented[12, 13]; subclinical reinfection is common[14].

Clinical description of varicella

The illness usually begins 14-16 days after exposure, although the incubation period can range from 10 to 21 days[1]. The incubation period may be shorter in immunocompromised patients. Subclinical varicella is rare. Before smallpox eradication, especially in adults, varicella was the most common disease confused with smallpox. Prodromal symptoms may be present, particularly in older children and adults. Fever (usually moderate, 100-102^{0}F or 37.7-38.8^{0}C) malaise, anorexia, headache, and occasionally mild abdominal pain may occur 24-48 hours before the rash appears and usually resolve within 2-4 days after the onset of the rash.

Varicella lesions often appear first on the scalp, face, or trunk[1]. The initial exanthem consists of pruritic erythematous macules that evolve through the papular stage to form clear, fluid-filled vesicles, superficially located in the dermis layer. Subsequent crusting of the lesions occurs in 24-48 hr. While the initial lesions are crusting, new crops form for about 5 to 7 days; the simultaneous presence of lesions in various stages of evolution is characteristic of varicella and distinguishes it from smallpox. The distribution of the rash is predominantly central or centripetal with the greatest concentration on the trunk and proximally on the extremities. The average number of lesions is about 300, but healthy children may have fewer than 10 to more than 1,500 lesions. In cases resulting from secondary household spread and in older healthy children and adults, more lesions usually occur. Hypopigmentation or hyperpigmentation of lesion sites persists for days to weeks in some children, but severe scarring is unusual unless the lesions were secondarily infected.

Because one dose of varicella vaccine is not 100% effective, some vaccinated persons will develop varicella. Varicella occurring in vaccinated persons more than 42 days after vaccination (also referred to as “breakthrough disease”) is always due to wild-type VZV. The clinical presentation is highly modified in the majority of patients (~70%) with mildly elevated or no fever and frequently an atypical rash with <50 lesions that are predominantly maculopapular[15, 16]. Lesions may be so few in number that they escape observation and present challenges for confirming the diagnosis. Among 2-dose vaccine recipients, disease may be even further attenuated. About 1 of every 5 children who received one dose of vaccine may experience breakthrough varicella; recipients of 2 doses of varicella vaccine are less likely to have breakthrough disease than those who received one dose[17].

Though varicella is usually self-limited in immunocompetent persons it may be associated with severe complications, mediated by either VZV or bacteria[1]. Groups at higher risk for severe complications are infants, adults, newborns and immunocompromised persons. The most common complications are secondary bacterial infections, mainly caused by group A ß-haemolytic streptococci or *Staphylococcus aureus* which affect primarily the skin and underlying soft tissue. Invasive infections (pneumonia, arthritis, osteomyelitis, necrotizing fasciitis or sepsis) can be life threatening. Pneumonia, commonly viral, is the most common complication in adults; it is

often severe, fatality was reported in 10%-50% of adults with pneumonia in the pre-antiviral era[18]. Complications of the central nervous system range from cerebellar ataxia (1 in ~4,000 cases[19]) where the prognosis is usually good to encephalitis (1 in 33,000-50,000 cases[19]) or meningoencephalitis where prognosis is less favorable. Hemorrhagic varicella with multi-organ system failure is rare in healthy children but is frequently fatal. Progressive varicella, with visceral organ involvement, coagulopathy, severe hemorrhage, and continued vesicular lesion development after seven days, is a severe complication of primary VZV infection with the highest risk in patients with congenital cellular immune deficiency disorders and those with malignancy. Rarely (about 1 case in 40,000[2]), these complications may result in death, especially among immunocompromised persons. The complication rates above were reported in studies from developed countries.

Congenital varicella syndrome occurs in 0.4%-2% children born to mothers with varicella during the first 20 weeks of gestation[20, 21]. It is characterized by cicatricial skin scarring in a zoster-like distribution, limb hypoplasia, and neurologic (e.g., microcephaly, cortical atrophy, seizures, and mental retardation), eye (e.g., chorioretinitis with scarring, microphthalmia, and cataracts), and autonomic nervous system abnormalities (neurogenic bladder, swallowing dysfunction, and aspiration pneumonia); low birth weight is common. Affected infants are developmentally retarded and their prognosis is poor. Infants whose mothers had varicella in pregnancy have a higher risk of zoster in the first years of life[22].

Varicella epidemiology

Methodological issues

Surveillance data to monitor varicella incidence and age distribution are reported predominantly from developed countries, more frequently those who have included varicella vaccination into the routine childhood immunization schedule. Even in these countries, the methods used to determine the number of cases differ, impacting completeness and ascertainment. Sources of data included household, healthcare provider and passive reporting systems. Seroprevalence data can also be used to estimate age specific incidence. Increasingly more VZV seroprevalence data are available, including from middle/lower-income countries. However, use of seroprevalence data to estimate varicella incidence is complicated by differences in the method for sample selection (nationally or regionally representative, convenience sampling) and laboratory tests which may vary in sensitivity and specificity and also may not be directly comparable over long periods of time. Methodological issues should also be considered when comparing surveillance data for severe disease outcomes. Severe disease is commonly described by hospitalization and deaths but use of these data sources can bias the comparison because of differences in access to medical care, available treatment (antiviral therapy, antibiotics), or validity of a varicella code on hospital discharge or death records from country to country.

Incidence

Varicella is a highly contagious disease that occurs worldwide and, in the absence of a vaccination program, generally affects nearly every person by mid-adulthood. Secondary attack rates are usually around 85% (range 61% and 100%)[23-25] for susceptible household contacts (all secondary attack rates were described from developed countries with temperate climate); in a community setting, where the contact is more casual, the attack rates are lower. The epidemiology of the disease differs between temperate and tropical climates[26-30]. The reasons for the differences are poorly understood and may relate to properties of VZV (known to be heat labile), climate, population density and risk of exposure (e.g., attendance at childcare or school or number of siblings in the household). Additionally, use of the varicella vaccine has changed the epidemiology of varicella in countries where the vaccine is routinely recommended.

In temperate climates the highest incidence of varicella occurs among pre-school aged children (1-4 years of age) or children in early elementary school (5-9 years of age) leading to >90% of people being infected before adolescence and <5% of adults being susceptible (fig. 1)[28]. Studies with complete ascertainment have shown that disease incidence in the total population is in the range of 13-16 cases per 1,000 persons per year, with substantial year to year variation[28, 31]. Based on seroprevalence and surveillance data, it was estimated that in developed countries with temperate climates, on average, the number of infections that occur annually

approximates the birth cohort[27, 28]. Varicella shows a strong seasonality, with peak incidence during winter and spring[26]. Periodic large outbreaks may occur with an inter-epidemic cycle of 2 to 5 years. Outbreaks occur in settings where children congregate such as childcare centers and schools but have also been described in hospitals, facilities for institutionalized children and adults, refugee camps and in adult settings including among healthcare workers, military personnel and correctional facilities.

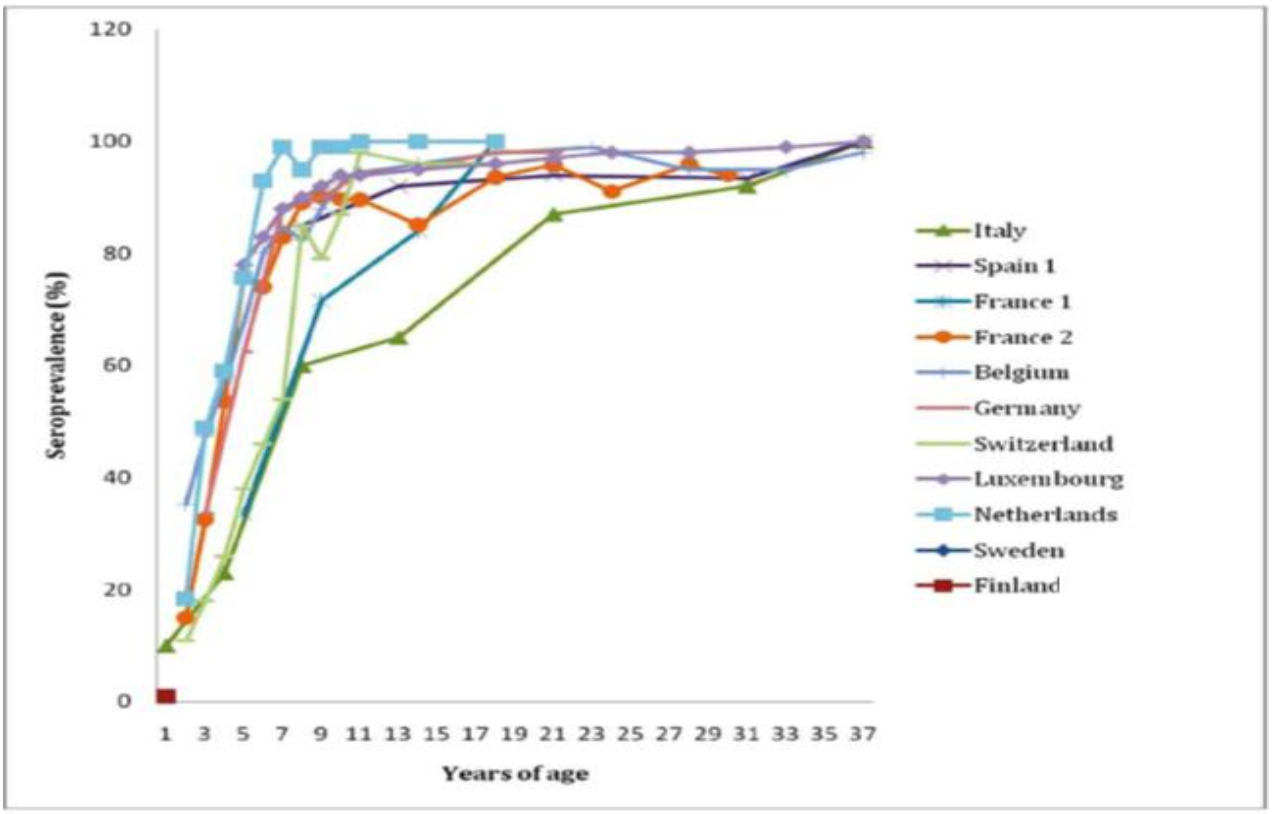


Fig. 1. Age specific incidence of VZV in European countries (from Sengupta and Brewer, Current Pediatric Reviews, 2009)

In tropical climates, the majority of studies have described later acquisition of varicella in childhood with a higher proportion of cases and higher susceptibility among adults (fig. 2)[26-30]. These features lead to a higher overall mean age at varicella infection compared with temperate climates and associated higher morbidity. A 2013 analysis of surveillance data from Sri Lanka found that in 2011 and 2012 most of the cases were reported in the 20-29 years age group (33% and 29% of all cases, respectively), with ~40% of cases occurring in persons age 30 years or older (unpublished data, Palihawadana P, personal communication, 2013). Crowding in densely populated urban cities or in household may overcome VZV's diminished ability to spread in tropical climates[29]. Population-based epidemiology data is less complete for countries in tropical climates but the highest incidence was described from a number of countries in the driest, coolest months[32, 33]. A study examining risk factors for susceptibility among newly arrived migrants in Canada found the highest varicella susceptibility among those originating from climates with the highest temperature and the most months of humidity per year (tropical rainforest)[29]. VZV seroprevalence from several tropical countries almost uniformly confirm higher adult susceptibility compared with adults in temperate countries[30, 34-38]. The lowest population seroprevalence has been reported from a single study conducted in St. Lucia, West Indies in the 1980s[39] (10%-20% among adolescents and young adults), with intermediate seroprevalence in Singapore[35] (41% among 15-24 year-olds and >86% for those age 25 years or older) and higher levels noted in large community surveys conducted during the 1990s in Thailand[37] (~70% among 10-14 year-olds and 96% for 30-39 year-olds), and Manila, Philippines[34] (57% among 10-14 year-olds and 96% for >30 year-olds). Studies in adult subgroups have demonstrated levels of seronegativity among healthcare workers ranging from 11% - 16% in Malaysia and Saudi Arabia, 22% or

higher in Thailand to as high as 51% among first year medical and engineering students in Sri Lanka[40-42]. Studies among women of child bearing age demonstrated 27% lacked VZV antibodies in Iran and 56% in Sri Lanka[36, 43]. 24% of Singapore military recruits were VZV seronegative[44]. In island populations that may not have sufficient size to support continuous endemic transmission seroprevalence can also vary with the timing of the last epidemic year in relation to the serologic study.

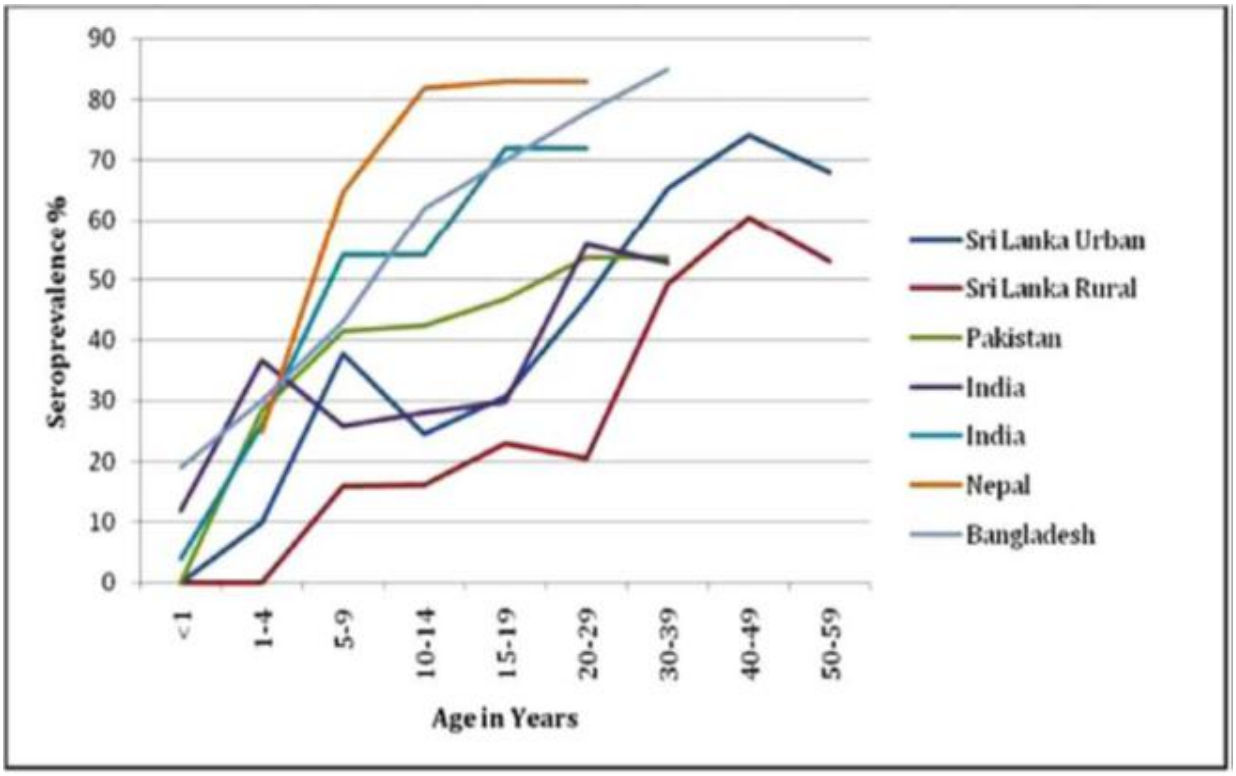


Fig. 2. Age specific incidence of VZV in different countries in the Indian subcontinent (from Sengupta and Brewer, Current Pediatric Reviews, 2009)

Severe disease burden

As presented in the Clinical description, varicella usually is a self-limited disease but can result in serious complications and sometimes death. The rates of serious complications may be described by the mortality rates but in developed countries, additionally, admission to hospital for varicella could be used as a reasonable surrogate measure for severe morbidity. However, when comparing results across countries, differences in methods that may affect ascertainment of hospitalization and cases and access to care must be considered.

Crude rates of admission to hospital with varicella in developed countries range from about 2 to 6 per 100,000 population-year[28, 31]. Most of these admissions (56%-67%) were children, which is consistent with the fact that 90% of varicella cases occur in this age group. For all ages combined, hospitalization rates have ranged from 2.2 to 4.7 per 1,000 varicella cases in studies in France, USA and UK[3, 45, 46]. In developed countries, average crude varicella mortality rates range from 0.3 to 0.5 per million population-year, and overall case fatality ratios are about 2-4 per 100,000 cases[28, 31]. Since most cases of varicella occur in healthy persons, most cases of severe morbidity and mortality also occur in healthy persons: 70% of all varicella deaths in France (1990-1997) occurred in people with no underlying high-risk medical disorders[3]; similarly, in the USA in the prevaccine era (1970-1994) 89% and 75% of varicella deaths in children and adults, respectively, occurred in otherwise healthy persons[2]. Almost 90% of persons admitted to hospital with varicella are described as healthy or immunocompetent[45, 47].

Population-based data for severe disease burden from developing countries and from those with tropical climates are sparse. A household study in Guinea-Bissau in 2000–2001, which identified 1,539 cases of varicella, reported that two cases died thus the case fatality rate in this small series was 130/100,000 cases[48]. With the caution that this is a small study and the confidence intervals are likely wide, the case fatality in this study was approximately 50 times higher than in the U.S. One study of all patients admitted to the main infectious disease hospital in Sri Lanka during 2000–2001 demonstrated that 58% of the total 1,690 hospitalizations were due to varicella[49]. Varicella was the most common disease treated at the infectious disease hospital and a significant cause of morbidity and mortality among adults. In India in late 1970s enhanced rash illness surveillance post smallpox eradication reported 433 deaths/862,155 reported cases; 80% deaths were adults[50]. The case fatality rate was 52/100,000 cases, 20 times higher than US/UK in the 1980s and 90s.

Risk factors for severe disease

Varicella is a more serious disease in infants, adults, and immunocompromised persons, in whom there are higher rates of complications and deaths than in healthy children[2, 3, 51, 52]. The risk of dying from varicella is highest at the extreme of age (fig 3); in the US, in adults the risk of death was 23-29 times higher, and in infants 4 times higher than in children in whom case fatality ratios were about 1 per 100,000[2]. Similarly, the risk of hospital admissions is higher for infants and adults than for children[3, 45]. Immunocompromised persons at high risk for severe varicella include those with deficiencies in cell mediated immunity due to illness (e.g., severe combined immunodeficiency syndrome, leukemia, lymphoma, HIV, etc.) or therapy (e.g., chemotherapy, radiotherapy, high dose of steroids). Leukemic children especially had a reported incidence of viscerally disseminated disease of 30% with a 10% fatality rate in the absence of antiviral treatment[53] and this burden of severe disease prompted vaccine development for this high risk group. Although severe varicella has occurred in children with HIV infection, the risk for death is not as great as for leukemic children[54, 55].

Data from case reports and case series suggest that varicella in pregnant women is more severe than in non-pregnant women but population-based studies are needed to confirm this finding. In utero transmission of VZV can occur. When pregnant women contract varicella early in pregnancy, experts estimate that as many as 25% of the fetuses may become infected. However, clinically apparent congenital disease in the infant occurs less commonly, the congenital varicella syndrome (that has poor prognosis) occurs in approximately 0.4%-2% of infants born to women who have varicella during the first 20 weeks of pregnancy[20, 21]. The incidence of varicella during pregnancy varies according to the susceptibility of women of childbearing age and the rate of exposure to the virus. Severe infection can also occur among newborns who lack maternal antibodies and who were transplacentally infected[56]. These newborns are at greatest risk for severe or fatal illness if the mother's rash occurs within 5 days prior to delivery to 2 days postpartum. The risk of death for these newborn is ~30% without treatment[57].

There are few data on severe varicella disease burden in low and middle income countries, in countries with high HIV seroprevalence and in countries with tropical climates where the average age at infection is higher. In these situations, varicella morbidity and mortality may be higher than described in developed countries.

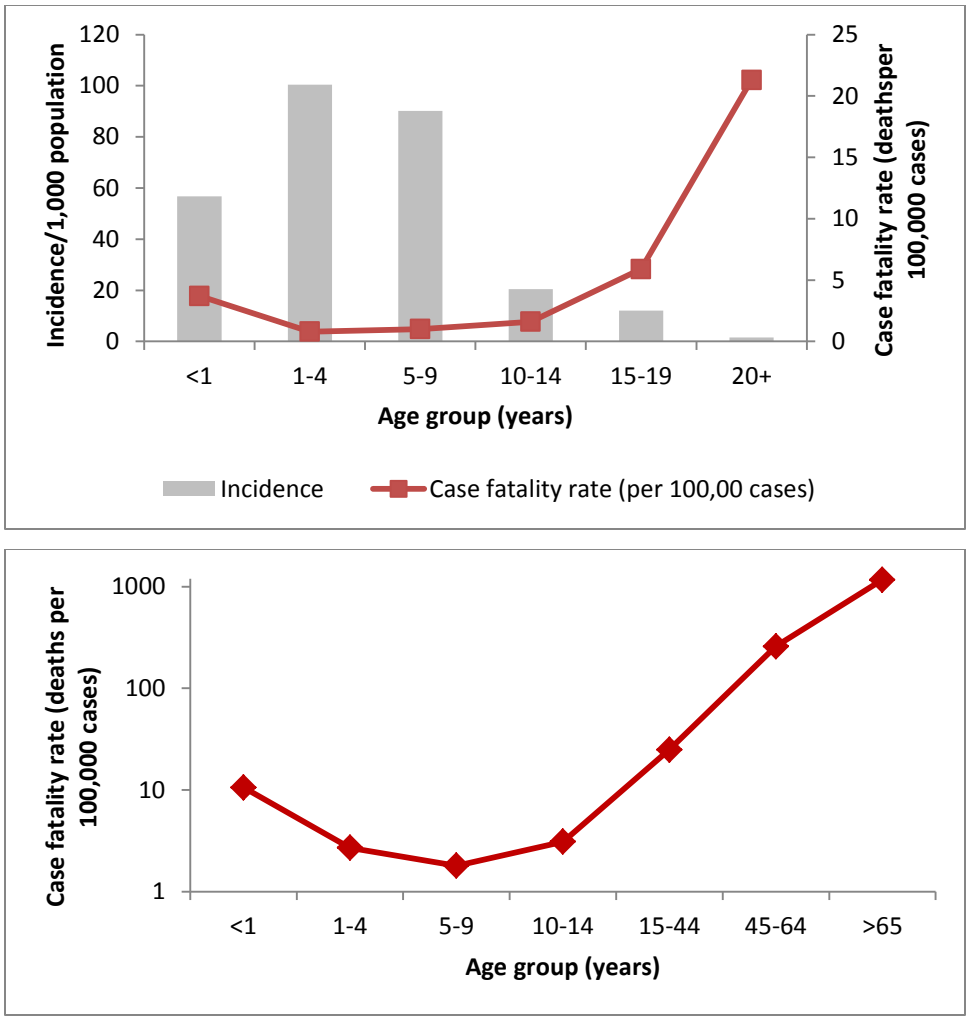


Fig. 3. Top graph: Varicella case fatality rate and incidence by age group, United States, 1990-1994 (pre-vaccine) (ref: Meyer et al, JID, 2000). Bottom graph: Varicella case fatality rate by age group, Brazil, 2001-2003 (logarithmic scale) (ref: Valentim et al, Vaccine 2008)

Epidemiology of varicella in the vaccine era

Countries that introduced varicella vaccination have experienced substantial reductions in varicella morbidity and mortality (figs. 4-6). In the United States, where a one dose childhood vaccination program was introduced in 1995, overall disease incidence declined > 70% within 5 years in communities where vaccine coverage among children age 19 to 35 months had reached ~ 80%[58]. Declines in incidence were apparent earlier in preschool aged children. By 2005, when vaccine coverage had reached approximately 90%, varicella incidence declined 90% or more[6]. The greatest declines (>90%) occurred in children aged 1 to 9 years but declines occurred in every age groups including infants (80%) not eligible for vaccination and adults (60%-80%) indicating considerable community protection effects (also referred to as herd immunity) outside of age groups targeted for vaccination. The peak age of varicella infection increased from 3-6 years in 1995, to 9-11 years in 2005 and the proportion of cases that were vaccinated increased from < 1% to 60% over the same time period but varicella incidence declined in all age groups. From 1995 to 2005, the declines in incidence were mirrored by declines in the number, size and duration of varicella outbreaks in childcare centers and schools[59]. In Veneto region, Italy, varicella incidence rates decreased significantly 2.5 years after the universal vaccination program was introduced and >70% vaccine coverage reached[60]. In Germany, where a one dose national vaccination program

was implemented in 2004, comparing varicella seasons in 2005 and 2009, a 63% decline in cases and 81% decline in varicella complications was observed using data from physician based sentinel surveillance[8].

Significant declines in varicella-related deaths, hospitalizations, ambulatory visits and health expenditures were also noted within 5-6 years of program implementation in the United States. Considering varicella as the underlying cause of death, pre-vaccine era deaths averaged 105/year. By 1999–2001, compared with the 5 years preceding the vaccination program (1990–1994), mortality rates declined 92% in children 1–4 years, and 74%–89% in infants < 1 year and persons 5 to 49 years[61]. By 2005-2007, which primarily reflected impact of the decade long one dose vaccination program in children, deaths averaged 15/year and the average age-adjusted mortality rate due to varicella as an underlying cause of death declined 88% to 0.05 per million population-year from 0.41 per million in 1990-1994[9]; during the same period, the age-specific mortality rates declined 97% among children and adolescents aged <20 years, 90% among adults aged 20-49 years, and 67% among adults aged ≥50 years (an age group in whom the validity of varicella as a cause of death on death certificates is lower). Varicella hospitalizations have declined significantly as well. By 2002, compared with 1994–1995, US hospitalizations for varicella declined by 88% and ambulatory visits by 59%, with > 90% declines in children < 10 years and adolescents 10–19 years old[62]. Direct medical expenditures for varicella hospitalizations and ambulatory visits decreased by 74%[62]. Updated analyses showed continued declines in varicella hospitalizations in all age groups from 2000 to 2006, with a 98% reduction in varicella hospitalizations by 2006, among patients 0-4 years old[63].

In Canada, where the varicella vaccination program was recommended in 1999, declines of 81%-88% in the number of hospitalized varicella cases were reported between 2000-2008, with effects of the vaccination program being noted beginning 1 to 2 years after the start of the program; indirect protection of persons outside the vaccinated cohorts was also documented[7]. Vaccination coverage were available for a few provinces and ranged from 74%-91% in 2007-2008. The impact of a one dose vaccination program on varicella and its severe morbidity has also been described from Taiwan, Uruguay, Sicily and Australia[64-67]. Additionally, several studies indicated the indirect protection afforded by vaccination, with declines in populations that are not directly targeted to receive the varicella vaccine (e.g., decline in incidence, hospitalization and deaths in infants and adults in the US mentioned above). Similarly, a study in Australia described 100% and >85% decline in congenital varicella syndrome and neonatal varicella following introduction of universal varicella vaccination[68].

A one dose program led to considerable successes in control of varicella disease and its severe complications. However, as experience demonstrated, cases and varicella outbreaks (although less in number, smaller in size, and of shorter duration) might continue to occur in highly vaccinated one dose populations[6, 59]. This, coupled with the evidence that two doses induce higher effectiveness[17], resulted in adoption of a routine 2 dose policy for children in the United States in 2006. During the first 5 years after introduction of the two dose program the reported varicella incidence was the lowest since the start of the vaccine program (with decline ~70% during the two dose program), with fewer outbreaks and milder disease[69].

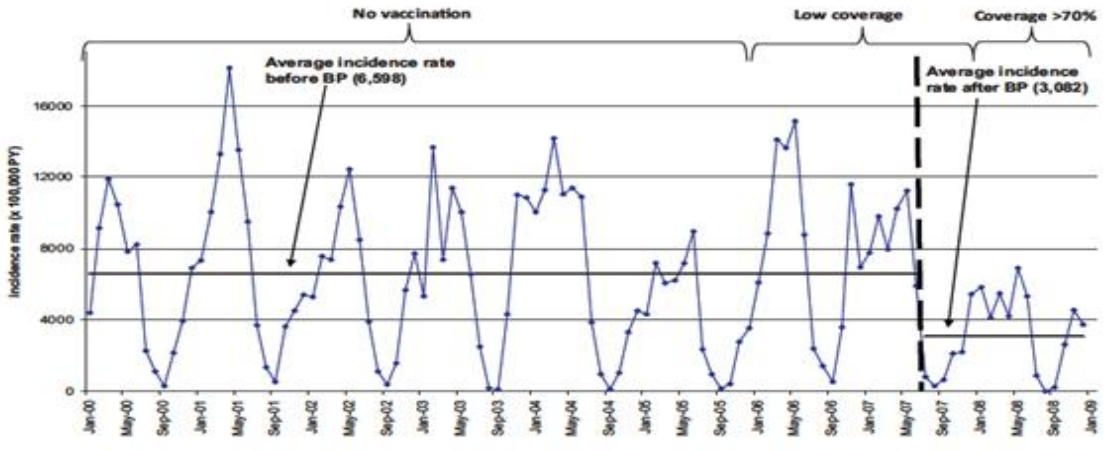


Fig. 4. Monthly incidence rates of varicella and change in the temporal trend in Veneto region, Italy; data from the sentinel surveillance based on a sample of pediatricians, 2000-2008 (from Pozza et al, Vaccine 2011)

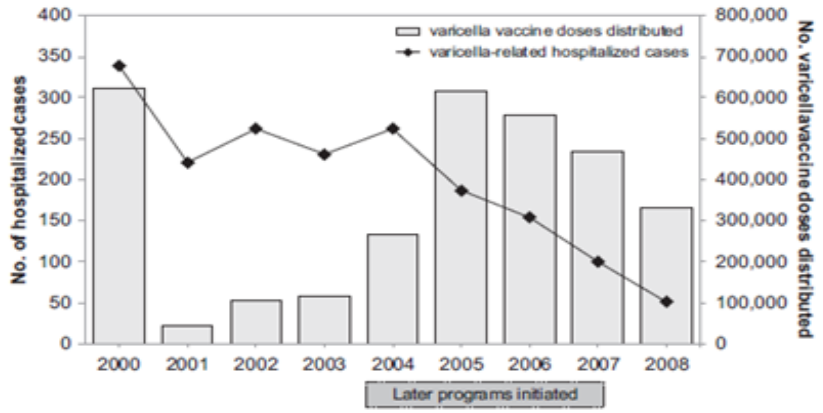


Fig. 5. Trend in varicella related-hospitalized cases, 8 Canadian provinces/territories (comprising 86% of the Canadian population), 2000-2008 (from Tan et al PIDJ, 2012). The bars show the combined number of vaccine doses (Varivax and Varilrix) distributed each year in these 8 settings.

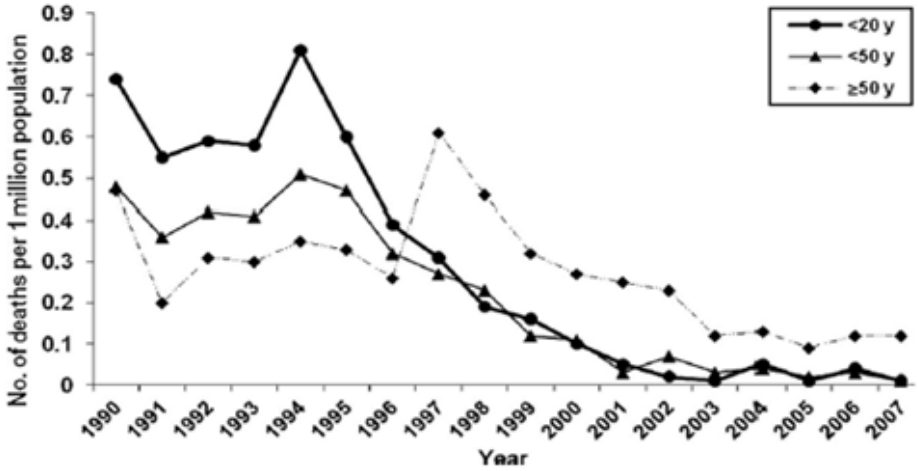


Fig. 6. Annual age-specific mortality rates for varicella listed as the underlying cause of death, United States, 1990-2007 (from Marin et al, Pediatrics, 2011)

Varicella vaccines

All available varicella vaccines are live attenuated vaccines and all but one formulation are based on the Oka strain of VZV isolated in Japan by Takahashi[11]. The vaccine licensed in Korea was developed from a different isolate (Korean)[70]. Currently, varicella vaccine is licensed as monovalent vaccine or combination measles, mumps, rubella varicella vaccine (MMRV). The monovalent varicella vaccine was first licensed in Japan in 1987, while the combination MMRV vaccine was first licensed in the US in 2005. Monovalent vaccine is produced in the United States (VARIVAX; Merck & Co., Inc), Belgium (Varilrix; GlaxoSmithKline [GSK]) Japan (OKAVAX; Biken, distributed by Sanofi Pasteur), South Korea (Green Cross), and China (4 manufacturers: Shanghai Institute of Biologic Products, Changchun Keygen Biological Products Co., Ltd., Changchun BCHT Biotechnology Co, [Baike], Changchun Changsheng Life Sciences Ltd.). MMRV is produced in the United States (ProQuad; Merck & Co., Inc) and Belgium (Priorix-tetra; GSK). The vaccine is marketed in a lyophilized form to improve stability. Varicella vaccine is stored at refrigerator temperatures (2^0C-8^0C or 36^0F-46^0F) or at freezer temperature (<-15^0C or <5^0F), according to the manufacturer's instructions. Monovalent varicella vaccines are licensed and available throughout the world for the prevention of varicella in healthy children, adolescents and adults. Combination MMRV vaccines which are licensed for prevention of varicella in children through 12 years of age are available in fewer countries. The minimum age for both types is either 9 or 12 months, depending on the manufacturer.

Varicella vaccines are contraindicated if there is a history of anaphylactic reaction to any component of the vaccine (including neomycin), during pregnancy (due to theoretical risk to the fetus) and in primary or acquired immunodeficiency states[71-74]. Pregnancy should also be avoided for 4 weeks following vaccination. Two vaccines allow use in immunocompromised patients in certain conditions: Okavax (Sanofi Pasteur) is licensed for use in leukemic patients who meet certain criteria (e.g. lymphocyte count, suspension of chemotherapy, etc.) and for one of the vaccines used in China, use is cautioned in leukemic and immunodeficient patients. However, vaccine may be recommended by certain vaccine advisory groups for specific groups of immunocompromised patients (e.g., the US Advisory Committee on Immunization Practices recommends vaccination for persons with impaired humoral immunity, HIV-infected children with CD4+ T-lymphocyte percentage ≥15%, or patients with leukemia, lymphoma, or other malignancies whose disease is in remission and whose chemotherapy has been terminated for at least 3 months[75]).

An estimated annual average number of 31 million varicella vaccine doses were distributed worldwide between 2007 and 2011, with approximately half of the doses in the WHO region of the Americas. From data that the working group could obtain, the price of the monovalent vaccine per dose ranges from $13 (Pan American Health Organization revolving fund) to $94 (United States). MMRV price is ~$148-$157 per dose.

Measure of vaccine protection

The Working Group focused its evaluation of varicella vaccine performance on effectiveness data that assess the performance of the licensed formulation vaccines in conditions of everyday clinical practice. Several factors were considered for this decision: 1) pre-licensure and post-licensure studies of immunogenicity and efficacy of varicella vaccine used varying concentrations of the Oka strain therefore comparisons across studies and inference of results to licensed vaccine formulations are difficult; 2) different serological tests have been used to assess immunogenicity including neutralization, FAMA, gpELISA and other IFA tests; 3) cutoff levels to define seroconversion with the gpELISA test have varied with initial studies using >0.6 gpElisa units/ml and more recent studies using a higher cutoff level or serologic response rate of ≥5 units/mL; 4) vaccine performance may be different under conditions of real world use; and 5) immune correlates of protection against varicella have been studied but need further clarification and development. A gpELISA titer of ≥5 units/mL or greater 6 weeks after vaccination is reported to be an 'approximate correlate of protection for individual vaccine recipients' but this cutoff was used in latter studies only; a positive FAMA titer (>1:4) at the time of exposure to the virus correlates with protection but few studies used FAMA to determine seroconversion. Nonetheless, prelicensure clinical trial data were reviewed and are presented briefly below. Immunogenicity data were reviewed and considered when effectiveness data were not available.

Pre-licensure vaccine efficacy

Three double-blind, placebo-controlled one dose efficacy studies have been carried out in healthy children. The first was conducted in the US in the early 1980s using Merck's vaccine among VZV seronegative children age 12 months to 14 years (mean age 4.7 years); 468 children were immunized and 446 were given placebo[76]. After 9 months of follow up, the vaccine was found to be 100% efficacious; after 2 years, efficacy was 98% overall and 92% after household exposure. During a 7-year follow-up, 95% of these vaccine recipients were estimated to have remained free of varicella[77]. These data cannot be directly compared with those of subsequent studies in the US, however, because these children received the highest dose of vaccine used in the US as a monovalent vaccine (17,430 plaque forming units (PFU) vs. a minimum of 1,350 PFU in the licensed vaccine).

A second double blind placebo controlled study was performed in Finland in the early 1990s, using vaccine produced by SmithKline Beecham (now GSK)[78]. This study included 513 healthy seronegative children ages 10 to 30 months who were divided into three groups to receive a high dose vaccine (10,000 or 15,850 PFU), a low dose vaccine (630 or 1,260 PFU) and placebo. After an average 29 months of follow up the efficacy was 88% for the high dose vaccine and 55% for the low dose vaccine.

The third double blind placebo controlled study was conducted more recently in China using the vaccine (10,000 PFU) manufactured by Changchun Keygen Biological Products Co., Ltd[79]. This study included 5,000 children aged 3-7 years with no history of varicella or varicella vaccine. Mumps vaccine was the placebo; the follow-up period was 12 months and vaccine efficacy was 90.8% (95% CI 88.7%-95%).

For the two dose vaccine efficacy, a 10 year follow up (1993-2003) of 2,216 healthy children aged 1 to 12 years (with a negative history of varicella) randomized to receive 1 or 2 doses of varicella vaccine (five different lots of vaccine ranging from 2,900 to 9,000 PFUs) 3 months apart yielded an estimated vaccine efficacy of 2 dose and 1 dose of varicella vaccine of 98.3% versus 94.4% ($P < 0.001$)[17]. Following household exposures, efficacy was 96.4% for 2 doses and 90.2% for one dose ($P = 0.112$).

Formal studies to evaluate clinical efficacy of MMRV vaccine have not been performed. MMRV vaccines were licensed on the basis of non-inferior immunogenicity of the antigenic components compared with simultaneous administration of MMR and varicella vaccines[72, 74]. Anti-varicella antibodies were tested using gpELisa (Merck vaccine) and indirect immune fluorescence assay (GSK vaccine).

Post-licensure vaccine effectiveness

To assess vaccine effectiveness (VE), 40 studies were identified by systematically searching the literature[80-119]. In addition, a meta-analysis[120] and a systematic review for VARIVAX[121] were identified. A variety of methods have been used to study the postlicensure effectiveness of varicella vaccine, including prospective and retrospective cohort, case-control, and secondary attack rate (household contact) studies. The populations studied have included children in different settings, such as child care centers and schools, clinical practices in the community, managed care organizations, and households. Most studies assessed protection against clinically diagnosed varicella. The definitions used for the severity of varicella differed between studies (table 1).

One dose vaccine effectiveness

For one dose VE, most of the estimates were for VARIVAX (Merck), fewer for Varilrix (GSK), and one each for the other vaccines; several studies either did not specify the vaccine or more than one type of vaccine was used in the country. Table 1 presents the summary finding of the review of the post licensure VE estimates for one dose for monovalent varicella vaccine by disease severity. Available evidence on vaccine effectiveness is for within the first decade after vaccination.

Table 1. One dose varicella vaccine effectiveness estimates by type of vaccine and varicella severity (monovalent vaccine)

Vaccine	Prevention of all varicella			Prevention of combined moderate and severe varicella[a]			Prevention of severe varicella		
	No. estimates	Median	Mean/ range	No. estimates	Median	Mean/ Range	No. estimates	Median	Mean/ Range
Varivax	28	83%	81% (44%-100%)	18	96.5%	96% (86%-100%)	11	100%	99% (97%-100%)
Varilrix	8	76%	70% (20%-92%)	5	95.0%	93% (80[b]%-100%)	3	100%	100%
Okavax	1	90%	90%	1	100%	100%	1	100%	100%
Shanghai	1	93%	93%	-			-		
Keygen/ Changchun	1	77%	77%						
Changsheng	2	80%	80%	-			-		
Baike	1	91%	91%	-			-		
Unspecified/ >1 vaccine used	10	80%	79% (60%-100%)	3	99.5%	96% (86%-100%)	3	100%	95% (85%-100%)

Note: 1) Data presented in the table are from 40 papers. However, the number of vaccine effectiveness estimates does not total 40 for several reasons: several papers presented more than one vaccine effectiveness estimate for the same outcome (e.g., investigation in 2 schools and estimates against all varicella presented separately by school); in the same paper vaccine effectiveness estimates are presented for more than one outcome (e.g., for prevention of all varicella, for prevention of moderate and severe varicella, or prevention of severe varicella)

2) Available evidence is on vaccine effectiveness within the first decade after vaccination

3) Two of the vaccine effectiveness estimates reported were below 50% (i.e., 20% and 44%). They were calculated during investigations of outbreaks that tend to underestimate the performance vaccines. While there are no definitive explanations for the low effectiveness, it is possible that vaccine effectiveness lies within a range and by chance a lower value could be identified. This emphasizes that to accurately assess vaccine effectiveness more than a few estimates are needed.

[a]Moderate: 50-500 lesions, no complications; Severe: 1) >500 lesions or a complication requiring physician visit, or any complication; 2) any hospitalization regardless of the number of lesions; 3) two studies defined severe disease as >250 and >200 lesions; 4) disease severity scale used in clinical trials: # lesions, fever, systemic signs and subjective assessment of illness

[b]80% is for prevention of moderate disease only

Only one study compared directly the effectiveness of one dose of VARIVAX and Varilrix and found lower effectiveness for Varilrix (49% vs. 83%) but the overlapping confidence intervals suggest that the values were not significantly different[110]. The same study provided the only estimate on VE for one dose of MMRV (62%) which was on the lower end of the range reported for monovalent vaccines but with wide confidence intervals that overlapped those of the monovalent vaccines. In summary, available data to date support similar performance of the various one dose monovalent varicella vaccines in preventing varicella. One dose varicella vaccine is moderately effective (~80%) for preventing all varicella and highly effective (>95%) for preventing moderate and severe varicella. The moderate effectiveness in prevention of all varicella supports the immunogenicity findings from the United States that primary vaccine failure occurs in 9%-14% of children after one dose of vaccine[17, 122]. A small study found that 24% of infants lacked VZV antibody measured by FAMA a median of 4 months after vaccination[123].

A number of potential risk factors for vaccine failure after one dose have been studied, including younger age at vaccination, time since vaccination, asthma, eczema, receipt of varicella vaccine within 28 days of MMR and problems with storage and handling[121]. Most studied were age at vaccination (variously defined as <14 months to ≤18 months) and time since vaccination (using a cut-off of 3 years or 5 years). The results did not show consistent findings but the sample sizes were usually not sufficient to assess the independent effect of each factor. Among studies that controlled for other risk factors, Chaves et al used cases clinically diagnosed and found that the risk and severity of breakthrough disease increased with time since vaccination[124] while Vazquez et al used laboratory confirmed cases and described a decline in vaccine effectiveness between years 1 and 2 after vaccination but not subsequently (up to 7 years of follow up)[117]; Verstraeten et al used a large retrospective cohort and found that children vaccinated at <15 months of age have a slightly higher risk for breakthrough disease[125] while Vazquez et al found that vaccination at age <15 months was associated with a higher risk for breakthrough within the first year after vaccination[117]. An increased risk for breakthrough disease was also found during the 3 months after prescription of an oral steroid and when varicella vaccine was administered within 28 days of MMR vaccination[125].

One-dose varicella vaccine administered within 3-5 days of exposure is highly effective for prevention of moderate or severe disease (79%-100%) but estimates varied for prevention of any disease (9%-93%)[126-129].

Two dose vaccine effectiveness

Fewer studies (5 with 6 estimates) assessed vaccine effectiveness after two doses of monovalent varicella vaccine in children, all for Varivax (table 2)[84, 90, 102, 108, 112]. Overall (mean =93%, median=95%) 2 doses of vaccine provided better protection than one dose, however, two of the estimates, both from outbreak investigations, were <90%. Additionally, one study reported 94% vaccine effectiveness of two doses of any varicella-containing vaccine used in the country (Varilrix, Varivax, or MMRV/GSK)[99] and one reported 93% vaccine effectiveness for two-doses of MMRV (GSK)[110]. Considering the vaccine effectiveness estimates, the immunologic findings of an improved humoral and cell mediated immune response after the second dose and the observed further decline in the incidence of varicella in the US following implementation of the 2nd dose recommendation for children[69, 130], 2 doses of varicella in children improve the performance of varicella vaccine for prevention of all varicella.

Table 2. Two dose varicella vaccine effectiveness (monovalent vaccine[a])

Author	Country	Prevention of all varicella	Setting/Design
Gould[90]	USA	88.1% (95% CI=82.2%-92.1%)	School outbreak retro/prospective cohort
Nguyen[112]	USA	95%[b]	School outbreak retro/prospective cohort
Shapiro[108]	USA	98.3% (95% CI=83.5%-100%)	Case-control study
Mahamud[102]	USA	84.2%[c] (95% CI=74.2%-90.3%); 94.7%[c] (95% CI=89.2%-97.4%)	School outbreaks retro/prospective cohort
Cenoz[84]	Spain	97% (95% CI=80%-100%)	Case-control study

[a] All estimates are for Varivax
[b] Not presented in the article but calculated based on the raw data presented in the article
[c] The investigation took place in two schools and the authors reported vaccine effectiveness by school
Data are for within the first 5 years after the second dose

Estimates of vaccine efficacy or effectiveness for persons 13 years or older are lacking. However, using data reported during open trials (i.e., without a control group) on attack rates among adult vaccine recipients of two doses administered 4-8 weeks apart (17%[71] and 26%[11]) and an 85% historical attack rate for wild-type varicella following household exposure to varicella among unvaccinated children, the efficacy can be estimated in the range of 70%-80%. Most adults who developed varicella after vaccination experienced a mild form. These efficacy estimates are backed by immunogenicity data that also support the need for 2 doses routinely in this age group. In prelicensure clinical trials in the United States using VARIVAX it was noted that the seroconversion measured by gpELISA in adolescents aged 13-17 years was only 79% after one dose; moreover, their GMT was half the levels seen in healthy children[131]. Likewise, immunogenicity studies in adults have indicated that adults require two doses of vaccine to achieve a seroconversion rate by gpELISA of >90%[132]. A study in Australia where 2 doses of Varilrix were administered to susceptible health care workers, found that 95% of subjects had detectable antibodies using a commercial immunoassay 2 months after the first dose and 100% of vaccines had antibodies 6 weeks after the second dose[133]. Additionally, the cell-mediated immune responses of adults to varicella vaccine are lower than those observed in children[134].

The quality of evidence was graded for following research questions:

- What is the scientific evidence of the effectiveness of one dose varicella vaccination in immunocompetent children (9 months to 12 years of age) in preventing all grades of severity of varicella (evidence available for the first 10 years after vaccination) (GRADE table 1)
- What is the scientific evidence of one dose varicella vaccination in immunocompetent children (9 months to 12 years of age) in preventing severe varicella (evidence available for the first 10 years after vaccination) (GRADE table 2)
- What is the scientific evidence of the effectiveness of two doses of varicella vaccination (versus placebo/no vaccination) against all grades of severity of varicella disease in immunocompetent individuals (evidence available for the first 5 years after the second dose) (GRADE table 3)

GRADE Table 1. Effectiveness of one dose varicella vaccination in immunocompetent children (9 months to 12 years of age) in preventing all grades of severity of varicella (evidence available for within the first 10 years after vaccination)

Population : Immunocompetent children (9 month to 12 years of age)
Intervention: One-dose varicella vaccination
Comparison: Placebo/ No vaccination
Outcome : All grades of severity of varicella disease

What is the scientific evidence of the effectiveness of one dose of varicella vaccination (versus placebo/no vaccination) in preventing all grades of severity of varicella in immunocompetent children (9 months to 12 years of age)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		40/ Observational[1]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect[2]	Applicable	+2
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**We are very confident that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**A single dose of varicella vaccination is effective to protect children of 9 months to 12 years against all grades of severity of varicella disease. Single dose varicella VE against all grades of disease severity ranged from 20 – 100%, with an approximate mean VE of 80% against all grades of disease severity, irrespective of vaccine type.**

[1] Two systematic reviews (Seward et al.; Bayer et al.) and a syst. rev. done by WHO of the current literature (through October 2013) identified 40 observational studies. Single dose varicella VE against all grades of disease severity ranged from 20 – 100%, with an approximate mean VE of 80% against all grades of disease severity, irrespective of vaccine type. Only one study demonstrated vaccine effectiveness against all varicella to be 20% (95%CI 0%-40%).
[2] Upgraded by two levels as strong evidence from observational studies of a vaccine effectiveness of 80% or higher with no major residual confounders. In addition to effectiveness on an individual level, decline in incidence in all age groups over time, not only age-group targeted by vaccination program, suggests induction of community protection (Marin et al 2008, Marin et al 2011, Lopez et al 2011, Guris et al 2008).

GRADE Table 2. Effectiveness of one dose varicella vaccination in immunocompetent children (9 months to 12 years of age) in preventing severe varicella (evidence available for within the first 10 years after vaccination)

Population: Immunocompetent children (9 month to 12 years of age)
Intervention: One dose varicella vaccination
Comparison: Placebo
Outcome: Severe varicella (mostly defined as >500 lesions, complication requiring physician visit, hospitalization, death); two studies defined severe disease as >250 and >200 lesions and two defined severity in accordance with a modified disease severity score from clinical trials

What is the scientific evidence of the effectiveness of one dose of varicella vaccination (versus placebo/no vaccination) in preventing severe varicella disease (≥500 lesions) in immunocompetent children (9 month to 12 years of age)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		29/ Observational[3]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[4]	+2
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**We are very confident that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**A single dose of varicella vaccination is highly effective to protect children of 9 months to 12 years against severe varicella disease, with vaccine effectiveness (VE) of 95% for preventing moderate-severe disease and VE of 99% for preventing severe disease only.**

[3] Two systematic reviews (Seward et al. 2008; Bayer et al. 2007) and a syst. rev. done by WHO on the current literature (through October 2013) identified 25 relevant observational studies. Included studies provided vaccine effectiveness data on the predefined outcome of severe varicella or on moderate-severe varicella. Studies that did not specifically report a VE value reported that no cases of hospitalization or severe complications were observed. Single dose varicella VE against moderate and severe disease ranged from 78 – 100%, with an approximate mean VE of 95%, irrespective of vaccine type. Of the sixteen studies reporting a VE value against severe varicella, fifteen reported a VE of 100% and only one study (Huang, 2011) reported a VE of 85%.

[4] Upgraded by two levels as strong evidence from observational studies of a vaccine effectiveness of 80% or higher with no major residual confounders. Vaccine effectiveness against severe varicella was 100% in 15/16 studies. In addition to effectiveness on an individual level, decline in incidence in all age groups over time, not only age-group targeted by vaccination program, suggests induction of community protection (Marin et al 2008, Marin et al 2011, Lopez et al 2011, Guris et al 2008).

GRADE Table 3. Effectiveness of two doses of varicella vaccination in immunocompetent individuals in preventing all grades of severity of varicella (evidence available for within the first 5 years after the second dose)

Population : Immunocompetent individuals
Intervention: Two doses varicella vaccination
Comparison: Placebo/ No vaccination
Outcome : All grades of severity of varicella disease

What is the scientific evidence of the effectiveness of two doses of varicella vaccination (versus placebo/no vaccination) against all grades of severity of varicella disease in immunocompetent individuals?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		7/observational[5]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[6]	+2
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**We are very confident that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**Two doses of varicella vaccination are effective to protect against all grades of severity of varicella disease. Two-dose varicella VE against all grades of disease severity ranged from 84 – 98%, with an approximate mean VE of 93%, irrespective of vaccine type.**

[5] Vaccine effectiveness of 2 doses of varicella vaccination was assessed in 7 observational studies identified by systematic review of the evidence with seven studies providing nine VE estimates of combined and non-combined varicella vaccine against all grades of disease severity. Cenoz et al. assessed VE against all varicella to be 97%. Gould et al as 88%, Liese et al as 94.3% (95%CI: 76.4 – 98.6%). Mahamud et al. estimated VE in two different settings as 95% and 84% respectively. Shapiro et al assess 98% VE. Spackova et al. provided two VE estimates for different types of vaccines as 93% (95%CI: 71 – 98%) and 95% (95%CI: 79 – 99%) against all grades of disease severity. Nguyen, 2010 estimated VE of two doses to be 95%.

[6] Quality rating was upgraded by two levels for strong evidence from observational studies of VE of 80% or higher

Duration of vaccine protection

Persistence of antibody in children after one dose of varicella vaccine was demonstrated in several studies[17, 135-137]. However, most studies were done while wild type VZV was still circulating in the community and could have provided external boosting.

Some epidemiologic evidence suggests waning of vaccine-induced immunity after one dose of vaccine while others do not. One large study which examined 10 years of active surveillance data (1995-2004) from a sentinel population of 350,000 subjects in California suggested that breakthrough varicella was twice as likely to be moderate/severe (defined as >50 skin lesions) in children who developed varicella more than 5 years after vaccination compared with those who became ill less <5 years after vaccination (Odds Ratio=2.6, 95%CI: 1.2-5.8)[124]. This study also found an increase incidence of breakthrough varicella with time since vaccination after controlling for likelihood of exposure and age although the rate of breakthrough disease was still low. A metaanalysis concluded waning immunity (based on 4 studies which all showed a decrease in vaccine effectiveness with time since vaccination) but changing varicella epidemiology and risk of exposure/force of infection were not considered[120]. Two recent studies reported lower effectiveness >3 years after vaccination compared with the first post-vaccination year[84, 99]. In contrast, a case control study in which cases were laboratory confirmed, found that vaccine effectiveness against all varicella decreased from 97% in the first year after vaccination to 85% in the second year post-vaccination but with no further drop during the subsequent 6 years of follow up[117]. An analysis evaluating vaccine effectiveness of one and two doses found one dose vaccine effectiveness 86% after a mean 8.5 years since dose one[108]. In the two dose clinical trial study over a 10 year follow up neither the incidence nor the severity of breakthrough disease increased over time[17]. Notably, no severe cases (≥300 lesions) of varicella were reported among breakthrough cases in this study in either one or two dose vaccine recipients. A second long term follow up study of a cohort of >7,300 vaccinated children reported a decline in the annual rates of varicella over 14 years[138]. This study reported occurrence of severe breakthrough varicella (defined as >300 lesions) in 2% of all breakthrough cases but no increase in severity of breakthrough over time. When interpreting the results of these last two studies consideration should be given to the fact that they did not adjust for likelihood of exposure or force of infection which declined over time.

In summary, duration of protection after one dose is not fully understood or studied, especially in a setting of low varicella incidence. The relative roles of waning immunity after an initial response and of a primary immunologic failure rate of 9%-14% (possibly 24% according to one study)[17, 122, 123] in the inability of a one dose of vaccine to provide complete protection is not known and there is still debate about whether breakthrough is primarily due to primary failure, waning of protection, or both. To date, there is no evidence of increased severe outcomes (death or hospitalization rates) at population level with time since vaccination[9, 63].

A routine two-dose schedule among children was only recently recommended in some countries therefore data on duration of protection of the two dose regimen are limited. In the clinical trial in the US comparing one and two doses VARIVAX, over 10 years, the efficacy of two doses in prevention all varicella was 98.3% after community exposure and 96.4% after household exposure (higher than after one dose)[17]. In this study, in years 7 to 10 after vaccination no breakthrough cases occurred in recipients of two doses while cases continued to occur in recipients of one dose. The two dose regimen also was 100% effective against severe disease. In a clinical trial of two doses of MMRV (Priorix-tetra) versus separate injections of MMR (Priorix) and varicella (Varilrix) vaccines, immunogenicity of the varicella component was sustained 3 years post-vaccination (>97% subjects in each arm had antibodies measured by immunofluorescence); no severe varicella cases (≥150 lesions) after one or two- doses varicella vaccination were reported[139]. A postlicensure study reported two dose vaccine effectiveness of 98.3% a median of 12 months (range 0-50 months) after receipt of the second dose with no varicella cases occurring among two dose recipients[108].

Data available for adults who received two doses of varicella vaccine show that 25%-31% of adult vaccine recipients who seroconverted after VARIVAX lost detectable antibodies (by FAMA) at multiple intervals (range: 1-11years) after vaccination[140, 141]; ~10% developed mild varicella after exposure (21% after household exposure)

however, severity of illness or attack rates did not increase over time[142]. A follow up of health care workers who received 2 doses of GSK varicella vaccine showed that 4% who had sera tested 12 months after the 2nd dose had lost detectable antibody[133].

The quality of evidence was graded for following research question:

- In immunocompetent individuals, is protection against severe varicella reduced ≥5 years after one dose of varicella vaccine compared to <5 years after vaccination? (GRADE table 4)
- In immunocompetent children (9 months to 12 years of age), what is the evidence for duration of protection against severe varicella with a two-dose versus a one-dose schedule? (GRADE table 5)

GRADE Table 4. Duration of protection of one dose varicella vaccination against severe varicella in regard to time since vaccination in immunocompetent individuals

Population: Immunocompetent individuals who have received one dose of varicella vaccine
Intervention: One dose varicella vaccination < 5 years
Comparison: One dose varicella vaccination ≥ 5 years
Outcome: Severe varicella (>300 lesions (or >500 lesions), complication requiring physician visit, hospitalization, death)

In immunocompetent individuals is protection against severe varicella reduced ≥5 years after one dose of varicella vaccine compared to <5 years after vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3/ observational[7]	2
	Factors decreasing Confidence	Limitation in study design	None serious	0
		Inconsistency	Serious[8]	-1
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			**We have very little confidence in the estimate of the effect on the health outcome**
	Conclusion			**In two large studies with more than 11 000 children, no higher annual rate of severe breakthrough cases was seen ≥5 years after vaccination than <5 years after vaccination. One large study which examined 10 years of active surveillance data (1995 to 2004) from a sentinel population of 350,000 subjects suggests the number of moderate to severe breakthrough cases is significantly higher ≥5 years after vaccination, than <5 years after vaccination.**

7 Observational study (Kuter et al. 2004), active surveillance (Chaves et al. 2007) and prospective cohort study (Baxter et al. 2013) and case-control study (Vasquez et al. 2004) with follow-up time of 10, 10 ,14 and 8 years respectively.

[8] Kuter et al.: No severe case (≥300 lesions) of varicella was reported among break-through cases. Baxter et al.: 13 severe (≥300 lesions) cases <5 years after vaccination (annual rate of severe varicella in break-through cases per 1000person years for one dose varicella ranges from 0.3 (95%CI: 0.1-1.2) to 0.6 (95%CI: 0.2-1.7)). 15 severe cases ≥5 years after vaccination (annual rate of severe varicella in break-through cases ranges from 0.0 (95%CI: 0.0-0.8) to 0.7 (95%CI: 0.2-1.8)). Chaves et al. 2007 suggests that number of moderate to severe breakthrough cases ≥5 years after vaccination was significantly higher than <5 years after vaccination (odds ratio: 2.6, 95%CI:12.-5.8). Vaccine effectiveness against all grades of severity of varicella disease decreased from 97% (p-value: <.001; 95%CI:91-99) in the first year after vaccination to 81% (p-value: .005; 95%CI:40-94%) in year 7-8 years in case-control study with 339 cases suggesting a non-linear decrease in vaccine effectiveness (Vazquez et al 2004).

GRADE Table 5. Duration of protection in immunocompetent children (9 months to 13 years of age) after two- dose varicella vaccination

Population: Immunocompetent children (9months-13years)
Intervention: Two dose varicella vaccination
Comparison: One dose varicella vaccination
Outcome: Duration of decreased severe varicella (>500 lesions, complication requiring physician visit, hospitalization, death)

In immunocompetent children (9 months to 12 years of age), what is the evidence for duration of protection against severe varicella with a two-dose versus a one-dose schedule?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3/ observational[9]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the health outcome is limited.**
	Conclusion			**Studies do not demonstrate increased duration of protection against severe varicella for two doses of varicella vaccination compared to a single dose varicella vaccination in immunocompetent children. No study reported cases of severe varicella after two doses.**

[9] RCT (Knuf et al. 2012), observational study (Kuter et al. 2004) and case-control study (Shaprio et al. 2011) follow-up 10, 3, and 2.5 years respectively. Kuter et al.: No severe varicella cases (>300 lesions) after single (MMR and MMR+V) vs. two- doses varicella vaccination (2x MMRV). Knuf et al: No severe varicella cases (≥150 lesions) after single vs. two- doses varicella vaccination. Shapiro et al. 2011: The matched odds ratio for 2 doses versus 1 dose of the vaccine was 0.053 (95% CI: 0.002–0.320; P < 0.001), no varicella cases after 2nd dose. No severe cases of varicella were reported in either of the studies.

Vaccine safety

Monovalent varicella vaccine

Monovalent varicella vaccine was well tolerated when administered to >11,000 healthy children, adolescents and adults during prelicensure clinical trials: overall, 19% of subjects reported pain at injection site, 6% localized varicella like rash and 15% of subjects reported fever[143]. However, local injection site reactions, fever and even rash are not uncommon in young children so the placebo-controlled trials are the best methodology for studying vaccine safety and attribution. Examining data from two placebo-controlled studies, the most common adverse events reported after varicella vaccination of healthy children were minor and included mild tenderness and redness at the injection site, and mild rash[76, 78]. In the US trial, pain and redness at the injection site were reported by 26.4% and 5% of vaccine recipients versus 17.5% and 2.5% of placebo recipients, respectively ($P < 0.05$)[76]. In a study comparing the safety of one dose of monovalent varicella vaccine with that of two doses administered 3 months apart, no serious adverse events related to vaccination were reported among approximately 2,000 healthy subjects ages 12 months to 12 years[144]. The safety profile of the two dose regimen was comparable to that of the one dose regimen. Incidence of injection site complaints observed ≤3 days after vaccination was slightly higher after dose 2 (25%) than after dose 1 (21%) ($p=0.015$). Incidence of systemic clinical complaints was lower after dose 2; fever incidence from days 7-21 post-vaccination was 7% after dose 1 and 4% after dose 2 ($p=0.009$), and varicelliform rash incidence after dose 1 was 3%, compared with 1% after dose 2 ($p=0.008$), with peak occurrence 8-21 days post-vaccination. Among persons ≥13 years of age, a higher percentage of injection site complaints was reported after both one and two doses of vaccine: 24.4% and 32.5%, respectively[71]. Varicella-like rash at the injection site occurred in 3% of 1 dose vaccine recipients and 1% of 2 dose recipients. A non-localized rash occurred in 5.5% of vaccine recipients after the first injection and in 0.9% of vaccine recipients after the second, at a peak of 7-21 and 0-23 days post-vaccination, respectively. There was no comparison group who received a placebo injection.

Postlicensure data have confirmed that the varicella vaccine is safe and well tolerated when administered to healthy persons. Considering approximately 48 million vaccine doses distributed in the US from 1995 to 2005, there were 25,306 adverse events reported (52.7/100,000 doses distributed) to the Vaccine Adverse Event Reporting System; 5.0% were classified as serious (2.6/100,000 doses distributed)[145]. The most common adverse events, accounting for 67% of all reports, have consistently been rash, fever and injection site reactions. Similarly, post-marketing surveillance over the first 5 years of Varivax use in Europe (~3.3 million doses distributed) found that most (88%) adverse events reported after vaccination were non-serious and the rate of reporting was 30 reports/100,000 doses[146]. By collecting information on a large number of persons (millions) who received the vaccine, post-marketing surveillance can also detect rare, serious adverse events. Serious adverse events that have been reported as temporally related to varicella vaccination include urticaria including some cases of recurrent papular urticaria, ataxia, thrombocytopenia, pneumonia, anaphylaxis, encephalitis, erythema multiforme, stroke, transverse myelitis, and death[11, 145, 147]. Most of these events were not found to be caused by the vaccine virus.

For reported adverse events following vaccination, laboratory testing of submitted specimens for VZV strain identification is critical. Rare complications that have been confirmed to be caused by VZV Oka strain include pneumonia, hepatitis, HZ meningitis, recurrent herpes zoster, severe rash and secondary transmission[145, 147-151]. Most of these patients were immunocompromised or had other serious medical conditions that were undiagnosed at the time of vaccination, but some were healthy. Some adverse events such are ataxia are biologically plausible and would be very challenging to confirm through laboratory testing. An Institute of Medicine systematic review of the epidemiologic, clinical, and biological evidence for adverse events associated with varicella vaccines through 2010 concluded that evidence supports causality in 5 adverse events[152]: 1) disseminated vaccine strain virus without organ involvement (e.g., varicella-like rash extending to dermatomes beyond the initial injection), 2) disseminated vaccine strain virus with organ involvement (e.g. pneumonia, meningitis, etc.) in individuals with demonstrated immunodeficiencies, 3) vaccine strain reactivation (HZ)

without organ involvement, 4) vaccine strain reactivation (HZ) with organ involvement, and 5) anaphylaxis. A follow up review of the evidence from the end of the IOM report through 2012 identified evidence consistent with the IOM report (F. Barash, presentation to the Global Advisory Committee on Vaccine Safety, December 2012). Several post-marketing studies examined the association between varicella vaccination and specific adverse outcomes: one study did not find an association with ischemic stroke[153], another found no increased risk of cerebellar ataxia or encephalopathy[154], while a third found an elevated risk for immune thrombocytopenic purpura among 11-17 year olds[155]. The results of this last study were based on only 1 case occurring in the first 42 days post-vaccination and the authors concluded that additional studies are needed to better explore this possible association. Two deaths confirmed to be due to the vaccine strain VZV have been reported to date, one in a 4 year old child from Germany[156] who received Varilrix while in remission from acute lymphoblastic leukemia and another one in a 15 month old child from the US who received VARIVAX and who did not have a known immunocompromising condition but did have a medical history (failure to thrive and repeated hospitalizations early in life for presumed infections and respiratory compromise treated with corticosteroids) that could suggest a primary or acquired immune deficiency[157].

A review of data reported after 16 years of pregnancy registry for VZV-containing vaccines that follows up pregnancy outcomes in women who inadvertently received Merck varicella vaccine during pregnancy showed no congenital varicella syndrome among 157 live born infants of seronegative women (Rate=0 per 100, 95% CI 0.0, 2.4) or in the overall registry (735 live births)[158]. However, the numbers of exposures are not sufficient to rule out a maximal theoretical risk for congenital varicella syndrome lower than 4% among seronegative women exposed during the high risk period (compared with ~2% risk after infection with wild-type VZV).

MMRV

In prelicensure clinical trials of Merck MMRV, fever and measles-like rash were reported at a significantly greater rate 0-42 days post-vaccination in children age 12-23 months who received a first dose of ProQuad than in children who received first doses of MMR and varicella vaccine: fever, reported as abnormal of elevated ≥102F (39C), 21.5% vs. 14.9% and measles-like rash, 3% vs. 2.1%[72]. Both of these adverse events were reported to occur more frequently 5-12 days post-vaccination and typically resolved without sequelae. Similarly, following the administration of the first dose of GSK MMRV, higher incidences of fever (approximately 1.5 fold) within 42 days postvaccination were observed when compared to the concomitant administration of MMR and varicella vaccines as separate injection to children age 9-27 months[74]. No differences in systemic reactions, including fever, occurring within 42 days of vaccination were observed when MMRV was administered as a second dose to children in the second year of life[159] or at age 4-6 years[160].

Because of the higher rate of fever seen in pre-licensure studies following the first dose of MMRV vaccine compared with MMR and varicella vaccines administered separately at the same visit, postlicensure studies to evaluate the risk for febrile seizures were conducted with a larger number of subjects. Compared to separate MMR and monovalent varicella vaccines administered simultaneously at the same visit, studies with Merck MMRV (>60.000 children received MMRV and ~400,000 received simultaneous MMR and varicella vaccines) demonstrated a doubled incidence of febrile seizures in vaccinated children 12-23 months of age, 5-12 or 7-10 days after the first dose of MMRV (RR 2.0; 95% CI 1.4 – 2.9, and RR 2.2; 95% CI 1.0 – 4.7), amounting to one extra febrile seizure for every 2,300-2,500 children vaccinated[161, 162]. A retrospective database analysis of the first dose GSK MMRV administered to children age 9 to 30 months reported a 2.4-fold increased risk for febrile seizures for the risk period of 5 to 12 days post-vaccination in the group who received MMRV compared with the group who received MMR and varicella vaccines separately (>82,000 children in each comparison arm) and one extra febrile seizure for every ~2,700 children vaccinated with MMRV instead of separate MMR and varicella vaccines, suggesting a class effect for these quadrivalent vaccines[74]. Postlicensure data did not find that children age 4-6 years who received MMRV as a second dose had an increased risk for febrile seizures after vaccination compared with children who received a second dose of MMR and varicella vaccine at the same visit[163].

Transmission of vaccine virus

Accumulated data from pre and postlicensure studies and surveillance suggest that transmission of vaccine strain VZV from healthy persons to susceptible contacts is very rare. In the postlicensure period with >130 million doses distributed, transmission of vaccine strain virus from healthy vaccine recipients to susceptible contacts has been documented by PCR analysis in 11 instances from 9 vaccine recipients (2 vaccinated persons transmitted virus to two contacts) most commonly following household exposure but also in institutional and school settings[146, 147, 164-168]. Transmission occurred only when the vaccine recipient had a rash (including 4 cases from herpes zoster caused by the vaccine strain) with one possible exception[169]: neonatal varicella with vaccine-strain VZV was diagnosed 22 days after maternal postpartum vaccination; the mother did not have a rash but the newborn was in the room when the mother was vaccinated and the most plausible mode of transmission was deemed aerosolization when the vaccine-filed syringe was cleared of air bubbles rather than transmission from the mother. Additionally, in prelicensure trials of leukemic recipients of varicella vaccine, only those with skin lesions as a side effect of varicella vaccination spread vaccine strain virus to varicella-susceptible close contacts (incidence of spread 10%-17%)[170, 171].

Herpes zoster after vaccination

The Oka strain, like wild-type VZV, may cause latent infection, and can reactivate from latency to cause HZ. In vaccinated children, HZ can also be caused by reactivation of latent wild-type VZV acquired either from unrecognized infection before or after vaccination or from breakthrough varicella. Some evidence suggested that HZ tends to be milder in vaccinated than in unvaccinated children[172, 173] however, determination of the causal agent (i.e. vaccine vs. wild-type strain) cannot be made on clinical grounds and attribution requires laboratory confirmation and genotyping. Some vaccine strain HZ cases have required hospitalization and few reported HZ cases had concurrent meningitis or encephalitis confirmed to be vaccine strain VZV[145]. Importantly, studies have documented that both immunocompetent and immunocompromised children vaccinated with varicella vaccines are at reduced risk for vaccine strain VZV HZ as compared with the risk for HZ from wild-type VZV in children with a history of varicella. Among immunocompromised children, one study indicated that varicella vaccine was 100% highly effective in preventing HZ among HIV-infected children[174] and a prelicensure study found the risk for HZ was approximately 65% less among leukemic children who had received the varicella vaccine compared with those with previous wild-type varicella infection[175]. In population-based studies of healthy vaccine recipients, Civen et al. described a 4 to 12-times lower risk of HZ among vaccinated children aged <10 years compared to children with a history of varicella and Weinmann et al. found that among children age <18 years HZ incidence was 79% lower among vaccinated than among unvaccinated and that wild-type virus caused half of HZ cases among vaccinated children[172, 173]. The risk for HZ in children after two doses of varicella vaccine and whether the reduced HZ risk documented in children after one dose is maintained as they become adults remain to be studied.

The quality of evidence was graded for following research questions:

- In immunocompetent individuals, what is the incidence of serious adverse events following the first dose of varicella vaccination (monovalent vaccine)? (GRADE table 6)
- In immunocompetent individuals, what is the incidence of serious adverse events (febrile seizures excluded) after vaccination with MMR and varicella or varicella alone? (GRADE table 7)
- In immunocompetent children (9 months to 12 years of age), what is the evidence for the increase in febrile seizures risk in those receiving one dose varicella vaccination with MMRV versus separate MMR and varicella simultaneously? (GRADE table 8)
- In immunocompetent children (9 months to 12 years of age), what is the risk of febrile seizures in those receiving two doses varicella vaccination with MMRV versus separate MMR and varicella simultaneously? (GRADE table 9)

GRADE Table 6. Vaccine safety of varicella vaccination in immunocompetent individuals (monovalent vaccine)

Population: Immunocompetent individuals
Intervention: Varicella vaccination (one dose)
Comparison: Placebo/no vaccination
Outcome: Serious adverse events

In immunocompetent individuals, what is the incidence of serious adverse events following any dose of varicella vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		9/ RCT[10]	4
	Factors decreasing confidence	Limitation in study design	Serious[11]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect**
	Conclusion			**Our confidence in the estimate of the effect is moderate that incidence of serious adverse events following one or two doses of varicella vaccination is low. Overall few reports and low incidence of serious adverse events in RCTs, observational studies and post-marketing surveillance data. Despite overall low incidence of serious adverse events, incidence after first dose of vaccination is higher than after second dose.**

[10] 6 RCTs Ferrera et al. 2009 ; Gatchalian et al.2004 ; Lau et al. 2004 ; Parment et al. 2003 ; Ramkissoon et al. 1995 ; Shinefeld et al. 2002), 3 observational studies (Black et al. 1999 ; Chaves et al. 2009 ; Ozaki et al. 2000) assess the vaccine safety of one dose of varicella vaccination. Consistent findings across studies, overall low incidence of serious adverse events

[11] Small number of study participants to assess very rare serious events

GRADE Table 7. Vaccine safety of varicella vaccination in immunocompetent individuals (MMRV vaccine)

Population: Immunocompetent individuals
Intervention: MMRV (one or two doses)
Comparison: MMR + V or V alone (one or two doses)
Outcome: Serious adverse events (febrile seizures excluded)

In immunocompetent individuals, what is the incidence of serious adverse events (febrile seizures excluded) after vaccination with MMRV compared with MMR + V or V alone?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		8/ RCT[12]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[13]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect.**
	Conclusion			**The risk of serious adverse events (febrile seizures excluded) in immunocompetent individuals is low, both after having received MMRV vaccination and MMR+V or V alone. The reported events resolved without sequelae.**

[12] 8 RCTs evaluate the risk of serious adverse events of MMRV compared to MMR+V or varicella vaccine alone. Observed serious adverse events comparing MMRV vs MMR+V are low: Czajka et al. 2009: 2/2206 vs 0/574; Goh et al.2007: 0/153 vs 0/146; Halperin et al. 2008 : 0/195 vs 0/195; Knuf et al.2006: 0/311 vs 0/108; Reisinger et al. 2006: 0/399 vs 0/195; Schuster et al. 2008: 7/732 vs 3/238; Watson et al. 1996: 0/57 vs 0/54; White et al 1996: 0/239 vs 0/239.

[13] Number of study participants is very small, difficult to identify rare serious adverse events.

GRADE Table 8. Risk of febrile seizures after first dose of MMRV in immunocompetent children (9months to 12 years)

Population: Immunocompetent children (9 months to 12 years)
Intervention: MMRV (one dose)
Comparison: MMR + V (one dose)
Outcome: Febrile seizures

In immunocompetent children (9 months to 12 years of age), what is the evidence for the extent (RR or attributable risk) of febrile seizures in those receiving varicella vaccination with MMRV versus MMR + V?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ observational[14]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the health outcome is limited**
	Conclusion			**The risk of febrile seizures 5-12 days after the first dose of combined measles, mumps, rubella, varicella (MMRV) vaccination in immunocompetent children is 2 fold higher than using non-combined vaccination (MMR+V). This higher risk was documented in studies among children 12 (9) to 23 months of age.**

[14] 2 observational studies indicate an elevated risk of febrile seizures 7-10 days (age 12-23 months) (RR: 1.98; 95% CI :1.43-2.73) and 5-12 days (age 12-60months) (RR: 2.2; 95% CI: 1.04-4.65) following the first dose of immunization with MMRV compared to MMR+V (Klein et al. 2010; Jacobsen et al. 2009).

GRADE Table 9. Risk of febrile seizures after second dose of MMRV in immunocompetent children

Population: Immunocompetent children
Intervention: MMRV (two doses)
Comparison: MMR + V (two doses)
Outcome: Febrile seizures

In immunocompetent children, what is the evidence for the extent (RR or attributable risk) of febrile seizures in those receiving two doses of varicella vaccination with MMRV versus MMR + V?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ observational[15]	2
	Factors decreasing confidence	Limitation in study design	None Serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the health outcome is limited**
	Conclusion			**The risk of febrile seizures 7-10 days after vaccination with the second dose of combined measles, mumps, rubella, varicella (MMRV) vaccination in immunocompetent children was no different from non-combined vaccination (MMR+V).**

[15] One observational study (Klein et al. 2012) found no elevated risk of confirmed febrile seizures in children (age 4-6 years) of MMRV compared to MMR+V 7-10 days after immunization (Incidence: 1.2/100 000doses; 95% CI:0.03-6.4)

Co-administration of monovalent varicella vaccine and MMRV with other childhood vaccines

Varicella vaccine was tested for concomitant administration with other childhood vaccines, included DTaP, DTaP-IPV, HibMenCY-TT, Influenza (LAIV), Hib, Comvax (Hib/HepB), and MMR[71, 73]. It was found to be safe (type, frequency and severity of adverse events reported were similar to those seen when each vaccine was given alone) with non-inferior immunogenicity. The co-administration of MMRV with other childhood vaccines was tested as well[72, 74]. Administration with DTP-IPV or DTPa-HBV-IPV/Hib or DTaP+Hib/HepB or hepatitis A vaccine was found to be safe with non-inferior immunogenicity. Co-administration with MenACWY-CRM at 12 months of age or meningococcal ACWY-TT conjugate vaccine was safe. MMRV given concomitantly with PCV-7 or 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) both showed uncompromised safety profiles. Concomitant administration of MMRV with 4CMenB was immunogenic but associated with increased reactogenicity (higher rates of fever with 4CMenB dose)[176].

In summary, simultaneous administration of the majority of widely used live and inactivated vaccines has produced seroconversion rates and rates of adverse events similar to those observed when the vaccines were administered separately. Monovalent varicella vaccine and MMRV may be administered simultaneously with other childhood vaccines. If not administered at the same time with other live vaccines the interval between administration of varicella vaccine or MMRV and other live vaccines (e.g., MMR, live attenuated influenza vaccine, yellow fever) should be at least 28 days.

Modeling the potential impact of a childhood varicella vaccination program on varicella and adult herpes zoster epidemiology

Potential for shift in the age at infection and increase burden of varicella

Prior to the introduction of the varicella vaccination program in the developed countries concerns were raised that widespread vaccination of children could decrease exposure to VZV in the population, resulting in an older age distribution of the remaining cases. Since complication rates in adults are higher than those in children there was concern that a shift in the age distribution of cases could increase overall morbidity, even though the total number of cases would be reduced[177]. In the United States, the average age at infection increased over the first ten years of the program from 3-6 years in 1995, to 9-11 years in 2005 but the age specific incidence decreased in all age groups[6]. A model developed to assess the effect of the varicella vaccination program on morbidity found that the total number of cases was more sensitive to the level of coverage than to variations in vaccine assumptions (effectiveness, duration of immunity)[178] and the United States achieved within a decade high coverage with the varicella vaccine among young children with important catch-up occurring. In addition, modeling results suggest that greater shifts in the age at infection are predicted when vaccine efficacy is high. However, according to model predictions, it is too early to see the effects of shift in the age at infection due to community protection effects.

Modeling performed to inform the working group deliberations to address the question of the shift in the age at infection indicated that for high income countries, at vaccine coverage levels of <30% and ≥80% very little risk exists of increased morbidity due to shifts in the age of infection (Brisson et al. The potential impact of varicella vaccination in low to middle income countries: A feasibility modeling study. Report to the SAGE working group on varicella and herpes zoster vaccines, unpublished, 2013). However, at moderate coverage levels (30%-70%), there may be a risk of increased morbidity due to shifts in the age at infection. The risk of increase in morbidity due to shifts in the age at infection increases with: higher vaccine efficacy (e.g., 2-dose vaccination), higher contact rates between children and adults and when severity/morbidity increases significantly with age (e.g., mortality). Based on findings from modeling using high income country data it was hypothesized that low/middle income countries may be at greater risk for shifts in the age at infection and increased morbidity after varicella vaccination due to higher risk for moderate coverage, less assortative mixing patterns and greater morbidity and case-fatality in older ages. In the absence of comprehensive data, for low/middle income countries, modeling was performed for countries representing a range of seroprevalence from different world regions: South Asia (India, urban and rural Sri Lanka), East Asia and Pacific (Thailand, Malaysia, Singapore), Latin

America and Caribbean (Brazil, Bolivia, St. Lucia) and Africa (Nigeria, Kenya). The analysis concluded that for low/middle income countries with medium/high seropositivity (most countries) there is a high risk of shifts in the age at infection when one-dose vaccination coverage is between 20% and 80% and this scenario can lead to increased mortality following varicella vaccination (fig. 6) (Brisson, unpublished, 2013). A coverage of at least 60% is required for substantial reductions in mortality. Low/middle income countries with very low seropositivity (e.g., Sri Lanka: less than 20%-30% in 20 year-olds) may see important reduction in mortality and morbidity, even with low vaccine coverage. There remain important data gaps for low/middle income countries: better seroprevalence data and morbidity outcomes to inform potential vaccination programs.

Potential impact on adult herpes zoster epidemiology

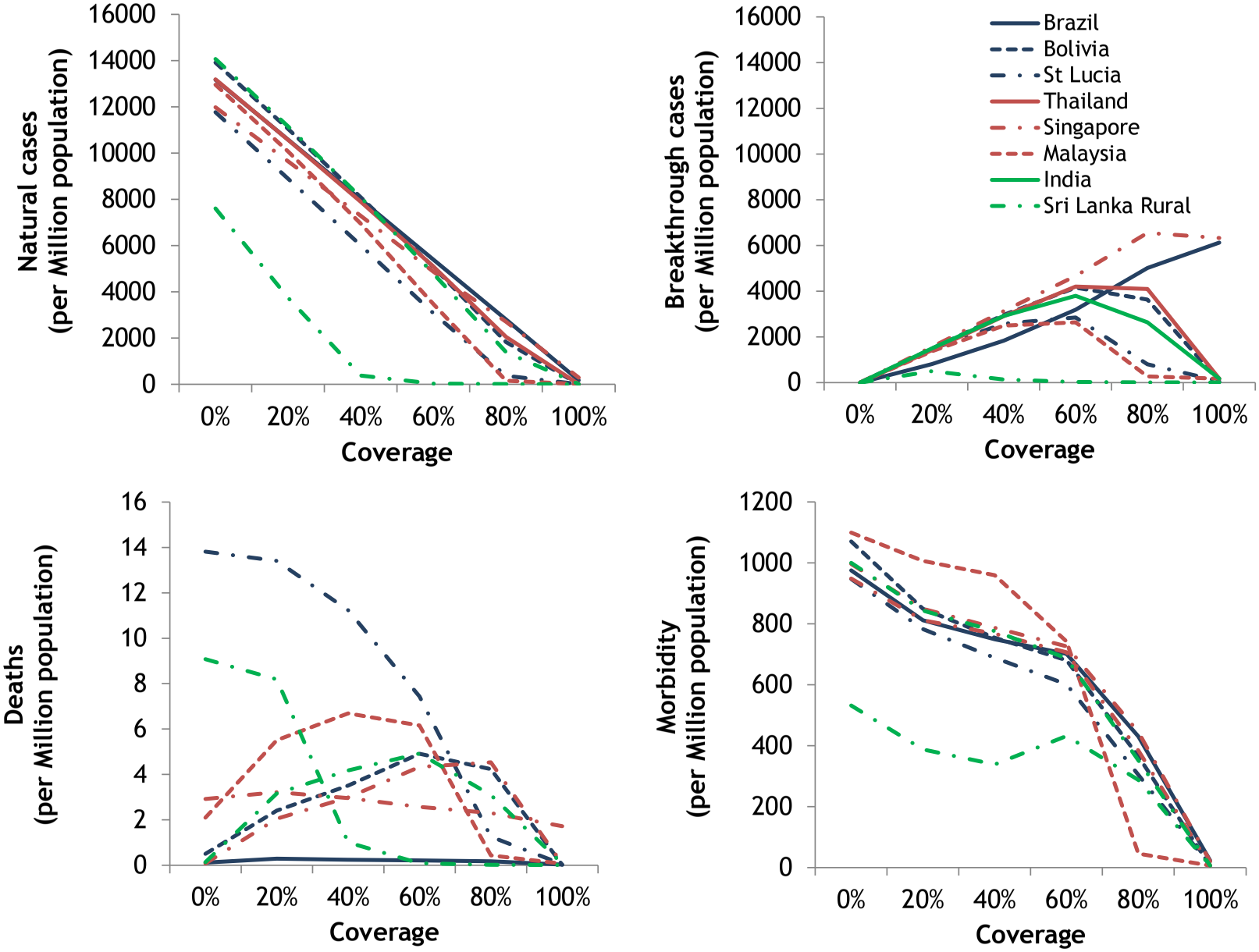
A number of studies have either directly or indirectly examined the role of exposures to varicella on the risk of HZ in both immunocompromised and healthy populations[179]. Exposure to varicella disease has been shown to boost VZV specific immunity[14]; whether ongoing exposures throughout life is needed to maintain immunity to VZV through external boosting, especially as the population ages, is not certain though some studies support this hypothesis (e.g., persons with >3 exposures to varicella have 1/5th risk of HZ compared to unexposed[180], adults living with children have higher exposure to varicella and significantly lower HZ incidence[181]) while others do not[182]. Under the assumption that external boosting is important, mathematical models predicted that widespread varicella vaccination, by reducing varicella infection, will lead to an increase in HZ incidence over short and medium term (over 10–40 years in one study and up to 70 years in another)[177, 183, 184]. Some countries have postponed universal varicella vaccination, at least partially based on this prediction. However, on long term a decrease in HZ incidence is expected as the cohorts infected with wild-type VZV will be replaced by those who have received vaccine virus and assuming that its lower reactivation rate is maintained on long term[177, 184].

Experience has now been gained with observing HZ epidemiology in countries implementing varicella vaccine programs as well as in countries without a varicella vaccination program. Multiple studies examining overall population rates of HZ were conducted in many developed countries (US, UK, Canada, Spain, Japan, Australia) and the majority show evidence of increasing incidence trends in HZ[46, 185-191]. In countries with a vaccination program, increases in HZ incidence had started years before use of varicella vaccine therefore it is difficult to attribute the increase to varicella vaccination. Further studies are needed to understand factors that may explain these increases including methodological issues, changes in access to healthcare or health seeking behaviors, demographic/societal changes common to all high income countries, and risk factors for HZ that have not been well described to date including chronic medical conditions like diabetes, stress, and possible immune compromising effects of new immune modulating medications (e.g., monoclonal antibodies used to treat rheumatologic diseases).

A 2013 systematic multidisciplinary review of herpes zoster risk reduction through exposure to varicella patients analyzed the peer-review publications on exogenous boosting studies: 13 observational studies on herpes zoster incidence after widespread varicella vaccination, 4 longitudinal studies on VZV immunity after re-exposure, 9 epidemiological risk factors studies, 7 mathematical modeling studies, 7 and other studies[179]. The authors concluded that exogenous boosting exists, although not for all persons, nor in all situations and that its magnitude is yet to be determined adequately in any field study.

Until additional evidence becomes available, countries will have to consider the impact of varicella vaccination on adult HZ as being uncertain on short and medium term and ranging from no impact to increase associated with increases in morbidity and health care costs and decide on use of varicella vaccine in light of this uncertainty. In low/middle income countries the incidence of HZ is unknown and no modeling work on the impact of varicella vaccination on HZ incidence in these countries has been performed.

Figure 5. Predicted incidence of a) natural varicella, b) breakthrough varicella, c) varicella-related deaths and d) morbidity at post- equilibrium by country and vaccination coverage. 1-dose base case vaccine efficacy, Equilibrium=80 years post-vaccination, Morbidity=Inpatient days, Seroprevalence/force of infection estimated using the Farrington function. (from Brisson et al. The potential impact of varicella vaccination in low to middle income countries: A feasibility modeling study. Report to the SAGE working group on varicella and herpes zoster vaccines, unpublished, 2013)



Cost effectiveness of varicella vaccination

A review of the literature found 41 studies that addressed the cost-effectiveness of childhood varicella vaccination, including two reviews[192, 193]. Most of the cost effectiveness studies were from Europe and North America (UK, Spain, Germany, Switzerland, US), two studies from Taiwan, and one each from Israel and Singapore. The study quality varied greatly. Most studies did not include dynamic models that account for community protection effects (only 9 studies used dynamic models) and likely underestimate the impact of varicella vaccination. However, the findings were highly consistent: studies found a childhood varicella vaccination program to be cost saving under the societal perspective, cost-effective under the health payer perspective when excluding any potential impact on HZ incidence and not cost-effective when including HZ natural history; this last approach predicts that the varicella vaccination program will increase morbidity on short term by increasing HZ incidence and that will counterbalance the benefits of varicella vaccination. In terms of magnitude of effect, most studies showed vaccinating children to be highly cost-effective or cost-ineffective depending on assumptions about HZ incidence. The evidence on these studies was indirect as they were based on modeling studies to account for community protection after varicella vaccination, uncertainties on duration of vaccine protection and impact of varicella vaccination on HZ incidence.

There appears to be agreement among models that over the long term (>50 years after childhood vaccination is initiated) the varicella vaccination program is likely to reduce HZ. This is the period when the incidence of HZ is expected to decline as the vaccinated cohorts enter the age groups when they are at greatest risk of developing zoster (with models assuming that the lower HZ risk seen among vaccinated children vs. those infected with wild-type VZV will be maintained into older ages). Increasing our understanding on the impact of varicella vaccination on zoster epidemiology was identified as a key issue that would help with refining the cost-effectiveness estimates. Data on cost-effectiveness from low and middle income countries is currently not available. Additionally, an accurate statement on what the cost-effectiveness would be in these countries cannot be made based on published studies because many of the parameters included in the modeling analyses are from high income countries and unknown for low and middle income countries (e.g., underlying epidemiology, mixing between ages, vaccine cost, health care costs).

Immunocompromised populations

Varicella in immunocompromised populations

Varicella causes much greater severity and mortality in populations who have compromised cellular immune function due to medical conditions or immunosuppressive therapy[1]. Persons with congenital deficits in cell-mediated immunity and those receiving chemotherapy, radiotherapy (or both), high doses of steroids, (e.g., severe asthma) are at greatest risk to develop varicella with dissemination of VZV throughout their organs and association with coagulopathy, severe hemorrhage, and continued vesicular lesion development after seven days (progressive varicella). Several studies have highlighted the severity of varicella among children with cancer/acute lymphoblastic leukemia (ALL), especially in those receiving chemotherapy[53, 194-197]. The risk for severe disease was particularly high if chemotherapy, and especially corticosteroids, was given during the incubation period[194, 195] and the absolute lymphocyte count was <500 cells/mm3[53]. In a study of 60 children with cancer who were still receiving chemotherapy when they developed varicella, 19 (32%) had disseminated disease and 4 (7%) died[194]. All four children who died had pneumonia and 3 also had encephalitis. There were no complications in the 17 children who had completed chemotherapy at least 2 months prior to onset of varicella. Further analyses on a larger number of immunocompromised children from the same center described that among 91 leukemic children on chemotherapy when they developed varicella and who were not treated with antivirals, 29 (32%) developed pneumonia and 9 (10%) died; the severity among leukemic children was greater than among children with other malignancies in which pneumonia occurred in 19% and no deaths were reported[53]. Mortality was much less (<1%) in the modern era (after 1984) when all patients received prompt antiviral treatment[198]. Nonetheless, clinical experience indicates that in settings with inadequate infrastructure and supplies for prevention, diagnosis and treatment VZV infection is an important cause of

morbidity and mortality among immunocompromised patients[198]. Children with ALL are also at a higher risk for HZ than healthy children.

Varicella also causes greater morbidity and mortality in HIV-infected persons than among the general population however, the risk of severe varicella and death is not as great as for leukemic children; while the illness is more extensive and lasts longer than in healthy children, fatalities and severe complications from varicella were unusual[54, 55]. Severely immunocompromised HIV-infected children can have persistent chronic infection, with continued appearance of new lesions for >1 month after primary infection[55, 199] and with atypical lesions (non-healing ulcers or necrotic, hyperkeratotic verrucous lesions). Chronic infection was reported in 14% of HIV-infected children with VZV in the pre-HAART era but it is uncommon in the HAART era[200]. An important burden of VZV infections among HIV-infected children is represented by HZ for which the risk of occurrence is >10-25 times higher than in the general population[201]. The CD4 count at the time of varicella correlates with the subsequent risk of developing HZ, 70% of HIV-infected children with <15% CD4-lymphocytes at the time of varicella developed zoster[202]. Ophthalmic complications due to VZV (either acute retinal necrosis or progressive outer retinal necrosis) associated with a high rate of visual loss have also been described in HIV-infected persons[201]. Since most individuals develop varicella by the age of 10 years, primary varicella in HIV-infected adults is rare. In the few reported cases, the clinical presentation and outcome were similar to those seen in HIV-infected children[203].

Varicella vaccine in imunocompromised populations

Because diseases caused by wild type VZV are more severe and fatal in persons with defects in cell mediated immunity, varicella vaccine (various regimens but mostly 2 doses administered 3 months apart) has been studied for safety and efficacy in select immunocompromised populations. Children with acute lymphoblastic leukemia (ALL) have been the most extensively studied immunocompromised group, >1,200 children with ALL received the vaccine in open-label trials[204]. The largest clinical trial in leukemic children was conducted in the United States and included children with acute lymphoblastic leukemia in remission (n=575) who were no longer receiving chemotherapy or had their chemotherapy suspended for at least one week before and one week after vaccination[205]. The most common adverse event was rash resembling mild varicella about 1 month after vaccination that occurred mostly after the 1st dose in 5% of leukemic children no longer receiving chemotherapy and in about 50% of those still receiving maintenance chemotherapy. 40% of those on chemotherapy developed a rash severe enough (>50 skin lesions) to require high dose acyclovir, for some administered intravenously (if >200 lesions). Rashes were less common after the second dose, occurring in only 10% of children still receiving maintenance chemotherapy. Seroconversion to VZV, measured by FAMA, occurred in 82% of leukemic children after one dose of vaccine and in 95% after two doses. In general, about 80% of vaccine recipients tested developed positive cell-mediated immune responses after one dose of vaccine and 90% after two doses, mirroring the experience with humoral immune responses. Over 11 years, 13% of vaccine recipients who originally seroconverted become seronegative[206]. Many were exposed to varicella but did not become ill. Prospective cohort studies also showed that children with leukemia who received varicella vaccine were 3 times less likely to develop HZ than those who had natural VZV infection (8 vs. 25 per 1000 person-years)[175].

Very few children with malignancies other than ALL were included in trials. Among children with lymphosarcoma an increased likelihood of severe rash was determined and these children were no longer included in future studies. Children with solid tumors who were given the vaccine did not have a greater frequency or severity of adverse events compared with leukemic children but further studies involving patients with solid tumors are needed[204].

One of the other major groups of immunocompromised patients evaluated for the safety of varicella vaccine was transplant recipients. In one small study, the live vaccine was administered to hematopoietic stem cell transplant patients with demonstrable immune reconstitution; 4% of vaccine recipients experienced mild-to-moderate symptoms potentially attributable to vaccination and there were no severe reactions[207]. Three studies with <100 subjects total examined varicella vaccine given to organ transplant recipients (kidney, liver) on

immunosuppressive therapy[208-210]. They concluded that the vaccine caused mostly local reactions, rash and fever. However, some of the rashes were severe and disseminated and required treatment with acyclovir.

Several studies have been conducted in approximately 220 VZV-seronegative HIV positive children[211-215]. For the most part these were 2 dose regimens with the second dose typically given after 3 months. Studies were done in those who had progressively more immunosuppression, however, none were in severely immunosuppressed (CD4+T-lymphocyte percentage <15%). In the two studies conducted by Levin et al. that account for >50% of all HIV positive subjects studied, local reactions were reported in 5%-20% of participants after dose 1 and 3%-12% after dose 2[212, 213]. Fever and rash also occurred and for the most part were mild and transient. Two cases of pneumonia and one of seizure were reported but these were found to be related to other causes. Regardless of immunologic category, at least one measure of VZV-specific immunity (antibody and/or cell mediated immunity) was present in at least at least 83% of vaccine recipients after 2 doses[216]. The percentage of children with detectable VZV antibody declined at one year post-vaccination but was similar to that found in a comparator group of HIV-infected children who had natural varicella in the prior year. No serious adverse events were reported from other trials. There were no studies of varicella vaccine conducted among HIV positive adults who were VZV seronegative.

The safety of varicella vaccine in pediatric and juvenile patients with a range of chronic and autoimmune diseases has also been demonstrated[217-221]. Use of varicella vaccine has been shown to be safe with no serious adverse events reported among children and adolescents with systemic lupus erythematous, juvenile rheumatic diseases (both groups also on immunossupressive medication), chronic renal failure, chronic liver disease, or atopic dermatitis. In general these were small studies, with all but one including less than 60 subjects; .

Data on vaccine efficacy/effectiveness of 2 doses varicella vaccination in immunocompromised children was gathered in a few studies. The vaccine was found to be 86% effective among leukemic children, 73% effective post renal transplant (children received the vaccine before transplantation) and, among HIV-infected children, 85% effective in protection against any varicella and 100% effective in preventing zoster[11]. Varicella that occurred in vaccinated children was generally a modified disease, less severe than in unvaccinated children with similar immunocompromising conditions.

All studies in immunocompromised populations were small and in very controlled settings with close follow up and monitoring, hence, results may not be generalizable. HIV status and CD4 count status of children in routine vaccination programs are typically not known. All but one of these studies were from developed countries. Compared to healthy children, varicella vaccine is associated with higher risk of adverse events, some severe, in selected subpopulations of children with deficiencies in cell mediated immunity. Available data suggest that the vaccine can prevent most cases of severe varicella in these populations.

The quality of evidence was graded for following research questions:

- What is the scientific evidence of the effectiveness of varicella vaccination against all grades of severity of varicella disease in HIV-infected individuals (with CD4+ ⩾15%)? (GRADE table 10)
- In HIV-infected individuals (with CD4+ ⩾15%), what is the (attributable) incidence of serious adverse events for any dose of varicella vaccination? (GRADE table 11)

GRADE Table 10. Vaccine effectiveness of varicella vaccination in HIV infected individuals (CD4+ ≥15%)

Population: HIV infected individuals (CD4+ ≥15%)
Intervention: Varicella vaccination (one or two doses)
Comparison: Placebo/no vaccination
Outcome : All grades of severity of varicella disease

What is the scientific evidence of the effectiveness of varicella vaccination (versus placebo/no vaccination) against all grades of severity of varicella disease in individuals with HIV (CD4+ ⩾15%)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4/ observational[16]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the health outcome is limited**
	Conclusion			**Varicella vaccination demonstrates to be effective in protecting individuals with HIV infection (CD4+ ≥15%) against all grades of severity of varicella disease.**

[16] Four studies evaluated the effectiveness or immunogenicity of varicella vaccination in children with HIV (Son et al. 2010 , Armenian et al. 2006, Taweesith et al. 2011, and Levin et al. 2006). Vaccine effectiveness in 72 children having received one (46%) or two doses (54%) was 82% (95%CI: 25%-99%; p=0.01) (Son et al. 2010). Among 34 children (57%) who were VZV seronegative at baseline, 11.8% (95% CI, 3.3%-27.5%) and 79.4% (95% CI, 62.1%-91.3%) were VZV seroconverted after first and second dose of vaccine, respectively (Taweesith et al. 2011). Seroconversion rates ranged from 11.8%-72% after the second dose and from 43%-65% one year after vaccination depending on the level of immunosuppression (Levin et al.2006). Varicella-zoster virus-specific lymphocyte proliferative responses were detected 100% (n=10) subjects 90% one year after vaccination (Armenian et al. 2006).

GRADE Table 11. Vaccine safety of varicella vaccination in HIV infected individuals (CD4+ ≥15%)

Population: HIV infected individuals (CD4+ ≥15%)
Intervention: Varicella vaccination (one or two doses)
Comparison: Placebo/no vaccination
Outcome : Serious adverse events

In individuals with HIV (CD4+ ⩾15%), what is the (attributable) incidence of serious adverse events for any dose of varicella vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		6/ RCT[17]	4
	Factors decreasing confidence	Limitation in study design	Serious[18]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect**
	Conclusion			**Reports of serious adverse events following one or two doses of varicella vaccination in individuals with HIV (CD4+ ≥15%) is low, yet the evaluated studies are conducted in controlled settings with a limited number of participants.**

[17] Levin et al.2001: N=41, Levin et al. 2006 :n = 97, Bekker et al. 2006. N =15, Armenian et al. 2006 : n=10, Taweesith et al. 2011, n= 60, Weinberg et al. : n= 82. Except Weinberg, all studies evaluated the safety in children. 5/6 studies reported no serious adverse events, only one report of report of seizure 19 days post vaccine (Levin et al. 2006).
[18] All studies reviewed were small and in very controlled settings with close follow up and monitoring

Varicella in healthcare settings

Nosocomial transmission of VZV is a well recognized medical and public health problem[222-233]. Sources of nosocomial exposure that have resulted in transmission in health-care settings have included patients, health-care personnel and visitors with either varicella or HZ. Due to generally close contact with their patients, health-care personnel are at higher risk of being exposed to VZV, and may become infected if they are not immune. On the other hand, health-care workers with incubating or clinical varicella are at risk to transmit VZV to their patients. Of special concern are certain groups of susceptible patients (e.g., neonates, premature, pregnant women, immunocompromised hosts due to immunosuppressive therapy or malignant diseases) who are at increased risk for severe varicella with complications[1]. Most of the patients at high risk of serious complications are ineligible for varicella vaccine therefore protection from exposure is important.

Nosocomial transmission has been attributed to delays in the diagnosis or reporting of varicella or HZ and in failures to implement appropriate control measures promptly. The recognition of patients and staff who represent a source for VZV is difficult because the infectious period for patients with varicella starts before rash (1-2 days) and also the diagnosis may be missed in the early stages. Additionally, airborne transmission of VZV from patients with either varicella or HZ has resulted in varicella among staff and patients who had no direct contact with the index case-patient[223, 224, 234].

VZV exposures among patients and health-care personnel can be disruptive to patient care, time-consuming, and costly even when they do not result in transmission[227, 233, 235, 236]. Identification of susceptible patients and staff, reassignment of staff until proof of immunity becomes available, medical management of susceptible exposed patients at risk for complications of varicella and furlough of susceptible personnel 8-21 days post-exposure all place a burden on health-care facilities.

The VZV immune status of health-care personnel is expected to mirror the immune status of adults in the respective country. Most adults in temperate regions are immune to varicella and outbreaks in health-care personnel are uncommon, more common are exposures that do not lead to transmission. A review of nosocomial outbreaks associated with VZV in the United States before introduction of varicella vaccination found that following nosocomial exposure to VZV, 2% to 16% of susceptible staff has developed clinical varicella[229]. From February 1996 to May 1999, 9 hospitals in the US National surveillance system for health care workers reported 72 exposures to VZV, affecting a total of 1111 staff and resulting in 113 lost work-days recorded; 36 patients, 26 staff and 7 visitors were identified as the sources of exposure; 6 staff developed disease following VZV exposure[237]. Therefore, a small but significant risk exists for nosocomial varicella when susceptible health care personnel are exposed to VZV. Because varicella among adults is more common in tropical regions, health-care personnel from the tropics may be at high risk for varicella.

Conclusions and recommendations

Use of varicella vaccine in the general population
Context

- Varicella-zoster virus causes varicella as an acute disease; the virus remains latent and can reactivate causing herpes zoster, usually later in life
- Varicella is a highly communicable viral disease with worldwide distribution that most persons acquire during their lifetime. It is considered to be transmitted primarily by inhalation of aerosols from vesicular fluid of skin lesions, and also by direct contact and possibly by infected respiratory tract secretions.
- In countries where the burden of disease is well described, the severe disease burden in children is much lower than for measles, rotavirus or pneumococcal disease

- In temperate climates, varicella exhibits strong seasonality with peak incidence in the period from late winter to early spring. Most cases occur before 10 years of age, hence the majority of adults are seropositive when tested. In tropical areas, varicella may show a seasonal distribution related to temperature and rainfall, but, a larger proportion of adults, especially in low population density areas, are seronegative.

Safety and effectiveness of varicella vaccination:

- There is strong scientific evidence that varicella vaccine is safe and effective in preventing varicella related morbidity and mortality in immuncompetent individuals.

Factors to be considered for vaccine policy decisions:

Burden of disease:

- Fewer data are available on burden of disease from low and middle income countries. However, considering access to care, specialized treatment options, acquired immune deficiency states such as HIV and, in tropical climates greater disease burden in adults due to later acquisition of varicella, it is likely that varicella-related morbidity and mortality would be higher than in developed countries.
- The relationship between the acute (varicella) and reactivated (zoster) phases of the infection in individuals and on a population level. Though concerns have been raised through mathematical models that herpes zoster incidence may increase over the short and medium term due to a varicella vaccine program, epidemiological studies have not confirmed that increases herpes zoster incidence that have been observed in many countries globally are attributable to varicella vaccine.
- Varicella causes higher morbidity and mortality in immunocompromised populations, especially those with defects in cell-mediated immunity and in non-immune young infants and adults including pregnant women.
- There are differences in the epidemiology of varicella between temperate and tropical climates. Other risk factors that affect seroprevalence in populations include area of residence, population density, attendance at childcare and school and number of siblings in the household.
- Due to the high incidence of varicella in children and low susceptibility among adolescents and adults, the impact of a vaccination program aimed at adolescents and adults is expected to be minimal (except in countries with a high average age at infection)
- The experience of countries that introduced universal childhood varicella vaccination indicates an important impact on varicella cases, hospitalizations and deaths

Coverage:

- A routine childhood vaccination program with coverage of <80% in children could result in an increase in morbidity and mortality due to a shift of varicella burden to older age groups
- Private market use of the varicella vaccine, in the absence of a routine immunization program, may reach coverage levels high enough to have a detrimental effect of increasing the median age of varicella disease and the burden of varicella but not sufficiently high to ensure protection at country level (it is estimated that an undesired effect occurs at coverage levels between 20% and 80%).

Cost-effectiveness:

- Cost-effectiveness is dependent on vaccine cost, safety and effectiveness and the impact of the vaccine in reducing overall direct medical and societal costs of varicella morbidity and mortality in a country.
- Cost-effectiveness studies and models on the impact of vaccination can further assist countries considering introduction.
- Cost-effectiveness results will be subject to the uncertainty that currently exists regarding the boosting effect of circulating varicella on the incidence of herpes zoster later in adulthood.

Resources:

- Countries need to consider the impact of varicella vaccination versus other important public health interventions.
- Countries should assess whether adequate resources can be allocated to implement and sustain varicella vaccination in a routine immunization schedule to achieve and maintain high coverage levels and/or to support recommendations for high-risk populations such as healthcare workers.

Recommendations for the general population:

- Routine childhood immunization against varicella (generally at 12-18 months of age) should be considered in countries where this disease is an important public health and socioeconomic problem. In countries where the vaccine is licensed for persons <12 months of age, vaccination can be considered at an earlier age. For countries considering a two dose program, a decision on the age at the second dose can consider the childhood vaccination schedule and vaccine licensure as well as scientific evidence on vaccine immune response and efficacy. Resources need to be sufficient to support a vaccination program so that sustained vaccine coverage ≥80% can be achieved and maintained.
- Countries in which coverage levels from use of varicella vaccine in the private sector reach between 20%-80% should give a higher priority to considering implementing a routine vaccination program to reach the coverage ≥80% due to the likelihood that the incidence of disease that occurs in adults would otherwise increase.
- Implementation of a one or two dose varicella vaccine schedule is dependent on the goal of the vaccination program: If the country focus is to reduce mortality and severe morbidity from varicella, a one dose schedule could be implemented into routine immunization. Two doses induce higher effectiveness and should therefore be recommended in countries where the programmatic goal is, in addition to decreasing mortality and severe morbidity, to further reduce the number of cases and outbreaks which might continue to occur with a one dose schedule.
- Countries with a high average age (≥15 years of age) of infection, could take into consideration alternate vaccination strategies such as vaccination of susceptible adolescents and adults. This strategy requires a two dose schedule.

Special groups/risk groups

Health care workers

Context:

- Due to close contact with patients, health-care workers are at higher risk of exposure and consequently transmission of the varicella-zoster virus to patients at high risk for serious complications.
- Nosocomial transmission and outbreaks may cause higher mortality and serious morbidity if they affect immunocompromised and other high-risk patients. Additionally, outbreaks are costly, and disruptive in healthcare settings.

Recommendations:

- Countries should consider vaccination of susceptible health care workers with two doses of varicella vaccine even in absence of varicella vaccination in the routine immunization schedule.
- In settings where financial constraints prohibit vaccination of all susceptible health care workers, priority should be given to vaccination of health care workers in close contact with persons at high risk of serious varicella complications such as immunocompromised individuals, neonates and pregnant women.

Immunocompromised patients

Context

- Varicella causes higher morbidity and mortality in immunocompromised populations, especially those with defects in cell-mediated immunity
- Varicella vaccine has been studied selectively, under strict protocols, in children with acute lymphocytic leukemia and HIV
- The label for varicella vaccines contraindicates their administration to persons with congenital or acquired immune deficiencies. However, the vaccine may be used in selected immunocompromised populations. Nevertheless, because of the risk of severe vaccine-related complications, use of the vaccine in these specific populations should only be considered in health care settings where specific antiviral therapy is readily available and physicians have expertise with the vaccine in these populations.
- MMRV vaccine has not been studied in these populations and should not be used for vaccination of immunocompromised patients.

Recommendations:

HIV

- Varicella vaccine has been shown to be safe, immunogenic, and effective in HIV-infected children with CD4 ≥15%. The use of the vaccine (2 doses administered 3 months apart) should be considered in clinically stable HIV-infected children including those receiving highly active antiretroviral therapy (HAART) with CD4 determinations ≥15%. The vaccine has not been studied in individuals with CD4 <15% or in those who are not clinically and immunologically stable, and should not be used in these situations.

Malignancies

- The vaccine has been studied in clinical trial settings in children with acute lymphocytic leukemia (ALL) and certain solid tumors, on maintenance chemotherapy in remission. Protocols defining timing of vaccination in terms of time in remission on maintenance chemotherapy, when to interrupt that chemotherapy, including corticosteroids, before and after vaccination, and minimal acceptable lymphocyte and platelet counts at the time of vaccination should be followed.
- Expert opinion varies, but in general, children who have successfully completed chemotherapy and remain in remission and are unlikely to relapse can receive vaccine approximately 3-6 months after all chemotherapy is completed.

Other types of immunodeficiencies

- Consideration of vaccine in other populations of patients, who are receiving or have received medications that may be immunosuppressive, should be discussed with specialists with expertise in this area.
- Vaccine can be safely given to subjects with isolated defects in antibody production (i.e. hypo- or agammaglobulinemia). It should not be given to those with conditions where defects in antibody production are part of an immunodeficiency condition that includes defects in cellular immunity (i.e. severe combined immunodeficiency, etc.) or on any condition characterized by defects in cellular immunodeficiency, except as described above for HIV, ALL and certain solid tumors.

Household contacts of immunocompromised patients

Context:

- Varicella vaccine can be safely used in household contacts of immunocompromised patients. The risk of transmission from a vaccinated person to the patient or their household contacts is very low.

Vaccination of household contacts provides protection for immunocompromised persons by decreasing the likelihood of exposure to wild-type varicella-zoster virus.

Recommendation:

- Susceptible household contacts of immunocompromised patients should be considered for vaccination with two doses of varicella vaccine spaced according to the minimum interval recommended by the manufacturer.
- Two doses are recommended for household contacts of immunocompromised persons to offer greater protection to household contacts even if the country has a routine one dose childhood program

Pregnant women

- Infection with wild varicella-zoster virus during the first 2 trimesters of pregnancy can result in congenital varicella syndrome (scarring on the skin, abnormalities in limbs, brain, and eyes, and low birth weight) in 1-2% of the offspring. Varicella vaccine is contraindicated during pregnancy
- Limited data from a pregnancy registry which followed the birth outcomes of pregnant women who had inadvertently received varicella vaccine has not detected any cases of congenital varicella syndrome in their offspring however the sample size has precluded exclusion of the 1-2% risk of congenital varicella syndrome associated with wild VZV infection during pregnancy; the maximal theoretical risk ruled out by the pregnancy registry data is 4% among seronegative women exposed during the high risk period. Nonetheless, the data are reassuring on the low risk for congenital varicella syndrome after varicella vaccination
- According to expert opinion, the risk of congenital infection is likely to be lower from an attenuated vaccine virus than wild virus and termination of pregnancy is not recommended if a pregnant woman was inadvertently vaccinated
- Routine laboratory documentation of pregnancy status prior to vaccination is not recommended
- Given implementation of varicella vaccination in the routine program, efforts should be made to counsel and vaccinate susceptible women post-partum in order to prevent infections during subsequent pregnancies

High priority research questions

Burden of varicella and age-specific varicella incidence, severe morbidity and mortality especially in low and middle income countries, including those with high prevalence of HIV

Long-term duration of protection for both 1 and 2 doses of varicella vaccine

More data to understand the effect of varicella vaccination on herpes zoster, both through observational studies and modeling

More evidence to examine how different varicella vaccine coverage levels would change varicella epidemiology

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Background paper

Herpes zoster vaccines

SAGE Working Group on Varicella and Herpes Zoster Vaccines

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Table of Contents

Background

Herpes zoster (HZ), commonly known as shingles, is caused by the reactivation of the varicella zoster virus (VZV). The clinical manifestation is a unilateral vesicular rash, characteristically restricted to a single dermatome, which is usually accompanied by radicular pain along that dermatome. Patients experience significant pain and discomfort that may last for weeks, months or even years in severe cases, diminishing the quality of life.

The VZV remains dormant inside multiple dorsal root ganglia after the initial varicella infection with the virus. Subclinical reactivation can occur intermittently in immune-compromised and immunocompetent individuals with detection of VZV DNA in the blood with consequent boosting in immunity (endogenous boosting)[1] or after exposure to varicella or HZ (exogenous boosting)[2]. Some studies have found that re-exposure to varicella-zoster virus or to children < 10 years is associated with a decreased risk of developing herpes zoster at a later stage in life,[3, 4] whereas other studies have not found this association.[5, 6] Clinical VZV reactivation (herpes zoster) occur as result of a reduction in the level of T-cell immunity to VZV, a correlate of protection against herpes zoster, which is observed with increasing age.[7] Reactivation leads to ganglionitis with damaging of neurons and supporting cells followed by intense inflammatory response.[8] In 70-80% of herpes zoster cases, prodromal pain occurs, restricted to the affected dermatome. Vesicles appear for 3-4 days, followed by umbilication, ulceration and crusting of the lesions. The rash is accompanied by pain which may be severe.[9]

The most common serious complication of herpes zoster is postherpetic neuralgia(PHN), defined as pain that persists more than a defined period of time (90 days was used in the vaccine clinical trials), after onset of rash or after cutaneous healing.[10] About 20% of patients with herpes zoster will develop PHN. Age is the most important risk factor for development of PHN, with most cases occurring in adults over 40 years of age and adults over 70 years having a four times increased risk of PHN than those younger than 60 years [11, 12]

Other serious complications of herpes zoster include blindness secondary to ophthalmic zoster, bacterial superinfections of zoster skin lesions and disseminated infections, which occurs more commonly in immunocompromised patients.[13] Based on limited available data from 366 mothers, herpes zoster during pregnancy does not appear to increase the risk of intrauterine infection in the unborn. [14] An increased risk of herpes zoster in infancy has been reported in children whose mothers had had varicella in pregnancy. [15]

Prompt antiviral therapy, if available, is recommended for herpes zoster in healthy and immunocompromised patients. Oral antiviral therapy should be commenced as early as possible, within 72 hours of rash onset. Treatment is usually given for 7 days in the absence of complications of herpes zoster. For immunocompromised persons who require hospitalization and in case of severe neurologic complications intravenous acyclovir is recommended. Management of acute pain associated with herpes zoster is complex. Non-steroidal anti-inflammatory drugs or in severe cases of severe pain, opioids may be used[16].

Since a prerequisite for developing HZ is a past primary VZV infection, the epidemiology of varicella may also affect the epidemiology of HZ. There is some variation described in the epidemiology of VZV infection between temperate and tropical climates[17-19]. More than 90% of primary VZV infections in temperate climates occur before adolescence, in contrast to the tropics where a higher proportion of adults have not yet been infected with VZV[18-21]. However, available data on varicella incidence and seroprevalence that is representative and population-based, suggest that it is uncommon not to acquire varicella by 40-50 years of age even in the tropical countries though exceptions exist, especially in island populations such as Sri Lanka[22, 23].

The incidence and severity of herpes zoster disease increase with age, with an exponential increase in incidence after the age of 50 years, which correlates with ageing-related decline in cell-mediated immunity.[24]Among adults aged 22 years and over, approximately 70% of HZ cases occur after 50 years of age[25-27]. Among adults who reach 85 years of age, it is estimated that approximately half will have suffered at least one episode of HZ[28, 29]. Studies in the US, Canada, Israel, Taiwan and Japan report age-adjusted HZ incidence in the total population ranging from 3.4 –5 per 1000 person years and 8 - 11 per 1000 person years over the age of 65[12, 30,31-34]. The Israeli study also reported comparative incidence density rate for HZ of 3.46 per 1000 person-years in the total population and 12.8 per 1000 person-years in immune-compromised patients[33]. Australia reported HZ and PHN incidence rates among adults ≥ 50 years of 10/1,000 and 1.45/1,000 persons respectively[35]. A study of 27 countries in Europe showed HZ incidence varying by country from 2.0 to 4.6/1 000 person-years with no clearly observed geographic trend[36]. A recent population-based study from Korea showed an annual prevalence of HZ (measured by clinic visits) of 7.93-12.54 per 1000 population with a rapid increase in age prevalence after 45–49 years of age, reaching the highest incidence in individuals in their 70s[37]. In Taiwan, a study conducted between 2000 and 2006 showed that the incidence rate of HZ for all age groups was approximately 5 per 1000 person years[34]which is similar to rates described in temperate climates[27, 38-40].

Surveillance activities to monitor the incidence of herpes zoster and assess the impact of varicella and zoster vaccination are more frequently reported from those countries having introduced one or both of these vaccines into routine childhood and/or adult immunization schedules[41-44]There is scarcity of literature on VZV and HZ incidence in low and middle income countries. Most estimates of HZ incidence have been made in developed countries with temperate climates[27, 38-40, 45]. Where the burden of disease of VZV and HZ are compared, the burden of HZ is higher, mainly due to longer hospital stays[46, 47]. However, challenges with studying herpes zoster health burden, especially in elderly populations, include appropriate attribution of herpes zoster as the primary cause of severe morbidity or mortality rather than a contributing cause or a coincidental finding[42].

Besides increase in age, immunosuppression from any cause, including hematologic malignancies, HIV and immunosuppressive medications, is an important risk factor for herpes zoster, increasing the risk of HZ by at least 10-fold[48,49]. In developed countries, the lifetime risk of herpes zoster disease is approximately 30%[27, 50]. Considering the importance of age as a risk factor, life expectancy in populations would be expected to affect HZ incidence and total disease burden to a large degree. Race is

also a well described risk factor with the Black population in the US and the UK having a much lower incidence (about one fourth to a half) of HZ than the white population[51, 52]. Other identified risk factors include sex (most studies show a higher incidence among women irrespective of patterns of health seeking behavior) and stress or trauma, diabetes and higher social class[33, 40].

Mathematical models that assume that external boosting plays an important role in maintaining VZV cell mediated immunity, and thereby delaying the onset of zoster in those who had primary VZV infection, predict that universal childhood varicella vaccination immunization programs will impact the incidence of herpes zoster, theoretically by reducing exposure to circulating wild virus and subsequent boosting[53]. Whilst an increase in herpes zoster incidence has been observed in the US and in other countries with childhood varicella vaccine programs[11,52], increasing trends have been noted in countries not using varicella vaccine universally in children[11, 32, 37]. Additionally, in the US, the trend precedes the introduction of universal varicella vaccination[30, 44]and the rate of increase in herpes zoster did not change in the pre and post vaccine time periods suggesting that other factors are affecting the increase. [41, 44, 54, 55]. Studies continue to examine this issue and to explore what factors, including potentially vaccination, may be responsible for the increasing trend observed widely throughout the developed world.

A live attenuated herpes zoster vaccine, (Merck and Co., Inc) was first licensed in 2006 and is currently licensed in over 60 countries including those in the EU, US, Canada and Australia. This VZV vaccine contains an OKA derived varicella- zoster virus strain that is given in a single dose and administered subcutaneously. It is licensed for use in immunocompetent individuals 50 years and over by the European Medicines Agency (EMEA), Australia's Therapeutic Goods Administration (TGA) and the U.S. Food and Drug Administration (FDA). Recommendations for routine vaccine administration by national policy setting groups, physicians associations or reimbursement agencies have been made in countries in Europe and Asia including Austria and Sweden (≥ 50 years), the U.S., Canada, Greece, Korea and Thailand(≥ 60 years), Australia (60-79 years) and the U.K. (70-79 years). This vaccine contains 19,400 plaque-forming units (PFU) and is similar in potency to one formulation of MMRV vaccine (ProQuad) and has an estimated 14 times higher potency than that of monovalent varicella vaccine guaranteed at expiration. Both lysophilized and refrigerator-stable vaccine formulations are licensed. The vaccine is contraindicated for people with a history of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine; with a history of primary or acquired immunodeficiency state, including leukemia, lymphoma, or other malignant neoplasm affecting the bone marrow or lymphatic system, or with acquired immunodeficiency syndrome or other clinical manifestation of infection with human immunodeficiency viruses; those receiving immunosuppressive therapy, including high-dose corticosteroids; or those who are or may be pregnant.

Objectives

The Strategic Advisory Group of Experts on Immunisation (SAGE) Working Group on Herpes Zoster Vaccine (established in May 2012) was tasked with reviewing the evidence, identifying information gaps, and guiding the work required to address the information gaps and formulate proposed recommendations related to the use of herpes zoster vaccines in order to update the current 1998 varicella vaccine WHO position paper for SAGE review.

1) This report identifies, assembles and reviews published literature and available evidence related to main topics considered by the working group, including:
   a) Data regarding the global prevalence and burden of disease caused by herpes zoster according to country development status
   b) Issues related to herpes zoster surveillance
   c) The safety, effectiveness and immunogenicity profile of herpes zoster vaccines and duration of protection following immunization
   d) Impact of co-administration of herpes zoster vaccines with other vaccines
   e) Evidence on the cost- effectiveness of different approaches to using the vaccine, in particular in low and low- middle income countries

2) The Working Group was asked to critically appraise this evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence of key literatures on predefined research questions (PICO questions) as specified in the SAGE Guidance for the development of evidence-based vaccine related recommendations[1].

Methods

The working group was informed by an update of the2012 Cochrane systematic literature review on herpes zoster vaccines[56]. The Cochrane literature review considered published, peer-reviewed literature as the primary source of data. Types of study designs included were: RCTs or quasi-randomized controlled trials. No restrictions were made to date of publication. References were retrieved from the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) www.thecochranelibrary.com MEDLINE, EMBASE, LILACS and CINAHL. Start date was from the beginning of each candidate database up to September, 2013. Two reviewers independently screened titles and abstracts of all retrieved citations. Study authors and leading experts in the field of herpes zoster vaccines were contacted to provide additional information and identify associated published reports that relate to the subject.

PICO (Population, Intervention, Comparison and Outcome) questions were formulated by the working group. Population was either immunocompetent or immunocompromised adults. Outcomes of relevance for the working group to assess vaccine efficacy, safety and duration of protection following immunization were:

[1] http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf

- all grades of severity of herpes zoster disease
- Post herpetic neuralgia (PHN)
- serious adverse events

Critical appraisal of evidence for the identified literature was done using the GRADE methodology. Evidence profiles summarizing the findings for each study question are provided in the Cochrane review.

Results

Vaccine efficacy and effectiveness

The pivotal clinical trial to assess pre-licensure efficacy and safety of Zostavax, the only licensed herpes zoster vaccine, was the Shingles Prevention Study, a randomized double-blinded placebo-controlled study initiated in November 1998, which enrolled 38,546 adults aged 60 years and over at 22 trial sites in the US. All vaccine and placebo recipients were actively followed for new cases of HZ through September 2003. The mean follow-up time was 3.13 years, 95% of enrolled participants completed the study, 1% were lost to follow up and 4% died in course of the study[57]. Less than 7% of subjects were aged 80 years of age or older, resulting in lower statistical power to evaluate the vaccine in this older age group. Herpes zoster cases were confirmed by PCR testing (93%), viral culture (1%), or evaluation by a panel of five physicians with expertise in zoster diagnosis (6%). Patients with confirmed herpes zoster were followed for at least 182 days to assess the outcome of the condition, including presence and severity of pain. The efficacy of herpes zoster vaccine in preventing herpes zoster disease as well as PHN and burden of zoster illness was evaluated. Reduced incidence of herpes zoster in the vaccine group was observed as early as 42 days following vaccination (RR: 0.29; 95%CI: 0.13-0.68). The overall vaccine efficacy against herpes zoster disease was 51.3% (5.42 cases/1000 person years vs 11.12cases/1000 person years; p <0.001).

The vaccine efficacy in preventing PHN was 66.5% (27 vs 80 cases; p<0.001) reflecting a significant reduction in the relative risk of PHN in the vaccinated group compared to the placebo group (RR: 0.34, 95%CI: 0.22-0.52).A burden of illness score for HZ (that incorporated the incidence, severity, and duration of pain and discomfort from HZ) was calculated, and efficacy against this outcome was 61.1% (95% CI 51.1-69.1).

In the Shingles Prevention Study, HZ vaccine efficacy against HZ decreased with age (from 64% among subjects aged 60–69 years to 38% among subjects aged 70 years). Vaccine efficacy against PHN remained constant with age (66% among subjects aged 60–69 years and 67% among subjects aged 70 years). An age-stratified analysis examined whether the HZ vaccine reduces the incidence of PHN beyond the reduction in PHN incidence provided by preventing herpes zoster. Results showed that, although there was no significant additional efficacy in preventing PHN in subjects aged 60–69 years, the vaccine efficacy in preventing PHN among subjects with herpes zoster who were aged 70 years and over was 49% (p=0.01). A burden of illness score for HZ (that incorporated the incidence, severity, and duration of pain and discomfort from HZ) was calculated, and efficacy against this outcome was 61% (95% CI 51-69).[58]

A subsequent RCT performed in 22,439 immunocompetent individuals aged 50–59 years in North America and Europe demonstrated vaccine efficacy of 69.8% (95% CI: 54.1–80.6) in preventing HZ. The incidence of herpes zoster was 1.99/1000 person-years in vaccinated vs 6.57/1000 person-years in the control group; (RR: 0.31 (95%CI: 0.2-0.5, p<0.0001)[59]One small RCT powered to look at safety and immunogenicity compared a higher potency versus a lower potency formulation of herpes zoster vaccine and reported a non-significant higher risk for confirmed herpes zoster cases in the higher potency group (RR 2.55, 95% CI: 0.012-52.99).[60]

Post-licensure data examining risk of HZ in 76,000 vaccinated persons compared to 227,000 unvaccinated adults 60 years and older demonstrated that the vaccine was 55% effective (95% CI 52-58%)in preventing herpes zoster cases. The incidence of herpes zoster among vaccinated individuals was 6.4 per 1000 person-years; 95% CI: 5.9-6.8, and for unvaccinated individuals it was 13.0 per 1000 person-years; 95% CI: 12.6-13.3. In addition to overall reduction of herpes zoster cases, the vaccine was 63% effective in preventing ophthalmic herpes zoster and 65% effective in preventing hospitalizations coded as herpes zoster (VE 65%).[61]

Concomitant administration of herpes zoster vaccines with other vaccines

Concomitant administration of herpes zoster vaccines with inactivated influenza vaccines in adults 50 and older has not demonstrated a reduced immunogenicity to either vaccine [62]. Although a study of simultaneous administration of HZ with pneumococcal polysaccharide vaccine demonstrated a significant reduction in VZV antibody when administrated concomitantly, [63]a retrospective cohort study of more than 76,000 vaccine recipients demonstrated that the efficacy of herpes zoster vaccine was not affected by concomitant pneumococcal polysaccharide vaccine administration [64].

Duration of protection

Data on duration of protection following HZ are limited. In the Shingles Prevention Study, the median surveillance period for assessing vaccine effectiveness was 3.12 years.[57] Results from the Short-Term Persistence Study (STPS) indicate possible waning of protection against HZ overtime. The STPS was a phase 3, randomized, placebo-controlled, double-blind trial at 12 sites in the US. STPS re-enrolled 7320 vaccine and 6950 placebo recipients from the 38 546-subject SPS population and followed them to year 7 post-vaccination. Initially, reduction of HZ was significantly higher for the vaccinated group (RR: 0.53, 95%CI: 0.38-0.74). In the STPS as compared to the SPS, vaccine efficacy for herpes zoster burden of illness decreased from 61.1%(95%CI: 51.1–69.1) in the years 0.0–4.9 to 50.1%(95%CI: 14.1–71.0) in the years 3.3–7.8, vaccine efficacy for the incidence of PHN decreased from 66.5% (95%CI: 47.5–79.2) in the years 0.0–4.9 to 60.1%(95%CI: −9.8 to 86.7) in the years 3.3–7.8, and vaccine efficacy for the incidence of herpes zoster decreased from 51.3% (95%CI: 44.2–57.6) in the years 0.0–4.9 t to 39.6%(95%CI: 18.2–55.5)in the years 3.3–7.8. The HZ burden of illness was defined as the sum of all of the HZ severity of illness scores using the Zoster Brief Pain Inventory in the respective randomization group divided by the person-years of observation. [65] Following completion of the STPS, the long-term persistence study (LTPS) evaluated the duration of protection against HZ, PHN and HZ BOI in a total of 6,867 subjects previously vaccinated with ZOSTAVAX in the SPS. The mean age at enrollment into the LTPS was 74.5 years and the

median follow-up period was ~3.9 years. A concurrent placebo control was not available in the LTPS; data from prior placebo recipients were used to estimate vaccine efficacy. The LTPS analyses for vaccine efficacy are based on data collected primarily from Year 7 through Year 10 following vaccination in the SPS. The estimated vaccine efficacy during the LTPS follow-up period was 21% (95% CI: [11 to 30%]) for HZ incidence, 35% (95% CI: [9 to 56%]) for PHN incidence and 37% (95% CI: [27 to 46%]) for HZ BOI[66].

The quality of evidence was graded for following research questions.

Efficacy of herpes zoster vaccination in immunocompetent adults (≥60 years)

Population: Immunocompetent adults (≥ 60 years)
Intervention: Herpes zoster vaccination (single dose)
Comparison: Placebo/no intervention
Outcome : Cases of herpes zoster

What is the scientific evidence of the vaccine efficacy against herpes zoster conferred by one dose herpes zoster vaccination (versus placebo/no vaccination) in immunocompetent adults (⩾60 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT[2]	4
	Factors decreasing Confidence	Limitation in study design	None serious[3]	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None Serious	0
		Publication bias	None serious	0
	Factors increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect**
	Conclusion			**A single dose of herpes zoster vaccination is efficacious and effective to protect immunocompetent adults (⩾60 years) against herpes zoster. A single dose of herpes zoster vaccination demonstrated vaccine efficacy of 51% to protect immunocompetent adults (⩾60 years) against herpes zoster disease.**

Reference List[56, 57, 67, 68]

Gagliardi AMZ, Silva BNG, Torloni MR, Soares BGO. Vaccines for preventing herpes zoster in older adults1. Cochrane Database of Systematic Reviews 2012;(10).

Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study
1. PLoS Med 2013;10(4):e1001420.

Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005 Jun 2;352(22):2271-84.

[2] A Cochrane review (Gagliardi et al. 2012) identified one large RCT (Oxman et al. 2005) with low risk of bias addressing the research question. Risk ratio for 60-69 compared to placebo: 0.36 (95% CI: 0.3-0.45) and 0.63 (95% CI: 0.53-0.75) in adults over 70 years. Incidence per 1000 Person Years: 5.4 in participants who had received herpes zoster vaccine; 11.1 in participants who had received placebo. Vaccine efficacy: 51.4% (95%Confidence Interval 44.2-57.6%). Analyses according to age groups indicated a greater benefit in participants aged 60 to 69 years, RR 0.36 (95% CI 0.30 to 0.45) and in participants aged 70 years and over, RR 0.63 (95% CI 0.53 to 0.75). One cohort study (Langan et al. 2013) calculated vaccine effectiveness in persons 65 years and over to be 0.48 (95% CI:0.39–0.56) compared to unvaccinated indivudals. Post-licensure data examining risk of HZ in 76,000 vaccinated persons compared to 227,000 unvaccinated adults 60 years and older demonstrated that the vaccine was 55% effective (95% CI 52-58%)in preventing herpes zoster cases (Tseng et al. 2011).
[3]Vaccine effectiveness over a longer period of time (>5 years) still needs to be assessed.

Efficacy of herpes zoster vaccination in preventing post-herpetic neuralgia (PHN) in immunocompetent adults (≥60 years) after herpes zoster vaccination

Population : Immunocompetent adults (≥60 years)
Intervention: Herpes zoster vaccination
Comparison: Placebo/no intervention
Outcome : Post herpetic neuralgia (PHN)

What is the scientific evidence of the vaccine efficacy against PHN conferred by one dose herpes zoster vaccination (versus placebo/no vaccination) in immunocompetent adults (⩾60 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT[4]	4
	Factors decreasing Confidence	Limitation in study design	None Serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None Serious	0
		Publication bias	None serious	0
	Factors increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**We are very confident that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**A single dose of herpes zoster vaccination is effective to protect Immunocompetent adults (⩾60 years) against PHN. Individuals vaccinated with herpes zoster vaccine had a reduced risk ratio (0.34 (95% confidence interval: 0.22-0.52)) of developing PHN compared to unvaccinated individuals.**

Reference List[57, 69]

Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005 Jun 2;352(22):2271-84.

Chen N, Li Q, Zhang Y, Zhou M, Zhou D, He L. Vaccination for preventing postherpetic neuralgia. Cochrane Database of Systematic Reviews 2011;(3).

[4]A cochrane review (Chen et al. 2012) identified one RCT with low risk of bias (Oxman et al. 2005) with a total of 38.501 participants measuring incidence of PHN in vaccinated and participants receiving placebo. Risk ratio 0.34 (95% Confidence Intervall: 0.22-0.52).

Duration of protection in immunocompetent adults (≥60 years) after herpes zoster vaccination

Population : Immunocompetent adults (⩾60years)
Intervention: Herpes zoster vaccination
Comparison: Placebo/no intervention
Outcome : Duration of decreased herpes zoster incidence

In immunocompetent adults (50+ years) what is the evidence for duration of decreased incidence of herpes zoster disease for any dose of herpes zoster vaccination compared to placebo?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3/ RCT[5]	4
	Factors decreasing Confidence	Limitation in study design	Serious[6]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[7]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the health outcome is limited**
	Conclusion			**The data is restricted to a seven year follow-up period, currently no data available on long-term duration of protection following herpes zoster vaccination.**

Reference List[57, 65, 70]

Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005 Jun 2;352(22):2271-84.

Levin MJ, Oxman MN, Zhang JH, Johnson GR, Stanley H, Hayward AR, et al. Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine. J Infect Dis 2008 Mar 15;197(6):825-35.

Schmader KE, Oxman MN, Levin MJ, Johnson G, Zhang JH, Betts R, et al. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy 2. Clin Infect Dis 2012 Nov 15;55(10):1320-8.

[5] Levin et al. 2008: Follow-up of 1395 subjects after high-potency live attenuated Oka/Merck varicella-zoster vaccine. Immune responses from vaccine recipients vs placebo differed significantly three years after vaccination. Oxman et al. 2005: Cumulative incidence significantly lower in vaccine vs. placebo group. Schmader et al. 2012: Seven year follow up of 7,320 zoster vaccine recipients compared to 6,950 placebo controls: RR 0.54 (95%CI: 0.48-0.61) for cases of herpes zoster. Vaccine efficacy during the Long-term Persistence Substudy follow-up period (from year 7 through year 10 following vaccination in the Oxman 2005 study) was 21% (95% CI: 11 %to 30%) for HZ incidence.

[6] Follow up restricted to three years (Levin et al. 2008) and 7 years after receiving herpes zoster vaccine (Schmader et al.2012). Mean duration of follow up 3.1 years (Oxmann et al. 2005). No data available on longer periods.

[7] Immunology data used as correlate of protection (Levin et al.2008)

Vaccine safety

Most studies on the safety of zoster vaccine relate to the licensed zoster vaccine, Zostavax. Zoster vaccine has been found to be safe in the SPS and a number of related and other RCTs, as well as in post-licensure safety studies. Among 38,500 subjects included in the SPS, the incidence of one or more serious adverse events 42 days post-vaccination was < 0.1% among vaccine and placebo groups[57]. In the more detailed vaccine adverse event sub-study[65], the risk of serious adverse events within 42 days of vaccination was 1.9% in the vaccine group compared to 1.3% in the placebo group (risk difference: 0.7 (95%CI: 0.1 to 1.3)). Reported adverse events were varicella-like rash at injection site (0.1% vs 0.04%; risk difference: 0.07 (95% CI: 0.02 to 0.13)) and HZ like-rash (0.1% vs 0.2%; risk difference:-0.10 (95%CI:-0.18 to -0.03)). Adverse events at the injection site were significantly more common in the vaccine compared to placebo recipients (48.3% and 16.6%; risk difference 31.7, 95% CI: 28.3 – 32.6). The most common injection-site AE in the vaccine group included erythema, pain/tenderness and swelling. The mortality rate was equal (4.1%) in both vaccine and placebo groups[57]. Similar safety data were reported from other studies[71].

Kerzner et al randomized HZ and flu vaccines given concomitantly or sequentially to adults 50 years and older and examined adverse events within 28 days of vaccination. Overall, a slightly higher proportion of subjects who received ZOSTAVAX concomitantly with influenza vaccine reported clinical AEs than did those in whom ZOSTAVAX was administered alone, although this difference was not statistically significant. Injection-site adverse events were the most frequently reported 44.7% vs 38.3% (concomitant vs nonconcomitant vaccination). Injection-site adverse events were more frequent in subjects aged 50-59 vs aged 60 and older (53.6% and 40.3%) and more common in concomitant than nonconcomitant group. Overall no serious vaccine-related AEs were reported in either group. [72]

MacIntyre et al conducted a randomized placebo-controlled trial in adults ≥ 60 years administering herpes zoster vaccine and pneumococcal polysaccaride vaccine either concomitantly or non-concomitantly. There was no significant difference in adverse events within 28 days of vaccination between arms.[63]

Gilderman et al compared refrigerated (n=182) vs frozen (n=185) formulations of herpes zoster vaccine in adults 50 years and older. Injection-site adverse events were reported in 35.6% vs 46.4% in refrigerated vs frozen formulation. No serious vaccine-related adverse events within 28 days of vaccination were observed in either study arms.[73]

In a two-dose herpes zoster vaccine study in adults ≥ 60 years, Vermeulen et al reported 49% vs 10.5% injection-site AEs in vaccine and placebo groups after the 1st dose, most commonly erythema, pain and swelling. Injection-site AEs were more frequent after the second dose of vaccine (49% vs 61.2%). No vaccine-related serious AEs within 42 days were reported in either group after 1st dose and 2nd dose of vaccine or placebo. [74]

Sutradharet al compared safety in two age-groups (50-59 years and ≥ 60years). No serious vaccine-related AEs were reported in either of the two arms. Injection-site adverse events (51% vs 34%) as well as systemic adverse events (5.8% vs 2.9%) were more common in the younger aged group.[75]

Mills et al evaluated the safety of herpes zoster vaccine for 28 days post-vaccination in 101 subjects ≥ 50 years with a prior history of HZ. A higher rate of injection-site adverse events was reported in the vaccine group compared to the placebo group (45.9% vs 4.2%). Systemic clinical adverse events were similar in both groups. No serious vaccine-related adverse events were reported in either arm.[76]

Post-licensure surveillance data is often better for evaluating rare adverse events, because the statistical power to detect such events may not be sufficient in RCTs. The best available post-licensure data come from a large US study which assessed the safety of zoster vaccine among 192,000 zoster vaccine recipients60 years and older using the Vaccine Safety Datalink system. Various risk intervals (1–14, 15–28, 29–42 or 1–42 days) were studied post-vaccination and medical record reviews were conducted if needed. A significant increase in risk of allergic reactions was reported 1-7 days post vaccination (RR 2.32, 95%CI: 1.85 2.91) using a self-controlled case study design. The age-specific relative risk of allergic reaction (1-7 days) was approximately 3-4 times higher in the younger age group (50-59 years compared to 60 and over). Review of medical records showed that > 80% of the events involved a localized inflammatory response with redness, swelling and/or pain at the injection site (in varying degrees and combinations). The authors concluded that this reflected the coding of localized inflammatory responses using allergic-related codes. No increased risk of serious adverse events such as stroke, cardiovascular events, meningitis, encephalitis, encephalopathy, Ramsay-Hunt Syndrome or Bell's Palsy were identified within 42 days of vaccination. [77]

Another US post-licensure study with 29,010 study participants ≥ 60 years reported no significant increase in risk of acute myocardial infarction (RR: 1.29, 95% CI: 0.66–2.43; unadjusted p-value = 0.44), or stroke (RR: 0.91, 95% CI: 0.43–1.81; unadjusted p-value = 0.80) within 42 days of zoster vaccination. No vaccine-related deaths occurred within 42 days after receiving zoster vaccine.[78]

Recent safety studies related to investigational vaccines include one by Leroux-Roels 2012 who conducted a phase I/II, open-label, randomized, parallel-group trial that evaluated the safety and immunogenicity of a recombinant adjuvanted vaccine(HZ/su) in comparison with live attenuated varicella zoster virus vaccine (OKA) in healthy younger (18-30 years) and older adults (50-70 years). There were no reports of vaccine-related serious adverse events and no deaths.[79] This vaccine is now in a phase III clinical trial.

The quality of evidence was graded for following research questions.

Safety of Herpes Zoster vaccine in immunocompetent adults≥60 years

Population: Immunocompetent adults (>60 years)
Intervention: Herpes zoster vaccination
Comparison: Placebo/no intervention
Outcome: Serious adverse events

In immunocompetent adults (60-69 years), what is the incidence of serious adverse events for any dose of herpes zoster vaccination compared to placebo?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT[8]	4
	Factors decreasing confidence	Limitation in study design	None Serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None Serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**We are very confident that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**Our confidence in the estimate of the effect is high that incidence of serious adverse events following one dose of herpes zoster vaccination in immunocompetent adults (>60 years) compared to placebo is low. Overall few reports and low incidence of serious adverse events in one RCT.**

Reference List[56, 57]

Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005 Jun 2;352(22):2271-84.

Gagliardi AMZ, Silva BNG, Torloni MR, Soares BGO. Vaccines for preventing herpes zoster in older adults 1. Cochrane Database of Systematic Reviews 2012;(10).

[8]A Cochrane review (Gagliardi et al. 2012) calculated the risk ratio for serious adverse effects in vaccinees compared to placebo in participants 60-69 years: 1.2 (95% confidence intervall (CI): 0.92-1.57) based on data from Oxman et al. 2005, a RCT with low risk of bias and >17 000 study participants.

Herpes zoster vaccination in immunocompromised

Live HZ vaccine is contra-indicated in persons who are immunosuppressed from any cause, whether acquired, congenital, iatrogenic or disease-based. The safety and effectiveness of HZ vaccination in immunocompromised persons has been assessed in few post-licensure studies [80-84]. Zhang et al evaluated the incidence of herpes zoster in 463 541 Medicare beneficiaries with autoimmune diseases (rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease) 50 years and over with and without immunosuppressive therapy. There was no significant difference in age- and sex-adjusted herpes zoster incidence rates between patients who had received herpes zoster vaccine and persons who had not been vaccinated however the study only included 551 vaccine recipients in whom 5 cases of herpes zoster developed. The authors claimed that no significant increase in serious AEs was observed however no details were provided on the safety assessment. Naidus et al assessed safety in a small study of 62 patients ≥ 50 years with hematologic malignancies and hematopoietic cell transplant; 25% of whom concurrently received antiviral prophylaxis at the time of and/or beyond the date of vaccination. Participants were selected based on clinical impression of intact immunity.No vaccine-related AEs were reported. One patient developed trigeminal herpes zoster 3 weeks after vaccination but strain identification was not obtained. Parrino et al conducted a RCT with 300 subjects ≥ 60 years on long-term chronic/maintenance systemic corticosteroid therapy (daily dose equivalent of 5 to 20 mg prednisone). Compared to placebo, zoster vaccine was demonstrated to be immunogenic 6-weeks post vaccination and no increase in serious AEs was reported through 182 days post vaccination. Chakravarty et al estimated the immunogenicity and safety of HZ vaccination in a small pilot study of 10 female patients with mild Systemic Lupus Erythematosus (SLE) taking mild-moderate immunosuppressive medications and ten control subjects[80]. Limitations of the study were small number of participants, mild SLE disease as well as restricted immunosuppressive therapy. No episodes of HZ, vesicular rash, serious adverse events or SLE flare were reported.The proportion of subjects with a > 50% increase in ELISPOT results following vaccination was comparable between both groups, although absolute SLE responses were lower than controls. Antibody titers increased only among controls following vaccination ($p < 0.05$).

A randomized, double-blind, placebo-controlled trial assessed immunogenicity and safety of live attenuated HZ vaccine in VZV seropositive HIV-infected adults ≥ 18 years (CD4 > 200 copies/µl; HIV RNA < 75 copies/mL for ≥ 6 months on stable antiretroviral therapy [ART]). Primary safety endpoints were defined by the International Conference on Harmonization defined serious adverse events or NIAID grade 3 (of 4) signs/symptoms during 6-week post-vaccination periods. These endpoints were observed in 5.1% of 295 adults who received zoster vaccine and 2.1% of 97 adults who received placebo ($p = 0.26$). Fever and rash were similar between the two groups and injection site reactions were more common in vaccine compared to placebo recipients (42.0% vs 12.4% respectively). The authors concluded that the vaccine was generally safe in HIV+ adults virologically suppressed on ART[85].

Cost- effectiveness of herpes zoster vaccination

One systematic review was conducted which took into consideration 11 studies from Europe and North America[86]. All studies except one provided consistent results and considered zoster vaccination to be

cost-effective in regard to gained quality-adjusted life years(QALY) when the vaccine is given at about 65-70 years of age, and if vaccine protection against PHN is longer than 10-15 years. The quality of evidence is generally good according to the BMJ criteria yet indirect as all results derive from modeling studies. Uncertainties remain in regard to the duration of vaccine protection as recent trial results indicate possible waning of protection[59]. Furthermore, cost- effectiveness data stems from high income countries- data on cost-effectiveness from low and middle-income countries is currently not available.

Conclusions and recommendations

Epidemiological data on the burden of disease is available from selected high and medium income countries. Data from more medium income countries are needed. Data from low income countries are lacking including the effect of life expectancy, HIV prevalence and availability of treatment, race and other factors. The impact of large-scale varicella vaccination programs on the impact of herpes zoster incidence warrants continued surveillance. Although an increase in HZ incidence has been observed in countries with universal VZV vaccination programs such as the US and Australia, the increase precedes the commencement of the vaccination programs and an increase has been observed in countries without childhood varicella vaccination programs. The contributing factors to the observed increase are probably multifactorial, and are not yet well understood.

Herpes zoster vaccine efficacy and safety were assessed in large clinical trials and post-licensure surveillance data from high-income countries. The vaccine is safe and demonstrated clinical protection against herpes zoster, post-herpetic neuralgia and other serious herpes zoster complications.

To date no data are available on long term protection induced by the vaccine. Available data shows short term protection and waning of immunity. Assuming long-term protection (10-15years), which appears now to be an unlikely scenario given the data cited above, modeling demonstrated the vaccine to be cost-effective in high-income countries. No data on cost-effectiveness is available from low- and middle-income countries.

Due to limited data and the unknown burden of disease in most countries, initial evidence of waning of protection over time and uncertainty of the optimal age for vaccination and the potential role of a booster dose, the working group cannot make any recommendation about routine herpes zoster vaccination at this time. However, some countries may decide to introduce vaccination if they have an important burden of disease and consider the program beneficial. Countries with an aging population and demographic shift towards older ages can also consider introduction of herpes zoster vaccination.

For those countries deciding to proceed with a herpes zoster vaccination program, the optimal age and dosing schedule of herpes zoster vaccination should take into consideration effectiveness, efficacy of booster doses, age-dependent burden of disease, cost-effectiveness and duration of vaccine protection.

High priority research questions:

Disease burden studies in low- and middle-income countries.

Duration of vaccine protection against HZ and severe complications (PHN, other).

Safety and efficacy of investigational vaccines in immunocompromised patients such as those with HIV.

Cost-effectiveness of herpes zoster vaccine in immunocompetent and immunocompromised populations, especially in low and middle income countries.

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Evidence based recommendations on Human Papilloma Virus (HPV) Vaccines Schedules

Background paper for SAGE discussions

March 11, 2014

TABLE OF CONTENTS

1. INTRODUCTION

The WHO's Strategic Advisory Group of Experts (SAGE) on Immunization has requested the WHO Secretariat to review the evidence concerning the optimal HPV immunization schedules.

Preparatory to such a review of the evidence by SAGE, it was deemed necessary to:

- systematically review all published and grey literature concerning schedules for HPV vaccines for adolescent girls in different epidemiological settings
- critically appraise the evidence using the WHO SAGE guidelines.

Methodology

Primary Question

The primary question of the review was what is the effect of a 2 dose HPV vaccine schedule compared with the licensed 3-dose schedule on immunological and clinical outcomes in pre-adolescent and adolescent girls?

The population included adolescent girls because this is the primary target group for primary vaccination. Data from both licensed bivalent and quadrivalent HPV vaccines were reviewed.

Sources of Evidence

This background paper for SAGE's consideration is informed by the data from the following four sources:

1. **Data presented during the *Ad hoc Expert Consultation on Human Papilloma Virus Vaccine schedules* organized in Geneva, November 18, 2013**. All the principal investigators of randomized and non-randomized studies were invited to attend the consultation as well as representatives of the two currently licensed HPV vaccines.

   The meeting was open to all participants except for the session on conclusions and recommendations that was only attended by those participants who were deemed to have no or non-significant conflict of interest. Some of the unpublished or confidential information presented during this consultation have subsequently been made publicly available (as of February 2014) and are therefore included in this public report. (List of participants is available in Annex 1).

2. **Results from a systematic review conducted by an team of independent investigators[1].** The investigators systematically reviewed all published and grey literature concerning data comparing the effects of 2-dose and 3-dose HPV vaccination. All data available on randomized comparisons between girls (or women) of the same age and non-randomized comparisons between girls receiving 2-dose and women receiving 3-dose schedules in the literature and studies presented during the WHO Ad – hoc Expert Consultation are included in the companion document entitled ***HPV***

[1] D'Addario M et al. HPV vaccines: review of alternative vaccination schedules: Preliminary overview of the literature. Report to WHO 3rd March 2014 (unpublished update)

vaccines: review of alternative vaccination schedules (D'Addario M et al 2014)[1]***.*** The report of this systematic review is presented in Appendix 1.

3. **Results from non-systematic review of the data from observational studies**[2]. All data available on schedule comparisons from observational studies in the literature and studies presented at this WHO consultation were summarized by the WHO Secretariat. The summary of this review is presented in Appendix 2.

4. **The bivalent vaccine received approval for a pre-adolescent and adolescent indication to allow for administration of the vaccine according to an alternative 2-dose schedule (0, 6 months) in females aged 9-14 years old**. The European Medicines Agency (EMA)[3] report was made available in December 2013 providing public access to the evidence for this new indication. In February 2014, the EMA communicated the positive opinion of the Committee for Human Medical Products (CHMP) for an adolescent indication using the quadrivalent vaccine[4].

2. BACKGROUND

Human papillomavirus (HPV) causes cervical cancer which is the forth most common cancer in women worldwide by age-standardized incidence rate (ASR). In 2012, there were an estimated 528,000 new cases and 266,000 deaths due to cervical cancer. More than 85 % of cervical cancer deaths are in developing countries, where it accounts for 13% of all female cancers. Therefore, most of the burden of HPV-associated malignant and indeed benign disease is in developing countries without effective screening programmes and poor access to medical services.

Two vaccines are currently available, bivalent vaccine (Cervarix ®) and quadrivalent vaccine (GARDASIL®). Both were licensed with a 3 dose schedule at 0-(1 or -2)-6 months. Both are prepared from purified L1 protein, the major capsid protein that self-assembles to form type-specific HPV virus-like particles (VLPs). These VLPs closely resemble the outer surface of HPV virions. VLPs contain no viral DNA and are therefore non-infectious[5].

The quadrivalent vaccine was first licensed in the United States in 2006. The L1 proteins for each type are expressed via a recombinant Saccharomyces pombe (type of yeast) vector. Each 0.5 ml dose contains 20 µg of HPV-6 L1 protein, 40 µg of HPV-11 L1 protein, 40 µg of HPV-16 L1 protein and 20 µg of HPV-18 L1 protein adsorbed onto 225 µg of the adjuvant, amorphous aluminium hydroxyphosphate sulfate (AAHS). The bivalent vaccine was first licensed in 2007. The L1 proteins for each type are expressed via a recombinant baculovirus (type of insect cell) vector. Each 0.5 ml dose contains 20 µg of HPV-16 L1 protein and 20 µg of HPV-18 L1 protein adsorbed onto a proprietary AS04 adjuvant system containing 500 µg of aluminium hydroxide and 50 µg of 3-O-desacyl-4'-monophosphoryl lipid A, a novel adjuvant.

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[2] Non-systematic review of the data from observational studies: 2 versus 3 dose schedule (unpublished report by the WHO Secretariat)

[3] European Medicines Agency-Assessment Report-Cervarix. Procedure No. EMEA/H/C/000721/II/0048, 21 November 2013, EMA/789820/2013 Committee for Medicinal Products for Human Use (CHMP).

[4] htpp://www.ema.europa.eu/docs/en_GB/document_library/EPAR-Assessement Report – Variation/human/000721/WC500160885.pdf

[5] WHO, The Immunological Basis for Immunization Series Module 19: Human papillomavirus infection(2011) http://whqlibdoc.who.int/publications/2011/9789241501590_eng.pdf?ua=1

Following a review of evidence and recommendations by SAGE at the November 2008 meeting, WHO issued a recommendation on the HPV vaccines in a Position paper that was published in 2009.[6]

WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and recommends that routine HPV vaccination of female adolescents should be included in national immunization programmes, provided that: prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost effectiveness of vaccination strategies in the country or region is considered.

The 2009 WHO position paper (excerpts follow)[6] states that HPV vaccines are most efficacious in females who are naive to vaccine-related HPV types; therefore, the primary target population should be selected based on data on the age of initiation of sexual activity and the feasibility of reaching young adolescent girls through schools, health-care facilities or community-based settings. The recommended primary target population is girls in the age range of 9-13 years. Vaccination of secondary target populations of older adolescent females or young women is recommended only if this is feasible, affordable, cost effective, does not divert resources from vaccinating the primary target population or effective cervical cancer screening programmes, and if a significant proportion of the secondary target population is likely to be naive to vaccine-related HPV types. HPV vaccination of males is not recommended for the prevention of cervical cancer because vaccination strategies that achieve high coverage (>70%) in the primary target population of young adolescent girls are expected to be more cost effective in reducing cervical cancer than including the vaccination of males. Little information is available on the safety and immunogenicity of HPV vaccines in people who are immunocompromised due to medications or diseases. Although the immunogenicity and efficacy of HPV vaccines may be reduced in HIV-infected females, they appear to be preserved[7] and the potential benefit of vaccination in this group is particularly great owing to their increased risk of HPV-related disease, including cervical cancer. Most target populations for HPV immunization are likely to include a few HIV-infected individuals, even in areas with a relatively low prevalence of HIV. Concerns about safety or reduced efficacy among females who may be infected with HIV should thus not defer the initiation of large-scale HPV immunization. HIV testing should not be a prerequisite before routine HPV immunization. A need for booster doses has not been established, for either immunocompetent or immunocompromised individuals. Both vaccines should be administered according to their manufacturer's specifications, schedules and advice on interrupted schedules.

The WHO Global Advisory Committee for Vaccine Safety (GACVS) has reviewed the safety of HPV vaccines on several occasions (2007, 2008, 2009 and 2013). Evidence from all sources continues to support their conclusions about the safety of both vaccines. With more than 170 million doses distributed worldwide and more countries offering the vaccine through national immunization programs, GACVS continued to be reassured by the safety profile of the available products.[8]

By the end of 2013, more than 40 countries had introduced HPV vaccine in their national immunization programmes (only three of them are developing countries). Most countries target vaccination at young girls (e.g. around 9 to 13 years of age) but there a few countries that also

[6] Human papillomavirus vaccines WHO position paper- April 2009 http://www.who.int/wer/2009/wer8415.pdf?ua=1

[7] Toft L et al 2013 ; Denny L, et al 2008

[8] GACVS Safety update on HPV Vaccines.Geneva, 13 June 2013.
http://www.who.int/vaccine_safety/committee/topics/hpv/130619HPV_VaccineGACVSstatement.pdf

offer the HPV vaccine to older girls (e.g. around 18 years of age) and women of reproductive age.

Although the cost per dose of vaccine has changed over time, current prices per dose for the PAHO revolving fund are USD $ 13.08 for bivalent vaccine and USD$ 13.79 for quadrivalent vaccine and, for GAVI procured vaccine through UNICEF Supply Division the prices are USD $4.50 and $4.60 respectively.

In addition to cost savings, there would be obvious programmatic advantages to reducing the number of doses (e.g. reduced delivery costs), and an increased flexibility of the intervals between doses (e.g. annual doses easier for school-based delivery) would probably also lead to increases in vaccination coverage.

3. USING IMMUNOGENICITY DATA TO INFORM POLICY RECOMMENDATIONS ON HPV SCHEDULES: CURRENT CHALLENGES

HPV vaccines were licensed based upon the demonstration of their clinical efficacy in young adult women. The age extension for adolescent girls, in whom efficacy trials would not be feasible, was granted because studies demonstrated that antibody responses in adolescent girls were not inferior to those elicited in women ("immunological bridging"). Alternative adolescent vaccine schedules should thus demonstrate that their immunogenicity is similarly non-inferior.

To seek licensing, a Phase III immunogenicity study of the quadrivalent HPV vaccine was conducted in adolescents with the objective of bridging the efficacy findings in young women to pre-adolescents and adolescents. The neutralizing anti-HPV GMTs at month 7 were non-inferior in adolescents - and indeed 1.7-2.7 fold higher than in the group of 16-23 year old females in whom efficacy was demonstrated[9] . Similar observations were made for the bivalent vaccine and for the nonavalent vaccines currently in clinical development.

The assumption is that the mechanism of protection afforded by the VLP vaccines is neutralizing antibody-mediated. This assumption is supported by animal models that demonstrate protection against viral challenge in animals immunized by passive transfer of hyperimmune serum from donors immunized with L1 VLPs[10] [11] [12]. Although immunization does elicit CD4+ T cells, their function is essentially to provide help to B cells. Effector T cells are important for HPV clearance following infection but are not considered as contributing to prophylactic vaccine efficacy as L1 is only expressed late during HPV infection.

Neutralizing antibodies are produced by plasma cells. The first wave of plasma cells elicited by priming results in the antibody peak observed 4 weeks later. Most of these plasma cells are short lived, such that peak antibody titers decline within a few months. However, some antibody-secreting cells become long-lived plasma cells. Long-lived plasma cells primarily reside in the bone marrow, continuously produce IgG antibodies and are responsible for long term antibody

[9] Block SL, Nolan T, Sattler C, Barr E, Giacoletti KE, Marchant CD, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. Pediatrics. 2006;118(5 Nov):2135-45.

[10] Breitburd, F. et al., Immunization with virus like particles from cottontail rabbit papillomaviruses (CRPV) can protect against experimental CRPV infection. J Virol 69:3959-63.

[11] Suzich, JA. et al., Systematic immunization with papillomaviruses L1 protection completely prevents the development of viral mucosal papilloma. PNAS 1995;92(25):11533-11557

[12] Day, PM., In vivo mechanisms of vaccine-induced protection against HPV infection. Cell Host Microbe, 2010 Sep 16;8(3):260-70.

persistence. Different sub populations may survive for different lengths of time.[13] Antibody titers measured 12-18 months after the last dose of a VLP vaccine reflect the activity of long-lived plasma cells and are the best predictor of antibody persistence.

Circulating antibodies generated by L1 VLP vaccination are thought to reach the site of infection by active IgG transudation at least in the female genital tract, and by passive exudation at sites of trauma that are believed to be required for initiation of HPV infection.

Immunization also elicits memory B cells. Memory B cells (MBC) are resting cells, which do not secrete antibodies and so do not protect unless reactivated by antigen exposure and instructed to differentiate into antibody-secreting plasma cells (recall response). They reside mainly in the spleen but extra splenic niches exist. A small proportion of memory cells may be found in the blood. Although generated in parallel, the memory B cell and plasma cell compartments are independent. A study with the bivalent HPV vaccine reported that a significantly increased HPV 16 MBC population at day 210 after the 3rd dose of vaccine compared to that after the 2nd dose. HPV 18 specific MBC were increased after the 3rd dose but this was not significant[14]. Memory B cells elicited by HPV priming are assumed to mature into highly specific B cells which, when reactivated by vaccine boosting, differentiate into large numbers of long-lived plasma cells producing high levels of specific antibodies. For hepatitis B, memory B cells are assumed to be reactivated by viremia and thus contribute to the maintenance of protection after antibody decline. It is unclear whether memory B cells are reactivated by / contribute to long term protection after HPV VLP vaccination given that HPV infection is exclusively mucosal.

Thus, HPV antibody titers represent a valid marker to compare the expected clinical efficacy of various vaccines and schedules. VLP vaccines elicit very high antibody concentrations. Therefore, when different schedules are compared non-inferiority of antibody concentration must be achieved for alternative schedules if it is expected that the clinical efficacy will be equivalent.

Protective efficacy depends upon the quantity but also the quality of vaccine-induced antibodies. This quality is reflected by measure of the affinity of the antibodies for the antigen. With this avidity threshold, higher concentrations of antibody are needed for protection. After the first immunization(s) (priming), various B cells producing antibodies with a range of affinities for the vaccine antigens are generated. Only B cells with high affinity surface receptors can continue to capture scarce antigen, to interact with helper T cells and thus enter the long-lived plasma cell and memory pool. This process, called affinity maturation, requires several months (empirically a minimum of 4 months). These affinity-matured B cells (and the antibodies they produce) dominate the anamnestic response after the booster immunization. These higher affinity antibodies continue to compete for antigen and this selects B cells that can secrete even higher affinity antibodies. The combination of these multiple affinity interactions between antibodies and antigens is called avidity. Above a minimal avidity threshold, protection against viral challenge requires minimal antibody concentration. Strong 4 year protection was reported in Costa Rican women who received just one dose of bivalent vaccine. Also one dose recipients had avidities at month 36 that were almost as high as three dose recipients, although avidities one month after one dose (measured in women who eventually received three doses were

[13] Mamani Matsuda et al 2008 Blood 111;4653 and Ahuja et al 2008 PNAS 105;4802

[14] Giannini SL, Hanon E, Moris P, Van Mechelen M, Morel S, Dessy F, et al. Enhanced humoral and memory B cellular immunity using HPV16/18 L1 VLP vaccine formulated with the MPL/aluminium salt combination (AS04) compared to aluminium salt only. Vaccine. 2006;24(33-34):5937-49.

rather low). Some authors argued that the higher avidity B cell preferentially survived as long lived plasma cells, even after just a priming dose[15].

Also important, is the ability to prevent infection, as measured by in vitro neutralization assays. Early vaccines against denatured L1 failed in animal studies because they did not induce neutralizing antibodies. Correlations between neutralizing activity and avidity were not observed for individuals enrolled in the clinical trials (thus, suggesting that the antibody response in almost all individuals is above the threshold required for good neutralizing activity, although more data is needed on this).

The antibody responses are different after natural infection compared with HPV L1 VLP vaccination. After natural infection, 70-80% of women seroconvert and their antibody responses are typically slow, weak and of low avidity. But this is sufficient for antibodies generated in natural infections to be usually protective against subsequent incident infection. Following HPV L1 VLP vaccination, in contrast, close to 100% of women seroconvert after the first vaccine dose (priming). Peak antibody titers reach levels 10-1000 times greater than in natural infections and are of much higher avidity – i.e. protective capacity (ref). Neutralizing antibodies persist for >9 years post immunization (longer time point assessed) in women. These high-level and high-avidity antibody responses persist such that unquestionable to date, vaccine failures have not yet been identified in clinical studies, precluding the identification of a minimal antibody threshold level that correlates with the protection. No specific immune correlate is thus yet available.[16]

In addition to quantity and quality, kinetics are critically important for HPV-vaccine induced protection : 1) memory B cells elicited by the first vaccine dose require at least 4-6 months to mature and differentiate into high-affinity B cells. This implies that any immunization schedule must include at least a 4 month interval before the last dose (prime-boost) to efficiently reactivate memory B cells. Two dose schedules with shorter intervals (prime-prime) might not allow this affinity maturation and are expected to be less immunogenic / protective. 2) antibody persistence, i.e. the plateau of antibodies produced by long-lived plasma cells, is best estimated at least 6 months and preferably 12-18 months after the last immunization.

4. EFFECT OF VARIOUS IMMUNIZATION SCHEDULES ON VARIOUS OUTCOMES

Antibody concentration is the parameter currently used to assess HPV vaccine immunogenicity; as there is no defined immune correlate of protection. Clinical studies have demonstrated that both licensed HPV vaccines are generally well tolerated, immunogenic and efficacious using a 3 dose schedule (0, (1 or 2), 6 months).

Under current regulatory guidelines, efficacy has been assessed in women aged 15-25 years on disease endpoints (e.g. CIN2+, CIN3+) and virological endpoints (e.g. 6 or 12 months persistent infection at 6 months). These endpoints require invasive gynecological examinations/sampling and might be considered unethical in girls younger than 15 years of age. For both licensed HPV vaccines in girls 9-14 years of age efficacy has been inferred based on antibody immuno-bridging studies.

[15] Dauner JG Vaccine 28:5407-13, 2010 and J Schiller (personal communication on unpublished results that will be presented at the IVP meeting in Seattle, August 2014)

[16] Safaeian et al. 2010 JNCI:102;165; Harper et al Lancet 2006, 367,1247 and; Rowhani-Rahbar A et al. Vaccine 2009;27:5612-5619; Olsson et al. Vaccine. 2007

If bridging studies show that the immune response in the 9 to13-14 year old population is non-inferior to that of the 15-25 year old population, the efficacy of the vaccine is also expected to be similar in the two age groups. This principle is independent of the dosing schedule being assessed.

The interpretation of clinical trials or observational studies reporting vaccine efficacy after 2 versus 3 doses should take into account whether a 2-dose schedule included at least 4 months before the last dose (prime-boost) or not (prime-prime).

Evidence on the effect of fewer than 3 doses of HPV vaccine

Studies assessing 2-dose schedules versus 3-dose schedules[1]

Quadrivalent vaccine

- Two randomised controlled trials (Canada[17,18,19] and India[20,21]) comparing a 2-dose (0, 6 months) with a 3-dose (0, 1 or 2, 6 months) schedule in girls.
- One study provides additional results about immunological outcomes from a within-person comparison of girls (Canada[22]).
- A cohort study in Australia[23] assessing the risk of cervical abnormalities among women ≤ 17 year of age,vaccinated at school.
- A cross-sectional study in Victoria, Australia[24] -the Vaccine Against Cervical Cancer Impact and Effectiveness (VACCINE) study- assessing HPV vaccine-related infection and disease (CIN3) outcome.
- A cohort study using individual-level data in Sweden[25] assessing genital warts (GW) incidence after on-demand vaccination in girls and women aged 10 to 44 years living in Sweden between 2006 and 2010.
- A population based study in Sweden[26] examining the association between HPV vaccination and first occurrence of condyloma acuminata in relation to vaccine doses received.

[17] Dobson, S.R., et al., *Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial.* JAMA, 2013. **309**(17): p. 1793-1802.
[18] Krajden, M., et al., *Human papillomavirus 16 (HPV 16) and HPV 18 antibody responses measured by pseudovirus neutralization and competitive Luminex assays in a two- versus three-dose HPV vaccine trial.* Clin Vaccine Immunol, 2011. **18**(3): p. 418-23.
[19] Sankaranarayanan, R., *2 vs 3 doses HPV vaccine schedule: low- and middle-income countries*, in *Eurogin 2013 International Multidisciplinary Congress*. 2013: Florence, Italy.
[20] Sankaranarayanan, R. Trial of Two versus Three Doses of Human Papillomavirus (HPV) Vaccine in India. 2013 [cited 2013 Nov 15]; Available from: http://clinicaltrials.gov/show/NCT00923702.
[21] Sankaranarayanan, R., Evaluation of Fewer Than Three Doses of HPV Vaccination in India, in WHO Consultation Meeting. 2013: WHO, Geneva.
[22] Institut National de Santé Publique du Québec. *La vaccination des pré-adolescents contre les virus du papillome humain (VPH) au Québec : deux ou trois doses?* 2013 [cited 2013 Nov 14]; http://www.inspq.qc.ca/pdf/publications/1683_VaccinPreAdoVPHQc_2ou3Doses.pdf.
[23] Gertig, D.M., et al., Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. BMC Med, 2013. 11(1): p. 227
[24] Garland, S.M., et al. Measures of vaccine effectiveness. Abstract no. SS 22-7 in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy
[25] Leval, A., et al., Quadrivalent human papillomavirus vaccine effectiveness: a Swedish national cohort study. J Natl Cancer Inst, 2013. 105(7): p. 469-74.

- A population based study in Denmark[27] assessing the association between receipt of at least one dose of HPV vaccine and its effect on risk of genital warts.
- A case control study in Australia[28] estimating the effectiveness of the vaccine in women partially (one or two doses) vaccinated or fully vaccinated (≥ 3 doses).

Bivalent vaccine

- One randomised controlled trial Canada/Germany1[29 30 31] comparing a 2-dose (0, 6 months) with a 3-dose (0, 1 or 2, 6 months) schedule in girls.
- Three non-randomised controlled trials, Canada/Germany29 30 31, Mexico[32], Multinational2[33 34 35] comparing a 2-dose schedule in girls with a 3-dose schedule in women.
- Two additional studies also reported on immunological outcomes. A study including randomised comparisons of women (Europe[36]) and, an observational study of girls (Uganda)[37].
- Two additional clinical trials reporting data about clinical outcomes from non-randomised comparisons of partially vaccinated women within clinical efficacy trials that enrolled women (Costa Rica[38 39 40] and Multinationalx[41 42]). Women receiving two doses at 0 and 1 month were compared to women receiving three doses at 0, 1 and 6 months.

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[26] Herweijer, E., Association of Varying Number of Doses of Quadrivalent Human Papillomavirus Vaccine With Incidence of Condyloma. JAMA. 2014;311(6):597-603. doi:10.1001/jama.2014.95.

[28] Crowe, E. et al., Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. BMJ 2014;348:g1458.

[28] Crowe, E. et al., Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. BMJ 2014;348:g1458.

[29] Romanowski, B., et al., Immune response to the hpv-16/18 as04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination, in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

[30] Romanowski, B., et al., Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study. Hum Vaccin, 2011. 7(12): p. 1374-86.

[31] GlaxoSmithKline. *Evaluation of the safety and immunogenicity of GlaxoSmithKline Biologicals' HPV vaccine 580299 when administered in healthy females aged 9 – 25 years using an alternative schedule and an alternative dosing as compared to the standard schedule and dosing.* 2013 [cited 2013 Nov 14]; Available from: http://download.gsk-clinicalstudyregister.com/files/ebe3f40a-ef27-469c-8874-35053b5a80d7

[32] Lazcano-Ponce, E.S., M.; Muñoz, N.; Torres, L.; Cruz-Valdez, A.; Salmerón, J.; Rojas, R.; Herrero, R.; Hernández-Ávila, M, Overcoming barriers to HPV vaccination: Non-inferiority of Antibody Response to Human Papillomavirus 16/18 Vaccine in Adolescents Vaccinated with a Two-dose vs. a Three-dose Schedule at 21 Months. Vaccine 32 (2014) 725-732..

[33] EMA. *European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) Assessment report EMA/789820/2013 Cervarix* 2013 21st November 2013.

[34] GlaxoSmithKline. Immunogenicity and safety study of GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV)-16/18 L1 AS04 vaccine when administered according to alternative 2-dose schedules in 9 - 14 year old females. 2013 [cited 2013 Nov 14]; Available from: http://download.gsk-clinicalstudyregister.com/files/1ae03c85-a5fe-4339-a1e1-03a3d97f6793.

[35] Puthanakit, T., et al., Immune responses to a 2-dose schedule of the hpv-16/18 as04-adjuvanted vaccine in girls (9-14) versus 3 doses in women (15-25): a randomised trial, in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

[36] Esposito, S., et al., Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted vaccine administered according to an alternative dosing schedule compared with the standard dosing schedule in healthy women aged 15 to 25 years: results from a randomized study. Pediatr Infect Dis J, 2011. 30(3): p. e49-55.

[37] Safaeien, M., Immunogenicity of the bivalent HPV vaccine among partially vaccinated young girls in Uganda, in 28th International Papillomavirus Conference & Clinical and Public Health Workshops, Abstract book page no. 326. 2012: San Juan, Puerto Rico. p. 326.

[38] EMA. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) Assessment report EMA/789820/2013 Cervarix 2013 21st November 2013.

[39] Kreimer, A.R., et al., Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women: a nested analysis within the Costa Rica Vaccine Trial. Lancet Oncol., 2011. 12(9): p. 862-70. doi: 10.1016/S1470-2045(11)70213-3. Epub 2011 Aug 22.

One additional RCT providing data for women aged 15-25 years[43, 3,4] . This trial in Europe (Italy, Romania, and Slovakia) compared two 3-dose schedules (extended: 0, 1, 12 months vs. standard: 0, 1, 6 months). For the extended schedule, data are available at month two (one month after the second dose) and compared with month seven (one month after the third dose of the standard schedule).

Summary of studies assessing 2-dose schedule versus 3-dose schedules[1]

Quadrivalent vaccine	Bivalent vaccine
Geometric mean antibody concentrations	
In randomised comparisons: ○ for HPV16, 1 month after the last dose, geometric mean concentrations (GMCs) in the 2-dose group were lower but non-inferior compared with the 3-dose group in Canada17 18 19. ○ in India[19,20,21] the ratio of antibody levels was higher in the 2-dose group. For HPV18 the GMC in the 2-dose group is non-inferior to that in the 3-dose group. ○ at 24 months, results from Canada17 18 19 were lower in the 2-dose group for both HPV16 and 18 and the lower 95% confidence interval included the non-inferiority margin. Lower bounds for the confidence interval are below the non-inferiority margin for HPV18. ○ The weighted mean difference for the GMC in girls receiving the 2-dose schedule in Canada17 18 19 is non-inferior to the 3-dose schedule. Results are inconclusive for the other measured outcomes. ○ at 36 months, the GMC ratio for HPV16 was non-inferior (0.81. 95% CI 0.55, 1.20) and inconclusive for HPV18 (0.43, 95% CI 0.26, 0.73). ○ in the India20 21 trial, comparisons favoured the 2-dose schedule. The weighted mean differences correspond to a mean fluorescence index for HPV16 of 1.2 (1.0, 1.2) and for HPV18 1.0 (1.0, 1.2)	In the randomised comparison: ○ for HPV16, 1 month after the last dose, geometric mean concentrations (GMCs) in the 2-dose group were lower but non-inferior compared with the 3-dose group In Canada/Germany29 30 31. The lower bound of the confidence interval is below that non-inferiority margin but the upper bound is above it so the result is inconclusive. ○ for HPV18 the GMC in the 2-dose group is non-inferior to that in the 3-dose group. ○ at 24 months, results from Canada/Germany29 30 31 were lower in the 2-dose group for both HPV16 and 18 and the lower 95% confidence interval included the non-inferiority margin. Lower bounds for the confidence interval are below the non-inferiority margin for HPV18 for HPV16 in Canada/Germany. In non-randomised comparisons, ○ GMCs were non-inferior or superior in girls receiving the 2-dose schedule compared with women receiving the 3-dose schedule in all four trials at all-time points assessed, up to 24 months after vaccination. ○ immunogenicity results showed that a 2-dose schedule of bivalent vaccine administered at 0, 6 months in 9-14 years old females was non-inferior to the standard 3-dose schedule in females aged 15-25 years at all-time points tested up to month 48[4].

[40] Kreimer, A.R., et al., Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. J Natl Cancer Inst, 2011. 103(19): p. 1444-51.

[41] EMA. *European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) Assessment report EMA/789820/2013 Cervarix* 2013 21st November 2013.

[42] Arguedas, A., et al., *Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines.* Vaccine., 2010. **28**(18): p. 3171-9. doi: 10.1016/j.vaccine.2010.02.045. Epub 2010 Feb 26.

[43] Esposito, S., et al., Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted vaccine administered according to an alternative dosing schedule compared with the standard dosing schedule in healthy women aged 15 to 25 years: results from a randomized study. Pediatr Infect Dis J, 2011. 30(3): p. e49-55

Quadrivalent vaccine	Bivalent vaccine
	In addition, exploratory or post-hoc analyses of vaccine efficacy at month 48 after the first vaccine dose among women aged 18-25 years who received only two doses demonstrate that two doses effectively protect against persistent infection due to HPV-16/18 combined (VE: 100 % [33.1%; 100] and 84.1% [50.2%; 96.3%][4] . Comparisons in women (Europe36), an observational study of girls (Uganda37) had overall findings about immunological outcomes that support those reported above. In the Europe36 trial, the investigators compared women one month after receiving two doses (of an extended 3-dose schedule) at 0, 1 month and women one month after receiving the licensed schedule (0, 1, 6 months). In this comparison of GMCs, the 2-dose schedule was inferior to the 3-dose schedule (weighted mean difference HPV16, -1.17, 95% CI -1.30, -1.05; HPV18, -0.53, 95% CI -0.66, -0.39).
Seroconversion and seropositivity	
Seroconversion and seropositivity, assessed in Canada17 18 19 were non-inferior at all-time points assessed except at 24 and 36 months in Canada17, 18, 19, when they were inconclusive.	Seroconversion and seropositivity, assessed in Canada/Germany29 30 31 were non-inferior at all-time points assessed. In non-randomised comparisons, available data for seroconversion and seropositivity showed non-inferiority of the 2-dose compared with the 3-dose schedule.
Clinical Outcomes	
The RCT in India20 21 provided limited data about clinical outcomes: incident infections with any of the vaccine types in the quadrivalent vaccine were more common in the 2-dose than the 3-dose group.	In non-randomised comparisons, there were no clinical outcome data available for these four controlled trials. Data about clinical outcomes come from non-randomised comparisons of partially vaccinated women within clinical efficacy trials that enrolled women (Costa Rica38 39 40 and Multinationalx41 42). Women receiving two doses at 0 and 1 month were compared to women receiving three doses at 0, 1 and 6 months. The results supported the 2-dose schedule. The efficacy against virological endpoints in initially HPV-naïve subjects who received 2 doses of vaccine in a trial in Europe (Italy, Romania, Slovakia) as observed at month 48 (end-of-study analysis) indicates that the HPV-16/18 vaccine also prevents HPV-16/18 infection in subjects who did not receive a complete 3-dose vaccination course[4].

Quadrivalent vaccine	Bivalent vaccine
Observational studies	
In the cohort study (Australia23) detection rates of histologically confirmed high-grade (HG) cervical abnormalities and high-grade cytology (HGC) were significantly lower for vaccinated women (any dose) (HG 4.8 per 1,000 person-years, HGC 11.9 per 1,000 person-years) compared with unvaccinated women (HG 6.4 per 1,000 person-years, HGC 15.3 per 1,000 person-years) HR 0.72 (95% CI 0.58 to 0.91) and HR 0.75 (95% CI 0.65 to 0.87), respectively. The HR for low-grade (LG) cytological abnormalities was 0.76 (95% CI 0.72 to 0.80). Vaccine effectiveness adjusted a priori for age at first screening, socioeconomic status and remoteness index, for women who were completely vaccinated, was greatest for CIN3+/ adenocarcinoma in situ (AIS) at 47.5% (95% CI 22.7 to 64.4) and 36.4% (95% CI 9.8 to 55.1) for women who received any dose of vaccine, and was negatively associated with age. In an interim analysis of the cross-sectional study in Victoria, Australia[24] 395 subjects for sub-study A, the prevalence of HPV16 was only 1.6% (95%CI 0.6-3.5%) and for any high risk HPV type was 14.4% (11.0 18.4%). No HPV18 was detected. Eighty one percent of the cohort was fully vaccinated. In the cohort study in Sweden25 vaccine effectiveness was 76% (95% CI = 73% to 9%) among those who received three doses of the vaccine with their first dose before age 20 years. Vaccine effectiveness was highest in girls vaccinated before age 14 years (effectiveness = 93%, 95% CI = 73% to 98%). In the population based study in Sweden26 among those individuals aged 10 to 16 years at first vaccination, receipt of 3 doses was associated with an IRR of 0.18 (95%CI, 0.15-0.22) for condyloma, whereas receipt of 2 doses was associated with an IRR of 0.29 (95%CI, 0.21-0.40). The number of prevented cases between 3 and 2 doses was 59 (95%CI, 2-117) per 100 000 person-years. A maximum reduction in condyloma risk was seen after receipt of 3 doses of quadrivalent HPV vaccine, receipt of 1 or 2 vaccine doses was also associated with a considerable reduction in condyloma risk. No GWs occurred among vaccinated girls in the youngest birth cohort.	The study in Uganda37 reported that ratio of HPV16 and HPV18 GMTs comparing 2 dose to 3 dose groups were 0.51 (97.5%CI=0.37-0.69), and 0.69 (97.5%CI=0.50-0.96).

Quadrivalent vaccine	Bivalent vaccine
The study in Denmark27 that included girls and women from birth cohorts 1989–1999, which had a vaccine coverage rate (at least 1 dose) >10% reported that where age was taken into account, the relative risk of of GWs among vaccinated girls compared to unvaccinated girls was significantly decreased in vaccinated girls (i.e. having received at least 1 dose), and varied between 0.12 (95% confidence interval,04–.36, P< .001) in girls born during 1995–1996 and 0.62 (95% CI, .50–.76, P< .001) in girls born during 1989–1990, the trend of an increasing risk reduction with the younger birth cohort being statistically significant (P <.0001) The case control study in Australia[28] reported that the adjusted odds ratio for exposure to three doses of HPV vaccine compared with no vaccine was 0.54 (95% CI 0.43 to 0.67) for high grade cases and 0.66 (0.62 to 0.70) for other cases compared with controls with normal cytology, VE of 46% and 34%, respectively. The adjusted exposure odds ratios for two vaccine doses were 0.79 (95% confidence interval 0.64 to 0.98) for high grade cases and 0.79 (0.74 to 0.85) for other cases, VE of 21%.	

2-dose schedule versus 2-dose schedule: comparing different intervals between doses

Two RCTs using the bi-valent vaccine compared two 2-dose schedules with different intervals (Canada/Germany[29] [30] [31], 0, 2 vs. 0, 6 months) and Multinational2[41] [42] (0, 6 vs. 0, 12 months).

Results for Canada/Germany[29] [30] [31] indicated that the 6-month interval resulted in superior GMCs compared with the 2-month interval one month after the last vaccine dose in all age groups enrolled (9-14, 15-19, 20-25 years). There are no data yet publically available from the Multinational2 study.

Summary of findings

2-dose schedule versus 3-dose schedules

- In randomised comparisons, 1 month after the last dose, geometric mean concentrations (GMCs) in the 2-dose group were lower but non-inferior or inconclusive compared with the 3-dose group. Seroconversion and seropositivity were non-inferior or inconclusive at alltime.
- In non-randomised comparisons, GMCs were non-inferior or superior in girls receiving the a 2-dose schedule compared with women receiving the 3-dose schedule at all time points assessed, up to 36 months after vaccination. All available data for seroconversion

and seropositivity showed non-inferiority of the 2-dose compared with the 3-dose schedule.

- Limited data about clinical outcomes. The efficacy against virological endpoints in initially HPV-naïve subjects who received 2 doses of bivalent vaccine at month 48 indicates that the two-dose schedule prevents HPV-16/18 infection in subjects who did not receive a complete 3-dose vaccination course[4]. In the randomized comparisons, in one study, incident infections with any of the vaccine types in the quadrivalent vaccine were more common in the 2-dose than the 3-dose group.
- Observational data overall support the findings from the trials. However, a number of considerations regarding these studies must be noted:
    - In the Australian observational linkage study (including attempts to reduce residual confounding) the vaccine effectiveness for two doses is estimated as less than for 3 doses for histological outcomes.
    - A stronger trend associated with age was observed. However, authors reported low evidence of effect until they control for age at vaccination and screening (an attempt to address issues associated with residual confounding).
    - There was a striking effect of vaccination associated with first screening (which in Australia takes place at 18 years of age). In addition, there were small numbers of girls 12-13 years of age receiving fewer doses, usually at a less than 4-6 months interval, and there are considerations to the effect that girls with incomplete immunization schedules maybe be different from those with 3-dose schedule.
    - In Sweden, an observational study using condyloma acuminata as the outcome of interest reported greater effect of greater number of doses. However, interpretations of results must include consideration to the so called *buffer period* (between vaccination and condyloma incidence – used as a proxy measure for prevalent HPV-infections) and interval between doses, which may result in an artifactual difference between 2 and 3 dose schedules. Data suggest that the differences between 2-dose schedule and 3-dose schedule were reduced, the *buffer* period was longer.

2-dose schedule versus 2-dose schedules: wider interval between doses

Two RCTs compared two 2-dose schedules with different intervals (0, 6 and 0, 12 months).

- Data from one of them reported that the 6-month interval resulted in superior GMCs compared with the 2-month interval one month after the last vaccine dose in all age groups enrolled (9-14, 15-19, 20-25 years).

5. ROLE OF MATHEMATICAL MODELS TO INFORM IMPACT EVALUATION OF VARIOUS IMMUNIZATION SCHEDULES

The anticipated impact and cost-effectiveness of HPV vaccination has been extensively investigated in high-income countries, and this has provided the economic case for widespread vaccine adoption by majority of countries in the developed world. The findings of two models one from the United Kingdom (UK) and one from Canada were reviewed. Details of both models are summarized below.

UK model[44]	Canadian model (HPV-ADVISE)[45]
Compartmental transmission dynamic model of HPV infection, sexual transmission and natural history.	Individual-based transmission dynamic model of HPV infection, sexual transmission and natural history.
Models cervical neoplasia and cancers (squamous and glandular) due to HPV 16, 18 and other high risk types.	Models cervical neoplasia and cancers (squamous and glandular) due to HPV 16, 18 and other high risk types.
Used to inform UK vaccination policy.	Used to inform Canadian vaccination policy.

Both the UK and the Canadian model predicted that under the hypothetical assumption that a female-only two dose schedule has a duration of protection of at least 20 years, there will be few additional cases prevented by adding a third dose. However, if duration of protection is assumed to be below 10 years, then the additional benefit of the third dose is much greater.

Therefore, assumptions on the duration of protection are important. HPV vaccines have already demonstrated no waning of efficacy (for 3 doses) for almost ten years when given to young adolescent girls (through the peak years of HPV acquisition). If 2 doses provide long-lasting protection, as expected from the similar durability of antibody responses, we would expect them to behave in the same way.

The Canadian model further suggests that there will be little benefit in extending the target group to include boys.

Relative importance of HPV vaccine characteristics (in terms of population impact):

Duration of protection > cross-protection > initial efficacy (within 85%-100% range).

In high-income settings (such as the UK and Canada), if it is documented that a 2-dose vaccination confers more than 10-20 years protection then adding the third dose is not cost-effective. If it is documented that a 2-dose vaccination only provides up to 10 years protection, then adding the third dose may be cost-effective. The cost-effectiveness of 2-dose vs. 3-dose vaccination in low/middle income settings still needs to be explored.

6. IMPORTANT ISSUES FOR CONSIDERATION

HPV experts reviewed and discussed the available evidence during the WHO Ad hoc Expert Consultation on Human Papilloma Virus Vaccine schedules organized in Geneva, November 18, 2013. In addition, the draft of this background document was circulated and comments were provided by the same experts via electronic mail in March 2014.

Below is a summary of the main points raised during these interactions.

[44] Jit et al. BMJ 2008; 337:a769; Choi et al. Vaccine 2010; 28:4091 and; Jit et al. BMJ 2011; 343:d5775
[45] www.hpv-advise.com; Van de Velde et al. Vaccine 2010; 28:5473 and; Brisson et al. Vaccine 2013

Progress and challenges with vaccine introduction

- There is disparity between the geographic distribution of the risk of HPV related cancer and the introduction of HPV vaccines, as most of the countries with the highest risk have not introduced the vaccine by November of 2013.
- Costs are among the main barriers for more widespread introduction of HPV vaccines.
- There are other implementation challenges with the introduction of HPV vaccines. Reaching high immunization coverage and estimating the HPV vaccine coverage achieved are both challenging. Some of the reasons for low coverage include the need to target various cohorts, the fact that current schedules require 3 doses to be administered within a 6 month period, the use of catch-up vaccination for introduction and the uncertainty of the denominator. Furthermore, tailored delivery strategies to reach all girls (including those not attending school), and special social communication strategies are required.

Use of immunogenicity data to inform policy recommendations on HPV schedules

- The available serological assays provide only a partial characterization of the immune status in vaccinated individuals. The observation that protection against HPV18 persists after antibodies become undetectable in some assays, as well as animal studies, suggests that the minimal antibody threshold required for protection is below the detection threshold of current assays. It is important to point out that the assay measuring HPV 18 antibody concentration measures only one antibody species, as when total anti-18 antibody is measured then seropositivity remains.
- Antibody concentration standard assay protocols are essential to compare various schedules in various settings. Antibody concentrations should be reported in International Units.
- The available immunogenicity data from bivalent vaccine indicates that both antibody quantity (titers) and quality (avidity) after a 2-dose (prime-boost) schedule in girls are non-inferior to responses after a 3-dose (prime-prime-boost) schedule in women: this is an informative element in risk assessment. It is important to emphasize the in vitro neutralizing titres since they encompass both elements of epitope specificity and avidity.
- The immunogenicity data for the quadrivalent vaccine leads to similar conclusions, but is currently more limited (in vitro neutralization, avidity).
- The induction and persistence at 12 months of non-inferior antibody titers after 2 prime-boost doses in the younger age group compared to adult women suggests that an alternate (0–6 months) and reduced dosing (2 instead of 3) schedule of HPV vaccination could be considered for the younger age group. These proposals, however, do not apply to immunocompromised individuals, because their vaccine responses may be less strong and there is no data with 2-dose schedules from these groups.
- There is limited immunogenicity data for a 0-6 or 0-12 schedule in less than 13 year old females.
- Decision makers need to assess the degree of risk and benefits of various schedules and their ability to implement effective surveillance post immunization and devise risk management strategies in the event of a worst case scenario after 2 or 3 initial doses (e.g. if longer term data indicate the need for additional doses of vaccine).

Evidence on the effect of fewer than 3 doses of HPV vaccine

- The interpretation of clinical trials or observational studies reporting vaccine efficacy after 2 versus 3 doses should take into account the immunological evidence suggesting that a 2-dose schedule must include at least 4 months before the 2nd dose to fulfill the criteria of a prime-boost (and not a prime-prime) schedule.
- Limited data on efficacy and effectiveness with limited follow –up (e.g. up to 4 years) support these findings. The bivalent vaccine has obtained EMA approval for a 2-dose schedule and the quadrivalent vaccine has already obtained a positive opinion of the CHMP. Longer term studies are underway.
- In countries where sufficient immunization coverage will be achieved in the target age groups, the strong herd immunity elicited by HPV vaccines is expected to make a large contribution to protection, reducing the likelihood of the need for late boosters.
- There are limited data on 3-dose schedules[46] in HIV infected populations and no data were identified on schedules using fewer than 3 doses in these populations. As cervical cancer is an AIDS-defining illness, recommendations about a 2-dose schedule might differ for populations with low and high HIV prevalence rates. However, 1) the limited data available indicate that HPV VLPs are strongly immunogenic even in HIV-infected women and 2) this concern might be mitigated if immunizing young adolescent girls prior to the onset of sexual activity to elicit strong and sustained HPV immunity prior to HIV acquisition and subsequent immunosuppression.

Role of mathematical models to inform impact evaluation of various immunization schedules

Models can be useful to inform choice of immunization policies and to estimate cost effectiveness at country and regional level. Information on the duration of protection of various schedules is important. As there are fewer data on duration of protection for the 2-dose schedule, additional data would be informative.

The anticipated impact and cost-effectiveness of 2-dose vs. 3-dose vaccination in low/middle income settings still needs to be explored. In particular it would be informative to explore various implementation scenarios and coverage assumptions and assess their anticipated impact. Moreover, model explorations would help to highlight data needed to inform key variables and assumptions such as the duration of protection and the herd immunity thresholds in various settings.

[46] For example, Quebec, Canada guidelines propose 3 doses, but extended (0, 6, 12) to immunosuppressed pre-adolescents. http://publications.msss.gouv.qc.ca/acrobat/f/documentation/piq/piq_complet.pdf

7. RECOMMENDATIONS FOR SAGE's CONSIDERATION

There are obvious programmatic advantages to reducing the number of doses (e.g. reduced delivery costs), and flexible intervals between doses (e.g. annual doses easier for school-based delivery) might also lead to increase in vaccination coverage.

The 2009 WHO position paper states that the first dose should optimally be given at 9-13 years of age as data suggest that HPV vaccines are most efficacious in girls who are naïve to vaccine-related HPV types; therefore, the primary target population should be selected based on data on the age of initiation of sexual activity[6].

Number of doses	
Recommendation	**Two dose (prime-boost) schedules (including at least 6 months between the first and the 2nd dose) are expected to provide similar protective efficacy compared to 3 dose schedules.** • A 2-dose schedule may be recommended to adolescent girls 9-13 years of age. • For girls primed before the age of 14 years, even if older at time of boosting (second dose), a 2-dose schedule may be considered.
Summary statement	The available evidence, and the understanding of HPV vaccine-mediated protection, indicates that two doses of HPV vaccine in girls 9-14 years of age are non-inferior to 3 doses in terms of immunogenicity when compared to 3 doses in girls 9-14 years or 3 doses in older women 15-24 years of age. The magnitude of the vaccine response is determined by the age at the first dose. Data indicate that following a 2-dose prime-boost schedule antibody titers in girls 9-14 years of age are mostly non-inferior to 3-dose titers in girls and are non-inferior to those in older young women. The inference is that a 2-dose vaccine schedule will be as efficacious as 3 doses, even though clinical efficacy data in girls are not available. Data on efficacy and effectiveness with limited follow–up (e.g. up to 4 years) support these findings. The bivalent vaccine has obtained EMA approval for a 2-dose schedule and the quadrivalent vaccine has already obtained a positive opinion of the CHMP.
Caution	There are fewer data comparing the efficacy of 2 versus 3 dose schedules. Longer term studies are underway. No data on fewer than 3 doses among HIV infected and immune-compromised populations are available.

Interval between doses	
Recommendation	**For 2-dose schedules, the minimal interval between doses should be 6 months.** The interval between the first and second dose may be extended up to 12 months should this facilitate administration – for example in school settings.
Summary statement	A second dose of vaccine given ≥ 6 months after the first dose (prime-boost) elicits an immune response non-inferior to that of a 3-dose schedule that uses a prime-prime boost approach. Data from one RCT reported that the 6-month interval resulted in superior GMCs compared with the 2-month interval one month after the last vaccine dose in all age groups enrolled (9-14, 15-19, 20-25 years). Results from a multi-centric study would be available in the mid-term.
Caution	Data available is from one RCT

Special populations	
Recommendation	**The recommendation to target very young (9-10 year old girls) prior to sexual debut and risk of HIV acquisition is especially important in areas where HIV is prevalent.** o A 3-dose schedule should be offered to individuals known to be immunocompromised at time of immunization
Summary statement	Although the immunogenicity and efficacy of HPV vaccines may be reduced in HIV-infected females, the potential benefit of vaccination in this group is particularly great owing to their increased risk of HPV-related disease, including cervical cancer.
Caution	There are limited data from HIV-infected individuals receiving a 3-dose schedule and, no data from HIV-infected individuals receiving a 2-dose schedule.

8. RESEARCH PRIORITIES

Although some additional evidence is desirable, the participants concluded that these research priorities should not delay the development of recommendations related to a 2-dose schedule for HPV vaccine. The following research questions that could help inform future policy recommendations were outlined:

- It is very important to ensure the follow up of the cohorts under study in India and to duplicate similar studies in other settings, especially in LMICs.
- Definition of end points for second generation vaccines (e.g. immunogenicity end points) would provide additional guidance for the evaluation of alternative immunization schedules including 2- or 1-dose schedules with different intervals between doses (e.g. extended schedules) and in different epidemiological settings.
- Given that the two currently licensed vaccines are different and use different adjuvants, there is value in conducting head to head comparisons of various alternative schedules.
- Longer-term clinical effectiveness studies are needed to formally define the duration of protection after a 3-dose schedule, and whether a booster may be needed at some point given that immune memory is unlikely to be reactivated by exposure. This also applies to 2-dose schedules. High efficacy over time is needed because women continue to be at risk for infection, and the period of risk may vary from one culture to another.
- Studies must be done in regions where high rates of vaccination have not yet occurred because of high herd protection conferred by the 3-dose regimen.
- Multicenter studies in low income countries among healthy adolescent girls and among special populations (e.g. HIV-infected, malnourished adolescents, endemic malaria infection) would also provide additional evidence.
- The impact of various HPV vaccination schedules among HIV-infected individuals is important. Perhaps all available data – also limited- should be systematically reviewed and assessed.
- The anticipated impact of cost-effectiveness of 2-dose vs. 3-dose vaccination in low/middle income settings still needs to be explored. Additional model and economic evaluations that consider alternative scenarios of low coverage and various assumptions on effectiveness and duration of protection in LMICs are important.
- The group noted that the US National Cancer Institute (NCI) is considering an RCT to assess the effect on persistence of DNA and immunogenicity of HPV vaccines after 1 or 2 doses in an area with low to moderate vaccine uptake.

9. Appendices

Appendix 1. HPV vaccines: systematic review of alternative vaccination schedules

Appendix 2. HPV vaccines: non-systematic review of the data from observational studies

10. Annexes

Annex 1
List of Participants and Agenda of the Ad hoc Expert Consultation on Human Papilloma Virus Vaccine schedules organized in Geneva, November 18, 2013

List of Participants
Sir Andrew Hall (Chairperson)

Julia Brotherton – Victorian Cytology Service (via Webex)
Maddalena D'Addario – University of Bern
Lisen Arnheim Dahlstrom – Karolinska Institutet
Simon Dobson - BC Children's Hospital
Dorota Gertig – Victorian Cytology Service (via Webex)
Vladimir Gilca – Institut national de santé public du Québec
Mark Jit – Public Health England
Eduardo Lazcano-Ponce – Mexico Institute of Public Health
Amy Leval – Karolinska Institutet
Lauri Markowitz – CDC
Rengaswamy Sankaranarayanan – IARC
Chantal Sauvageau - Institut national de santé public du Québec
John Schiller – NIH/NIAID
Claire-Anne Siegrist – Centre Médical Universitaire
Margaret Stanley – University of Cambridge

Industry representatives
Attila Mihalyi – GSK
Alfred Saah - Merck

WHO Secretariat
Paul Bloem, EPI/IVB
Philippe Duclos, DO IVB
Tracy Goodman, EPI/IVB
Sami Gottlieb, RHR
Ana Maria Henao-Restrepo DO/IVB
Olivier Lapujade, HIS/EMP
Drew Meek, HIS/EMP/PQT
Ximena Riveros, IVR/IVB
Susan Wang, EPI/IVB

Appendix 1

UNIVERSITÄT BERN

HPV vaccines: systematic review of literature on alternative vaccination schedules

Report on a two doses vs. three doses schedule

3rd March 2014

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Contents

Summary

This report summarises data to inform the discussion about optimal schedules for HPV vaccines for adolescent girls living in different epidemiological settings.

The included studies were identified in a systematic review and cover available immunological and clinical outcomes for comparisons of: 2-dose schedules in adolescent girls (the target group for primary HPV vaccination) versus 3-dose schedules in adolescent girls or women; and 2-dose schedules versus alternative 2-dose schedules.

2-dose schedule versus 3-dose schedules

Comparisons between 2-dose HPV vaccination schedules in girls in the target age group and the licensed 3-dose schedule cannot be randomised if the comparison group is women in the age group amongst whom clinical efficacy was established. The least biased comparisons are controlled trials that enrol girls and women concurrently using the same clinical trial protocol. Randomised comparisons are possible between girls (or women) of the same age who are enrolled and allocated at random to a 2-dose or 3-dose schedule.

We identified three randomised controlled trials (RCTs, Canada1 (quadrivalent), Canada/Germany1 (bivalent), India (quadrivalent)) comparing a 2-dose (0, 6 months) with a 3-dose (0, 1 or 2, 6 months) schedule in girls and four non-randomised controlled trials (Canada1, Canada/Germany1, Mexico (bivalent), Multinational2 (bivalent)) comparing a 2-dose schedule in girls with a 3-dose schedule in women.

In randomised comparisons, 1 month after the last dose, geometric mean concentrations (GMCs) in the 2-dose group were lower but non-inferior or inconclusive compared with the 3-dose group in Canada1 and Canada/Germany1. In India the ratio of antibody levels was higher in the 2-dose group. At 24 months, results from Canada1 and Canada/Germany1 were lower in the 2-dose group and the lower 95% confidence interval included the non-inferiority margin. Seroconversion and seropositivity, assessed in Canada1 and Canada/Germany1 were non-inferior at all time points assessed except at 24 and 36 months in Canada1, when they were inconclusive. The RCT in India provided limited data about clinical outcomes: incident infections with any of the vaccine types in the quadrivalent vaccine were more common in the 2-dose than the 3-dose group.

In non-randomised comparisons, GMCs were non-inferior or superior in girls receiving the 2-dose schedule compared with women receiving the 3-dose schedule in all four trials at all time points assessed, up to 24 months after vaccination. All available data for seroconversion and seropositivity showed non-inferiority of the 2-dose compared with the 3-dose schedule. There were no clinical outcome data available for these four controlled trials.

2-dose schedule versus 2-dose schedules

Two-dose schedules can vary according to the interval between doses or the dosage of vaccine subtypes. Schedules can be evaluated in RCTs in girls in the target age group for HPV vaccination.

We identified two RCTs comparing two 2-dose schedules with different intervals (Canada/Germany1, 0, 2 vs. 0, 6 months) and Multinational2 (0,6 vs. 0,12 months). Results are only available for Canada/Germany1. The 6-month interval resulted in superior GMCs compared with the 2-month interval one month after the last vaccine dose in all age groups enrolled (9-14, 15-19, 20-25 years).

We found one trial (Canada/Germany1) that compared different dosages of HPV (40µg vs. 20µg) given in a 2-dose schedule (0, 6 months). The higher dosage elicited higher GMCs.

1 Introduction

1.1 Background to comparisons of 2-dose and 3-dose HPV vaccine schedules

HPV vaccine has been licensed in >100 countries around the world. High levels of vaccine uptake have been achieved in some countries, e.g. Australia, but uptake has been sub-optimal in many countries. There are fewer organised opportunities for vaccinating adolescents, especially where secondary school attendance is low. Vaccination schedules would be simpler and cheaper if fewer doses could be used to achieve the same clinical effect.

Two HPV vaccines are licensed for use in adolescent girls, a bivalent vaccine containing purified L1 proteins (referring to the late protein expression region of the genome) from HPV types 16 and 18 (Cervarix, GlaxoSmithKline) and a quadrivalent vaccine containing purified L1 proteins from HPV types 6, 11, 16 and 18 (Gardasil, Merck).

The randomised trials (RCTs) that were done to obtain licensure compared 3 doses of HPV vaccine with placebo in 16-26 year old women. Pre-coital adolescent girls could not be enrolled for ethical and practical reasons. Both vaccines showed high levels of protection against cervical intraepithelial neoplasia grade two or above.

The license for use in adolescent girls was obtained through bridging studies showing that antibody responses in adolescent girls receiving the same 3-dose schedule were non-inferior to those in 16-26 year old women (Figure 1).

There are some interesting challenges involved in comparing the effects of 2-dose and 3-dose HPV vaccine schedules:

a. The published clinical efficacy data about cervical intraepithelial neoplasia from RCTs are in women, but the main target population for vaccination is 9-14 year old girls;
b. These groups cannot be compared in RCTs because you cannot allocate people to different age groups;
c. There might be age-related immunological differences in the initial response to HPV vaccine and to the persistence of immune responses over time;
d. The published data to date are for immunological outcomes and there are no publicly available data from RCTs about the clinical efficacy of 2-dose schedules in adolescents.

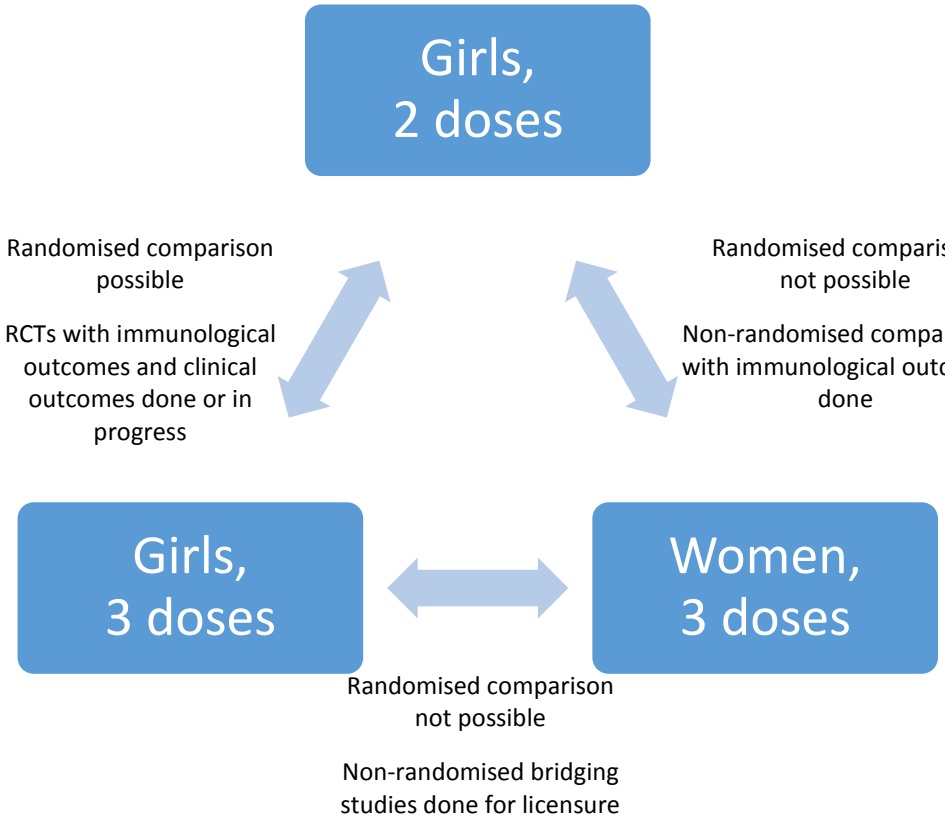

Figure 1: Desired and available comparisons between schedules and target populations

Girls, includes pre-coital girls and adolescents, generally aged 9 to 14 years; women, includes pre- or post-coital women, generally aged 16 to 26 years

1.1.1 Description and terminology used for comparisons between two and three doses of HPV vaccine

We describe two main types of comparisons between schedules for which we present data about the effects of two doses and three doses of HPV vaccine:

a. **Randomised comparisons within girls of the same age group of a study population that has been randomly allocated to receive different schedules of HPV vaccine;**

b. **Non-randomised comparisons between different age groups that have received different schedules of HPV vaccine in girls and women enrolled using the same study protocol and, according to age, allocated to receive two or three doses.**

Additional evidence can be derived from studies with other study populations or other designs. The risk of bias is higher for non-randomised comparisons within the same age group than for randomised comparisons:

c. **Randomised comparisons within women of the same age group of a study population that has been randomly allocated to receive different schedules of HPV vaccine;**

d. **Non-randomised comparisons within the same age group of a study population in which participants**
   i. Were randomly allocated to a 3-dose vaccination schedule but some received only two doses;
   ii. Were not randomly allocated and participants received different numbers of vaccine doses, e.g. non-randomised controlled clinical trial or observational study within a demonstration project;

1.1.2 Immunological outcomes of HPV vaccination

HPV vaccine induces high levels of antibody against type-specific HPV L1 virus like proteins, which protect against clinical disease in women without evidence of previous exposure to a specific HPV type [1]. Seroconversion from antibody negative to antibody positive (any detectable antibody) status occurs in almost all vaccinated individuals. There is currently no immune correlate of protection.

Laboratory tests to measure antibody concentrations differ for the two HPV vaccines [1]. This makes it difficult to compare absolute levels of antibody between studies that have used different vaccines.

Immunological responses can be presented as:

- Absolute levels of antibodies (usually presented as geometric mean antibody concentrations, GMCs)
- A percentage of the study population with antibodies above a given threshold which, for HPV is an antibody concentration greater than the assay threshold for a specific HPV type. The percentage with antibodies can be presented as:
    - The overall percentage seropositive
    - The percentage with evidence of seroconversion, i.e. post-vaccination seropositivity amongst individuals without detectable antibody before vaccination.

For trials of HPV vaccines, the percentages seropositive and seroconverting are often the same because analysis in RCTs is often restricted to participants who have no serological evidence of pervious exposure to HPV.

In published studies, data are more often presented as GMCs than as percentages seroconverting or seropositive after vaccination.

Non-inferiority between immunological responses with two and three doses

Given that the licensed 3-dose HPV vaccination schedule is highly efficacious in preventing pre-cancerous cervical lesions caused by HPV 16 and 18, the evidence about 2-dose vaccination schedules needs to come from trials designed to show non-inferiority. Non-inferiority means that a new treatment (e.g. a 2-dose schedule) is no worse than the existing treatment (3-dose schedule), by more than a pre-determined amount [2]. A standard approach is to hypothesise that there is no real difference between the two vaccination schedules. The confidence intervals of the observed absolute difference are then used to decide whether the new treatment is non-inferior.

Figure 2 shows different possible scenarios in trials and how the confidence intervals for the observed difference are interpreted in a non-inferiority trial. We based the figure on one presented by the authors of the CONSORT (Consolidated Standards of Reporting in Trials) Statement on the

reporting of non-inferiority trials [2]. The orientation of the figure corresponds to the convention that we used in this review; 2-dose (new treatment) *minus* 3-dose (conventional treatment).

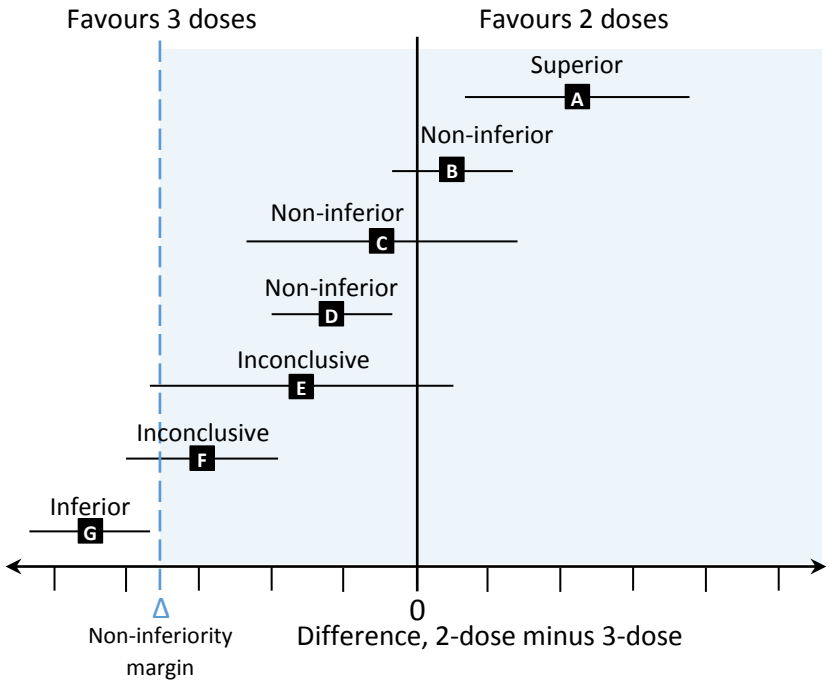

Figure 2. Interpretation of differences between 2-dose and 3-dose schedules of HPV vaccines in non-inferiority trials

Generic forest plot. Boxes indicate point estimates of effect size, error bars are 95% CI. Solid black line is null effect. Blue dashed line is the non-inferiority margin at Δ (difference between 2-dose and 3-dose schedule). Scenario A, 2-dose schedule is superior to 3-dose schedule; scenarios B, C, D, 2-dose HPV schedule is non-inferior to the standard 3-dose schedule because the lower 95% CI is to the right of the non-inferiority margin; scenarios E and F are inconclusive because the lower 95% CI includes the non-inferiority margin; scenario G, 2-dose schedule is inferior to the 3-dose schedule. Based on Piaggio G et al. [2].

2 Review methods

This report covers all evidence deriving from the systematic review of literature on comparisons 1 as described below in order to answer the review question. . The systematic review concerning comparison 2 and 3 is still in progress . We state in the methods and results sections tasks that have yet to be completed.

Here we report on comparison 1 and present tables in the Appendix showing trials identified so far for all three comparisons.

2.1 Objective

The objective of this study is to systematically review trials comparing the effects of 2-dose and 3-dose HPV vaccination schedules.

2.1.1 Review question

What is the effect of 2 doses of HPV vaccine compared with the licensed 3-dose schedule on immunological and clinical outcomes in adolescent girls?

2.1.2 Population, Intervention, Comparisons, Outcomes, Study design (PICOS)

Population: Adolescent girls aged 9 to 14 years (priority age group because this is the target group for primary vaccination)

Intervention: licensed bivalent (Cervarix, GlaxoSmithKline) or quadrivalent (Gardasil, Merck) HPV vaccine

Comparison:

1. Two doses vs. three doses of the same vaccine and the same dosage (3-dose arm using the WHO recommended schedule);

2. Two doses vs. two doses comparing schedules with different intervals (same vaccine and same dosage) or different dosage (where one comparator arm uses the licensed dosage);

3. Three doses vs. three doses (with one arm using the WHO recommended schedule) comparing schedules with different intervals (or different dosage where one comparator arm is the licensed concentration) (to be done if time allows).

Outcomes:

1. Immunological (including, but not limited to GMC, seropositivity, seroconversion, avidity);

2. Clinical (including, but not limited to CIN3+, CIN2+, genital warts, incident infection).

Study design: Randomised controlled trials (RCTs) examining comparisons 1-3; for comparison 1, non-randomised prospective controlled trials comparing two doses in girls with three doses in women. For all comparisons, we will document studies using other designs that might provide additional evidence.

2.1.3 Search strategy

We searched the US National Library of Medicine electronic database (PubMed), the Cochrane Central Registry of Controlled Trials (CENTRAL) and trials register from their earliest publication date to the last week of January 2014. We also searched abstracts from the 2013 meeting of the European Research Organisation on Genital Infection and Neoplasia (EUROGIN), regulatory dossiers provided by representatives of the vaccine companies GlaxoSmithKline and Merck, and studies presented at a WHO ad hoc meeting in November 2013.

The search terms were chosen to optimise sensitivity for the identification of RCTs. Comparisons between girls receiving a 2-dose schedule and women receiving the licensed 3-dose schedule are non-randomised. We assessed this non-randomised comparison in items retrieved from the searches, studies cited in reference lists or mentioned by experts and studies reported in manufacturers' dossiers. This strategy might, however, have missed eligible studies.

2.1.4 Study selection

One reviewer conducted the search, de-duplicated titles and screened titles for potential eligibility, excluding those that did not fit any inclusion criteria. Two reviewers then independently screened titles and abstracts of the remaining items to select potentially eligible articles. Two independent reviewers are reading the full text of potentially eligible articles to decide on their inclusion. This stage is ongoing.

2.1.5 Study organisation and terminology

We refer to studies first by the countries in which participants were enrolled, and then by the valency of the vaccine. When more than one study has been done in the same country we number them 1, 2, 3, etc. Many studies have more than one document associated with them, including trial registry listings, manufacturers' clinical trial reports, conference abstracts and meeting presentations and journal publications. We grouped together all documents associated with the same trial and refer to

the trial by its study name. The first time a study is mentioned in the results, we give the study name and citations to all its associated documents.

We also stratify results by geographical setting, with high income countries in one stratum and low- and middle-income countries in another, based on World Bank thresholds for per capita income. We grouped one multinational RCT with participants from Canada, Germany, Italy, Taiwan and Thailand in the high income stratum; more than half of participants were from high income countries in Europe (53.4%), Taiwan (20.7% of participants) is not considered as a separate country but its income level is above the threshold for high income countries and Thailand (23.8% of participants) is an upper middle income country.

2.1.6 Data extraction

One reviewer extracts data into a structured form created in Epidata (Odensk, Denmark). A second reviewer checks the extracted data. The reviewers discussed discrepancies and make corrections if necessary.

We used data described in the text as well as in tables. If authors gave approximate numbers for near complete seroconversion/seropositivity, we assigned values of 100%. For example, in the trial Canada1, for HPV16, the study report says, “The majority of participants (>99%) remained seropositive for HPV-16…” [3].

2.1.7 Data analysis

We used Stata version 13 (StataCorp, Austin, USA) for analysis to prepare forest plots and, where appropriate, conduct meta-analysis.

We have used data from per-protocol populations, where available, because most comparisons were made to investigate non-inferiority of one vaccination schedule compared with another and the per protocol study population gives a more conservative estimate of the difference between two schedules.

For analyses of the proportion of participants with any antibody detected after vaccination we use, where stated, participants who were seronegative at baseline. This gives the proportion that seroconverts after vaccination. For longer follow up times we then report the proportion remaining seropositive. If seropositivity data were not stratified by pre-vaccination status we used the whole study population.

Outcome measures

We compare available data about serological antibody responses measured as GMCs or seroconversion/seropositivity. We present the following:

a. GMCs: for HPV16 and HPV18 separately, weighted mean difference (95% CI) between GMCs, calculated as i) girls receiving two doses *divided by* girls receiving 3 doses and ii) girls receiving 2 doses *divided by* women receiving three doses. The weighted mean difference on the log scale is the number needed if meta-analysis is planned because precision is expressed in terms of the log standard error. The point estimate and lower and upper confidence intervals can be exponentiated to give the ratio of GMCs and its confidence intervals. These are comparable to published data presented as a GMC ratio. For non-inferiority, we use the non-inferiority margin cited by Dobson et al. as “the lower bounds… for a GMT ratio… greater than 0.5” [3]. On the log scale this is -0.693.
b. Seroconversion/seropositivity: for HPV16 and HPV18 separately, difference (with 95% confidence intervals, 95% CI) between percentage seroconverted/seropositive, calculated as i) girls receiving

two doses *minus* girls receiving three doses and ii) girls receiving two doses *minus* women receiving three doses. If a non-inferiority margin of 5% is set, the lower 95% confidence interval for the difference should be above -5%.

We do not compare absolute levels of antibody concentrations because of the different methods used to measure them. We have assumed that it is valid to compare: a) the log difference, which corresponds to a ratio of GMCs on the natural scale; and b) the difference in percentages seropositive after vaccination. We examine heterogeneity between results of different studies visually in forest plots and quantitatively using the I^2 value. If meta-analysis is appropriate, we use a random effects model to estimate the weighted average of the pooled effects.

2.1.1 Search results

The search strategies yielded a total of 923 hits. We are assessing 280 items for inclusion in analysis of eligible comparisons (Figure 3).

Table 5 (in the appendix) summarises the main characteristics of identified RCTs so far, including the schedules compared.

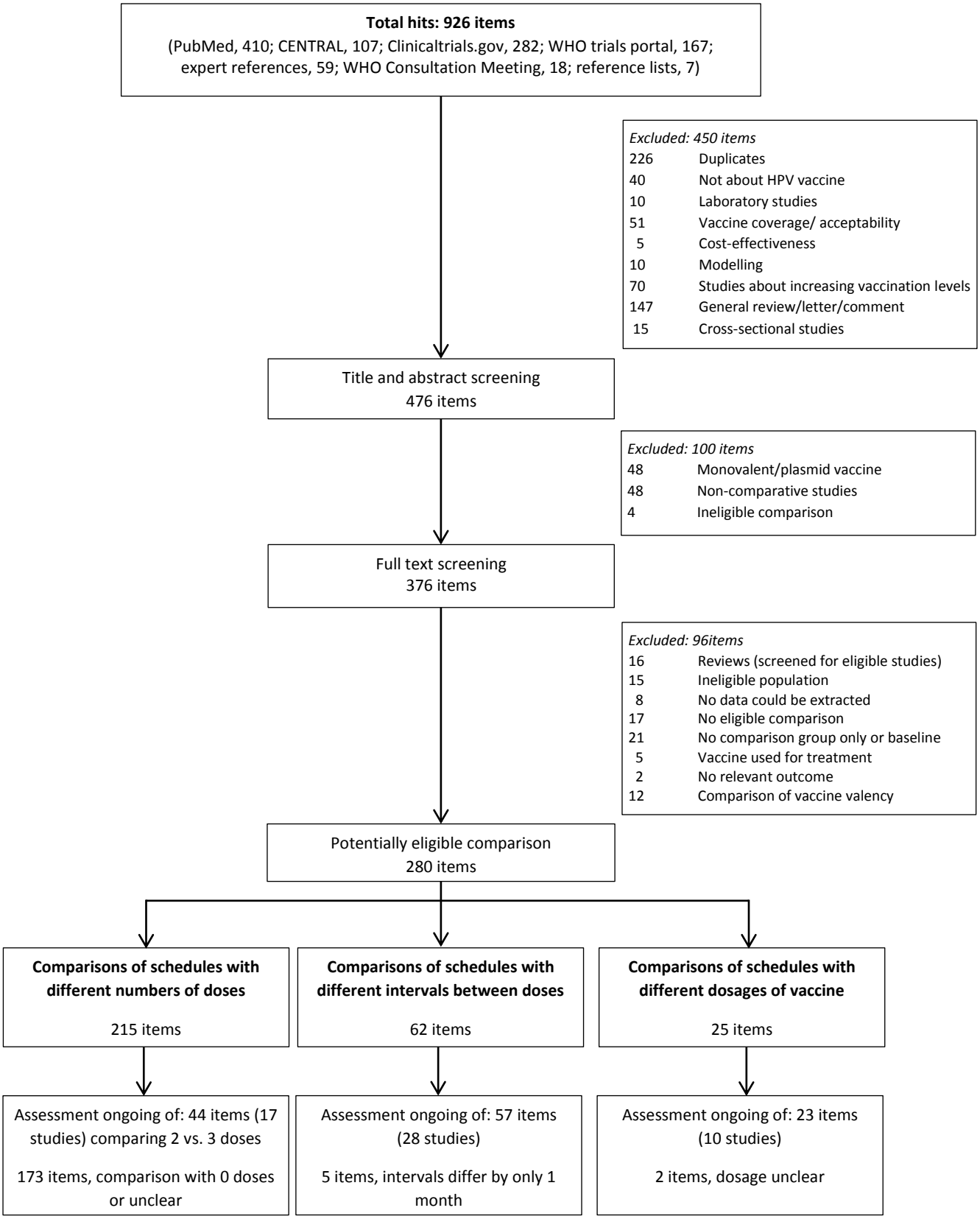

Figure 3. Flow chart of retrieved items, excluded and included items, and number of studies according to comparison, as of 28.02.2014.

3 Comparison 1: two doses vs. three doses of the same vaccine and the same dosage (3-dose arm using the WHO recommended schedule)

We summarise the studies identified in the search strategy as of 01.03.2014. We then present results for randomised comparisons in girls, followed by non-randomised comparisons between girls and women and then we summarise results from studies with other designs or populations. Within each group of studies we present available results for GMC, seroconversion/seropositivity, and clinical outcomes.

3.1 Studies identified

Table 1 summarises the comparisons made in this section of the report for primary evidence about the effects of 2-dose vs. 3-dose HPV vaccine schedules and forest plots showing the results. Table 2 shows the basic characteristics of all identified studies comparing 2-dose and 3-dose schedules.

Table 1. Comparisons made with data available for primary sources of evidence

Study name	**Girls, randomised comparisons**					**Girls vs. women, non-randomised comparisons**				
	GMC		Seroconversion/ positivity		Clinical	GMC		Seroconversion/ positivity		Clinical
	1 month	later	1 month	later		1 month	later	1 month	later	
Canada1	+	+ (24, 36)	+	+ (24, 36)	-	+	+ (24, 36)	+	+ (24, 36)	-
Canada/Germany1	+	+ (24)	+	+ (24)	-	+	+ (24)	+	+ (24)	-
India	+	-	-	-	+	-	-	-	-	-
Mexico	-	-	-	-	-	+	+ (21)	+	+ (21)	-
Multinational2	-	-	-	-	-	+	-	+	-	-
Figure	Figure 4,	Figure 5,	Figure 6		None	Figure 7	Figure 8	Figure 9		None

We included three RCTs that compared a 2-dose and 3-dose schedule in girls between 9 and 18 years old: Canada1 [3-5]; Canada/Germany1 [6-8]; and India [9, 10], all of which provide data about antibody concentrations at month seven (one month after the last vaccine dose). All three trials have been designed to investigate differences in immunological outcomes. There are limited data about the methods of the India trial, which does not yet have published results. The authors present the ratio between antibody concentrations as the mean fluorescence index (MFI). We assumed that this corresponds to the geometric mean antibody concentration used in other trials. The India trial has also been designed to investigate clinical outcomes, with planned follow up of more than 20 years. The authors will use blood samples to assess incident HPV infections and cervical cell collection starting after marriage or the first delivery.

One additional RCT provides data for women aged 15-25 years [11]. This trial in Europe (Italy, Romania, Slovakia) compared two 3-dose schedules (extended: 0, 1, 12 months vs. standard: 0, 1, 6 months). For the extended schedule, data are available at month two (one month after the second dose) and compared with month seven (one month after the third dose of the standard schedule).

Table 2. Summary of identified studies reporting on comparisons between two and three doses of HPV vaccine, by study design, study name and population

Study name [refs], (vaccine)	Alternative study names	Study design details relevant to 2-dose vs. standard 3-dose comparison	Schedules, months*	Comparisons presented of 2-dose vs. 3-dose schedules
Primary evidence, controlled trials				
Canada1 [3-5, 12], (quadrivalent)	BCGov01	RCT, non-inferiority: girls (9-13 yrs) allocated to 2-dose or 3-dose schedule; women (16-26 yrs) enrolled concurrently and given 3-dose schedule	0, 6 0, 2, 6	Randomised, girls Non-randomised, girls vs. women Immunogenicity
Canada/Germany1 [6-8, 13], (bivalent)	HPV-048	RCT, non-inferiority, dose-range: girls (9-14 yrs); women (15-19, 20-25 yrs) allocated to 2-dose or 3-dose schedule (and, within 2-dose schedule)	0, 6 0, 1, 6	Randomised, girls Non-randomised, girls vs. women Randomised, women Immunogenicity
India [9, 10], (quadrivalent)	NCT00923702 BMGF48979	RCT: girls (10-18 yrs) allocated to 2-dose or 3-dose schedule (unpublished, methods from trial registration and meeting report)	0, 6 0, 2, 6	Randomised, girls Immunogenicity, clinical
Mexico [14], (bivalent)		Controlled trial: 81 schools in two clusters allocated to two 3-dose schedules; girls (9-10 yrs) receive vaccine; concurrent enrolment of women (18-24 yrs) to receive 3-dose schedule. Compared after extended schedule group receives two doses. No account taken of clustering.	0, 6 (60) (extended) 0, 1, 6	Non-randomised, girls vs. women Non-randomised, girls Immunogenicity
Multinational2 [13, 15, 16] (Canada, German, Italy, Taiwan, Thailand), (bivalent)	HPV-070; GSK 11470; GSK580299	RCT, non-inferiority: girls (9-14 yrs) allocated to two 2-dose schedules; concurrent enrolment of women (15-25 yrs) to 3-dose schedule.	0, 6 (0, 12) 0, 1, 6	Non-randomised, girls vs. women Immunogenicity
Additional supporting evidence				
Canada2 [17-19]	ICI-VPH; NCT02009800	RCT, non-inferiority girls who received 2 doses (at age 9-11) 5 years before enrolment allocated to 3rd dose or not	0,6 0,6,60	No results yet Randomised, girls Immunogenicity, clinical
Europe [11] (Italy, Romania, Slovakia) (bivalent)	NCT00552279	RCT, non-inferiority: women (15-25 yrs) allocated to two 3-dose schedules. Compared after extended schedule group receives two doses.	0, 1 (12) (extended) 0, 1, 6	Randomised, women Immunogenicity
Costa Rica [5, 13, 20-23], (bivalent)	HPV-009	RCT, efficacy: women (18-25 yrs) allocated to 3-dose schedule or 0 doses. Compared fully (three doses) with partially vaccinated (two doses).	0, 1, 6 (0)	Non-randomised, women Immunogenicity, clinical
Multinationalx [13, 24], 14 countries, (bivalent)	HPV-008; PATRICIA	RCT, efficacy: women (15-25 yrs) allocated to 3-dose schedule or 0 doses. Compared fully (three doses) with partially vaccinated (two doses).	0, 1, 6 (0)	Non-randomised, women Clinical
Multinational4 [25, 26] (France, Hong Kong, Singapore, Sweden) (bivalent, quadrivalent)	HPV-071 PRI GSK 11541; NCT01462357	RCT, girls (9-14 yrs) allocated to 2 vs 3 doses quadrivalent or 2 doses bivalent	0, 6 (0, 6) 0, 2, 6	No results yet Randomised, girls Immunogenicity
Uganda [27], (vaccine not	PATH	Observational study, demonstration project: girls invited to receive 3-dose schedule. Compared fully (three doses)	0, 1, 6	Non-randomised, girls Immunogenicity

stated)		with partially vaccinated (two doses).		
Canada3 [18, 28-30] , (quadrivalent)		RCT, co-administration and alternative third dose: girls allocated to concurrent or sequential hepatitis A vaccine. After two doses allocated to third dose bivalent or quadrivalent. Compared same girls after two and three doses.	0, 6, 42	Within-person, girls
Canada4, (quadrivalent) [3, 31]	QUEST	Observational study, longitudinal cohorts of girls (9-12) who received 2 or 3 doses followed up until age 19 or 10 years after 1st dose	0,6 0,2,6	No results yet Non-randomised, girls Immunogenicity, clinical

* Vaccine doses in brackets are in study protocol but data not used in this report.

We included four studies with concurrent enrolment of girls and women that provide data about non-randomised comparisons between a 2-dose schedule in girls and a 3-dose schedule in women: three were comparisons within RCTs, Canada1 [3-5]; Canada/Germany1 [6-8], Multinational2 (Canada, Germany, Italy, Taiwan and Thailand) [15, 16]. One non-randomised controlled trial was included in this group (Mexico) [14]. This trial, in Cuernavaca, enrolled women from a primary health care centre and girls from schools. Girls were grouped into "2 clusters, each of which included students from a different set of local public schools." Girls in one group of schools received an extended schedule of bivalent vaccine (0, 6, 60 months) and provided a blood sample at months seven and 21, which could be compared with results from women at the same intervals after the standard 3-dose schedule. Of note, the authors do not mention any adjustment for clustering when calculating confidence intervals for estimates from girls.

We also identified four additional studies presenting non-randomised comparisons between groups of the same age receiving two or three doses of HPV vaccine. Two RCTs of clinical efficacy in Costa Rica [13, 22] and in 14 different countries [13, 24] compared partially and fully vaccinated women; one non-randomised controlled trial allocated girls two clusters of schools in Mexico non-randomly to different schedules [14]; and one demonstration project in Uganda compared partially and fully vaccinated girls [27].

3.2 Randomised comparisons in girls

Three RCTs (Canada1, Canada/Germany1 and India) contribute to these comparisons. All three present immunological outcomes as GMCs. Canada1 and Canada/Germany1 also present these data as seroconversion (percentages of girls initially seronegative who are seropositive after vaccination. India presents limited clinical outcomes about incident HPV infections. The numerical data extracted from these RCTs are summarised in Table 6 (appended).

3.2.1 Geometric mean antibody concentrations

Figure 4 shows the difference in GMCs between girls receiving two or three doses of HPV vaccine one month after the last vaccine dose.

For HPV16, the trials have inconsistent results (I^2 93%).

- The 2-dose schedule in the Canada1 trial is non-inferior to the 3-dose schedule.
- In Canada/Germany1, the GMC is lower in the 2-dose than the 3- dose group. The lower bound of the confidence interval is below that non-inferiority margin but the upper bound is above it so the result is inconclusive.

For HPV18 the results of the trials are consistent and the GMC in the 2-dose group is non-inferior to that in the 3-dose group (the weighted mean difference corresponds to a GMC ratio of 0.72, 95% CI 0.62, 0.84).

Limited data from the India trial were presented at the WHO *ad hoc* meeting in November 2013. In the India trial, comparisons favoured the 2-dose schedule. The weighted mean differences correspond to a mean fluorescence index for HPV16 of 1.2 (1.0, 1.2) and for HPV18 1.0 (1.0, 1.2).

Figure 5 shows the results at 24 months for both studies. Point estimates for the weighted mean difference are lower for the 2-dose group in both trials for both HPV16 and 18. Lower bounds for the confidence interval are below the non-inferiority margin for HPV18 in both trials and for HPV16 in Canada/Germany1. The weighted mean difference for the GMC in girls receiving the 2-dose schedule in Canada 1 is non-inferior to the 3-dose schedule. Results are inconclusive for the other measured outcomes. The published report for Canada1 also provides results at 36 months, when the GMC ratio for HPV16 was non-inferior (0.81. 95% CI 0.55, 1.20) and inconclusive for HPV18 (0.43, 95% CI 0.26, 0.73).

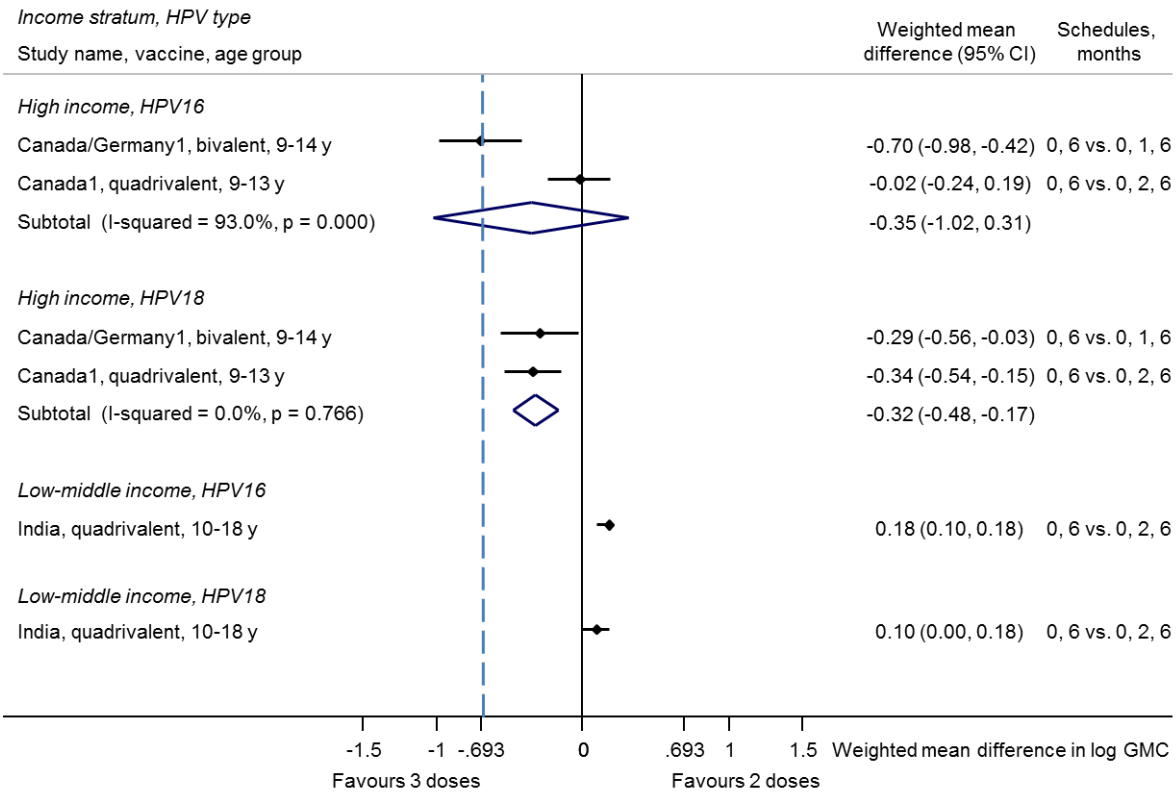

Figure 4. Forest plot, weighted mean difference between GMCs in girls receiving 2-dose and 3-dose schedules, one month after last dose, by income level and HPV type; two trials in high income and one trial in low-middle income strata.

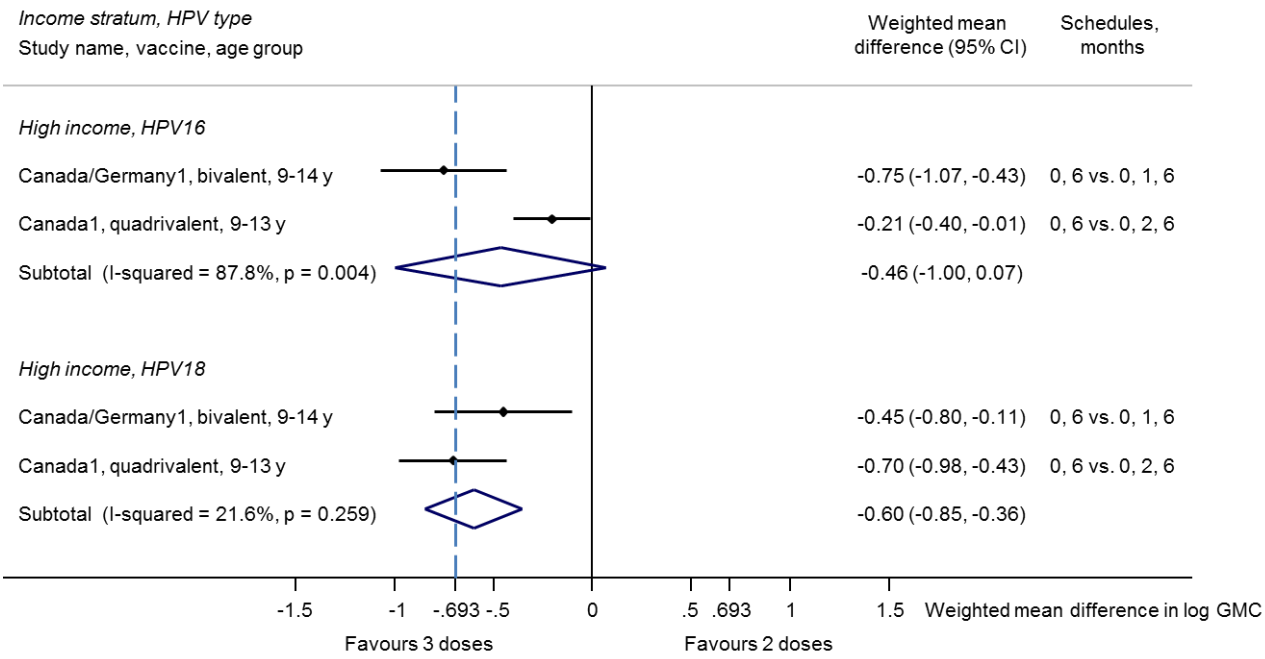

Figure 5. Forest plot, weighted mean difference between GMCs in girls receiving 2-dose and 3-dose schedule, by HPV type, 24 months after last dose; two trials in high income countries.

In both plots, blue dashed line shows the non-inferiority margin; $\log_e$ -0.693 is equivalent to a GMC ratio of 0.5 on the natural scale. For non-inferiority of the 2-dose schedule the lower 95% CI of the difference should be less than 0.5 on the natural scale. Blue diamond shows the pooled average difference estimated from random effects meta-analysis. I-squared value is the percentage of heterogeneity between trials due to factors other than random variation.

3.2.2 Seroconversion and seropositivity

Canada1 and Canada/Germany1 presented data about seroconversion in girls who were initially seronegative. These results are presented in the text of the articles and describe all participants as being antibody positive for HPV16 and HPV18 one month after the last vaccine dose. In Canada/Germany1 the authors state, “all subjects evaluated at Month 24 were still seropositive” [7]. In Canada1, numerical data are provided in the text [3].

In neither of these trials was there a pre-specified non-inferiority margin for seroconversion. If the non-inferiority margin had been set at 5% (as specified in the Multinational2 trial [8]), the 2-dose schedule in both trials would be non-inferior at all time points for HPV16 in both trials and for HPV18 in Canada/Germany1 (Figure 6). In Canada1, all participants had seroconverted by month 7. At months 24 and 36, fewer participants in the 2-dose than the 3-dose group remained seropositive, but the lower 95% CI includes the non-inferiority margin.

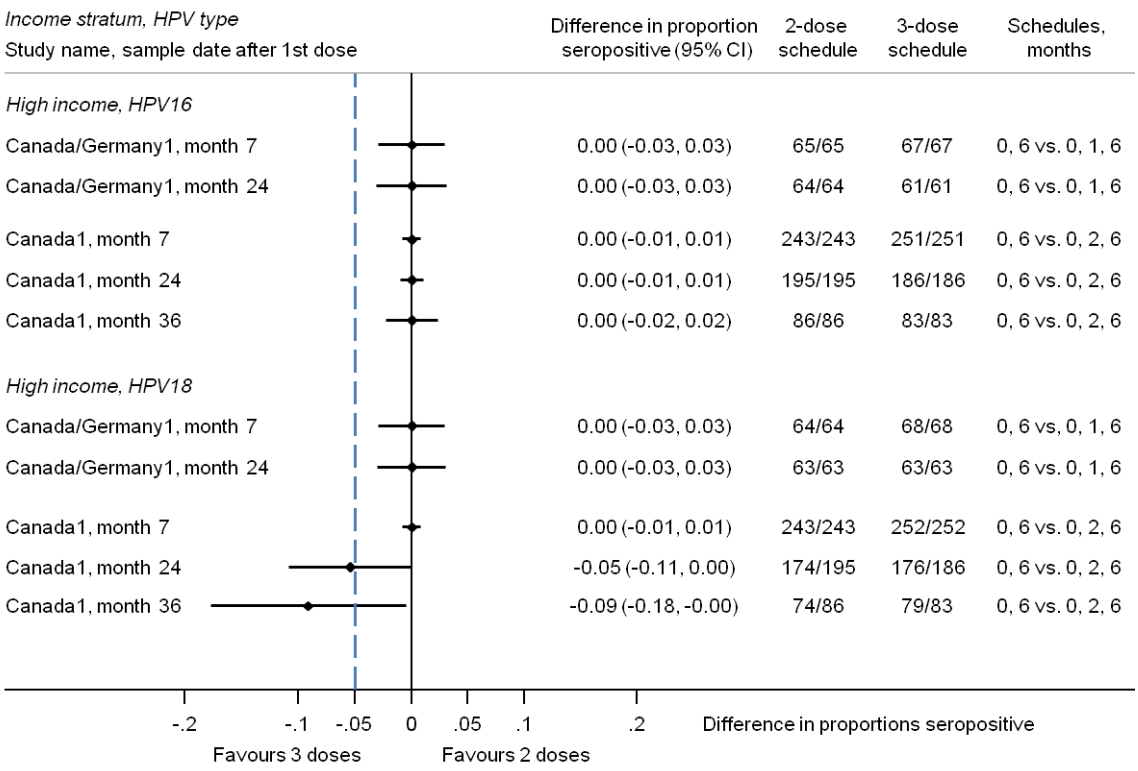

Figure 6. Forest plot of differences in proportions seroconverting 7 months after the first vaccine dose and being seropositive 24 and 36 months after the first dose of HPV vaccine in girls receiving a 2-dose or 3-dose schedule, where data are available.

Horizontal axis is on the natural scale; the solid line at zero represents no difference in % seroconverting between the groups; the blue dashed line at -0.05 is the non-inferiority margin, assumed here to be 5%. The estimates have not been pooled because we present data from all available time points in the same studies.

3.2.3 Clinical outcomes

Limited clinical data were presented at the WHO *ad hoc* meeting in November 2013. The authors reported the frequency of any vaccine type incident infection (HPV6, 11, 16, or 18) in 181 girls aged 18 years or older. Assuming that the results relate to randomised groups, there were more incident infections in the group receiving two doses than three doses.

Additional clarification is needed about these data.

3.3 Non-randomised comparisons between girls and women

Four studies contributed to this comparison (Canada1, Canada/Germany1, Mexico, Multinational2). Results are stratified into high income and middle income strata. As noted, Multinational2 includes about a fifth of participants from Thailand, which is a middle income country. The numerical data extracted from these RCTs are summarised in Table 7 (appended).

3.3.1 Geometric mean antibody concentrations

All trials met the criteria for non-inferiority trials for both HPV16 and HPV18 (Figure 7). For most comparisons, GMCs were also superior in girls receiving the 2-dose schedule than in women receiving the licensed 3-dose schedule. Only for HPV16 in Canada/Germany1 and Canada1 did the 95% CI include the null effect.

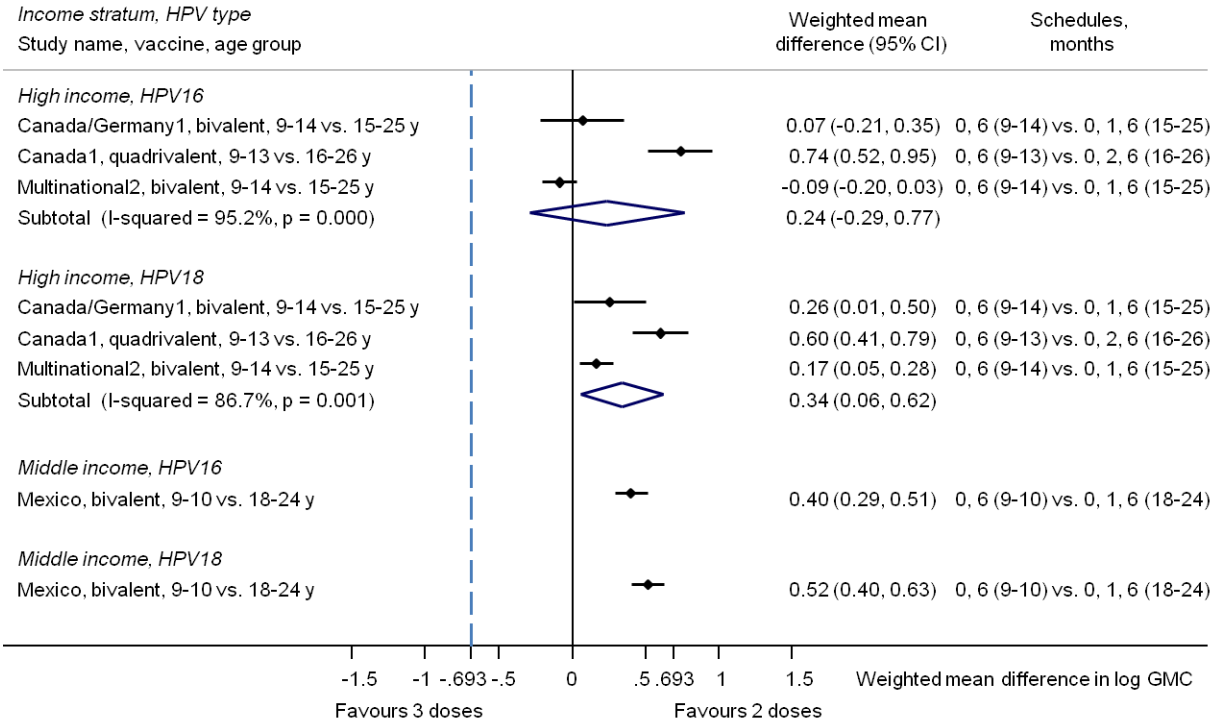

Figure 7. Forest plot, weighted mean difference between GMCs in girls receiving a 2-dose schedule and women receiving the licensed 3-dose schedule, one month after last dose, by income level and HPV type; three trials in high income and one trial in middle income strata.

Blue dashed line shows the non-inferiority margin; $\log_e$ -0.693 is equivalent to a GMC ratio of 0.5 on the natural scale. For non-inferiority of the 2-dose schedule the lower 95% CI of the difference should be less than 0.5 on the natural scale. Blue diamond shows the pooled average difference estimated from random effects meta-analysis. I-squared value is the percentage of heterogeneity between trials due to factors other than random variation.

Three trials provided data at later time points; Canada1 at 24 and 36 months, Canada/Germany1 at 24 months and Mexico at 21 months after the first vaccine dose. The data from months 21-24 are shown in Figure 8. The findings and interpretation are similar to those at month seven.

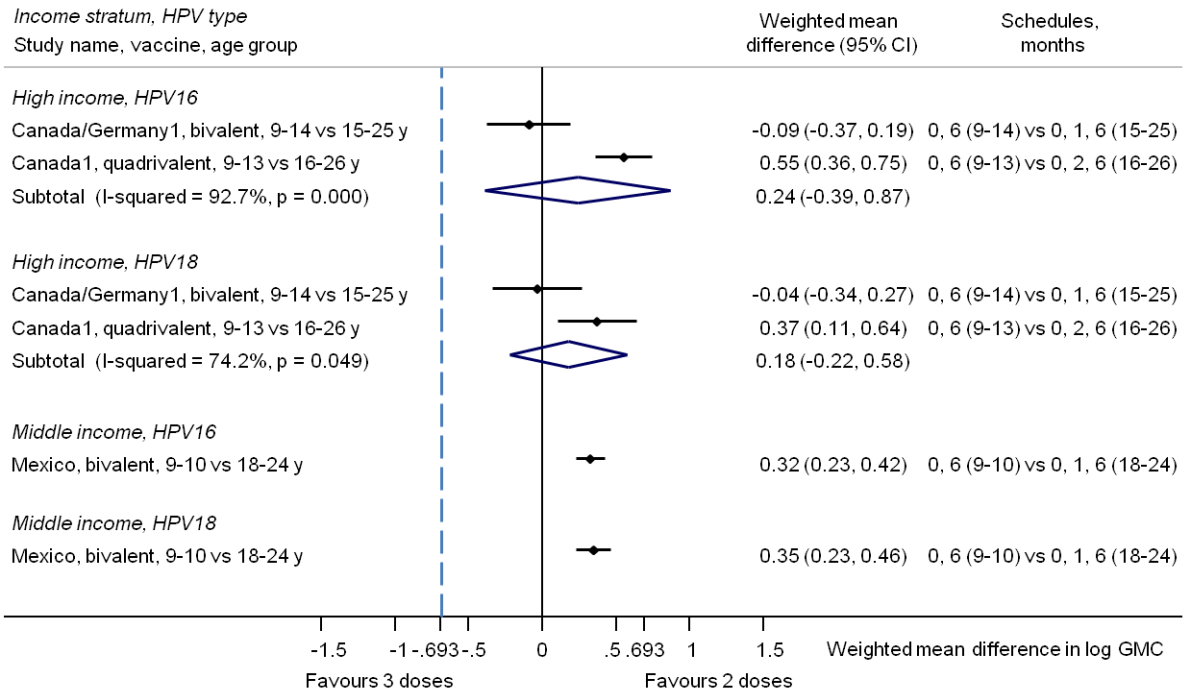

Figure 8. Forest plot, , weighted mean difference between GMCs in girls receiving a 2-dose schedule and women receiving the licensed 3-dose schedule, 21 months (Mexico) or 24 months (Canada1, Canada/Germany1) after last dose, by income level and HPV type; two trials in high income and one trial in middle income strata.

Blue dashed line shows the non-inferiority margin; $\log_e$ -0.693 is equivalent to a GMC ratio of 0.5 on the natural scale. For non-inferiority of the 2-dose schedule the lower 95% CI of the difference should be less than 0.5 on the natural scale. Blue diamond shows the pooled average difference estimated from random effects meta-analysis. I-squared value is the percentage of heterogeneity between trials due to factors other than random variation.

3.3.2 Seroconversion and seropositivity

Data about seroconversion and seropositivity are available for Canada1, Canada/Germany1 and Multinational2 at month seven and for Canada1 (months 24 and 36) and Canada/Germany1 (month 24). The findings are similar to those for girls, with non-inferiority criteria fulfilled. In Canada1, seropositivity in girls at 24 and 36 months was higher than in women who received three doses, although confidence intervals for the differences include the null effect.

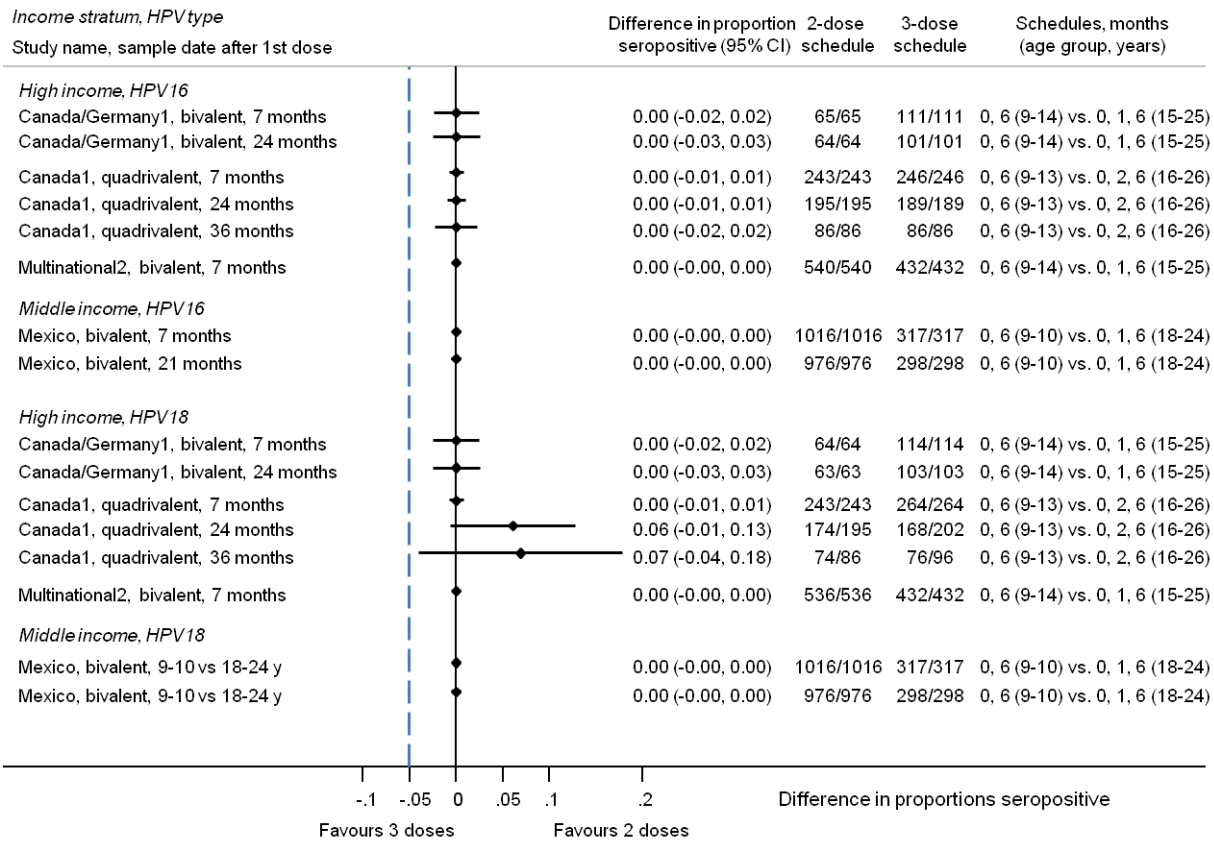

Figure 9. Forest plot of differences in proportions seroconverting 7 months after the first vaccine dose and being seropositive 24 and 36 months after the first dose of HPV vaccine in girls receiving a 2-dose schedule and women receiving the 3-dose schedule, where data are available.

Horizontal axis is on the natural scale; the solid line at zero represents no difference in % seroconverting between the groups; the blue dashed line at -0.05 is the non-inferiority margin, assumed here to be 5%. The estimates have not been pooled because we present data from all available time points in the same studies.

3.3.3 Clinical outcomes

None of the four trials reported on clinical outcomes.

3.3.4 Other comparisons providing evidence

Table 1 summarises five studies that provide additional results about immunological outcomes in randomised comparisons in women (Europe), an observational study of girls (Uganda) and a within-person comparison of girls (Canada3). The overall findings about immunological outcomes support those presented above. Of note, in the Europe trial, the investigators compared women one month after receiving two doses (of an extended 3-dose schedule) at 0, 1 month and women one month after receiving the licensed schedule (0, 1, 6 months). In this comparison of GMCs, the 2-dose schedule was inferior to the 3-dose schedule (weighted mean difference HPV16, -1.17, 95% CI -1.30, -1.05; HPV18, -0.53, 95% CI -0.66, -0.39).

Data about clinical outcomes come from non-randomised comparisons of partially vaccinated women within clinical efficacy trials that enrolled women (CostaRica and Multinationalx). Women receiving two doses at 0 and 1 month were compared to women receiving three doses at 0, 1 and 6 months. These analyses were presented as supporting evidence for the GlaxoSmithKline application to the European Medicines Agency for licensure of the 2-dose schedule [13].

4 Comparison 2: two doses vs. two doses of the same vaccine (different intervals, same dosage and same intervals, different dosage)

We found two RCTs that directly compared two 2-dose schedules (Table 3). One of these (Canada/Germany1) has published results.

Table 3. Summary of comparisons available

Study name, schedule in months (dosage) (age group, years)	GMCs		Seroconversion/ positivity	Clinical
	1 month	Later	Any time point	Any time point
Different interval, same dosage		(24)		
Canada/Germany1,				
0, 6 (20µg) vs. 0, 2 (20µg) (9-14 yrs)	+	-	-	-
0, 6 (20µg) vs. 0, 2 (20µg) (15-19 yrs)	+	-	-	-
0, 6 (20µg) vs. 0, 2 (20µg) (20-25 yrs)	+	-	-	-
Multinational2	-	-	-	-
0, 12 (20µg) vs. 0, 6 (20µg) (9-14yrs)				
Figure	Figure 10			
Same interval, different dosage				
Canada/Germany1				
0, 6 (40µg) vs. 0, 6 (20µg) (9-14yrs)	+	-	-	-
0, 6 (40µg) vs. 0, 6 (20µg) (15-19 yrs)	+	-	-	-
0, 6 (40µg) vs. 0, 6 (20µg) (20-25 yrs)	+	-	-	-
Figure	Figure 11			

Table 4. Summary of studies

Study name [refs], (vaccine)	Alternative study names	Study design details relevant to 2-dose vs. 2-dose comparison	Schedules, months (dosage)	Comparisons presented of 2-dose vs. 2-dose schedules
Primary evidence, controlled trials				
Canada/Germany1 [6-8, 13], (bivalent)	HPV-048	RCT, non-inferiority, dose-range: girls (9-14 yrs); women (15-19, 20-25 yrs) allocated to 2-dose dose schedules	0, 6 (20µg) 0, 2 (20µg) 0, 6 (40µg)	Randomised, different intervals, girls and women Randomised, different dosages, girls and women Immunogenicity
Multinational2 [13, 15, 16] (Canada, German, Italy, Taiwan, Thailand), (bivalent)	HPV-070; GSK 11470; GSK580299	RCT, non-inferiority: girls (9-14 yrs) allocated to two 2-dose schedules;	0, 6 (20µg) 0, 12 (20µg)	Randomised, different intervals, girls No data available yet for this comparison because most recent follow up reported is at 7 months after first vaccine dose
Additional supporting evidence				
Europe [11] (Italy, Romania, Slovakia) (bivalent)	NCT00552279	RCT, non-inferiority: women (15-25 yrs) allocated to two 3-dose schedules. Compared after extended schedule group receives two doses.	0, 1 (12) (20µg)	Single group, women Immunogenicity There is no control/comparison group for these data

4.1 Two dose schedules, comparing different intervals between doses

One trial contributes to this comparison (Canada/Germany1) (there are no data yet available from the Multinational2 study). The investigators compared two 2-dose schedules (0, 2 months and 0, 6 months) with the standard dosage (20µg) of each serotype. The numerical data extracted from these RCTs are summarised in Table 8 (appended).

Data are available for the comparison of GMCs but not seroconversion. The longer interval results in higher GMCs in all age groups. There is no statistical evidence of heterogeneity between the older age groups.

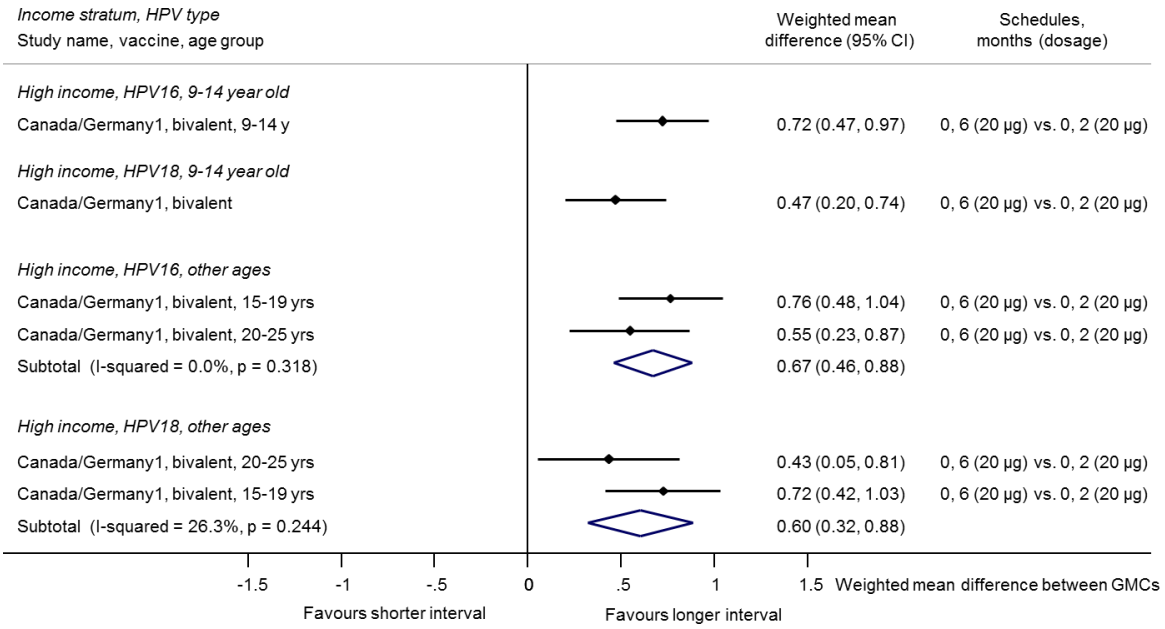

Figure 10. Forest plot, weighted mean difference between GMCs one month after the last vaccine dose in girls (9-14 years) and women at older ages (15-19 and 20-24 years) receiving two doses at 0, 6 months with participants receiving two doses at 0, 2 months.

Blue diamond shows the pooled average difference estimated from random effects meta-analysis. I-squared value is the percentage of heterogeneity between trials due to factors other than random variation. Non-inferiority margin not defined because neither schedule is current standard.

4.2 Two dose schedules, comparing different dosages

One trial (Canada/Germany1) provides data about this comparison (Table 3), with randomised comparisons in girls and two older age groups. The numerical data extracted from these RCTs are summarised in Table 9 (appended).

Figure 11 shows that, in all age groups, GMCs are higher in participants who received the higher dosage of vaccine serotypes.

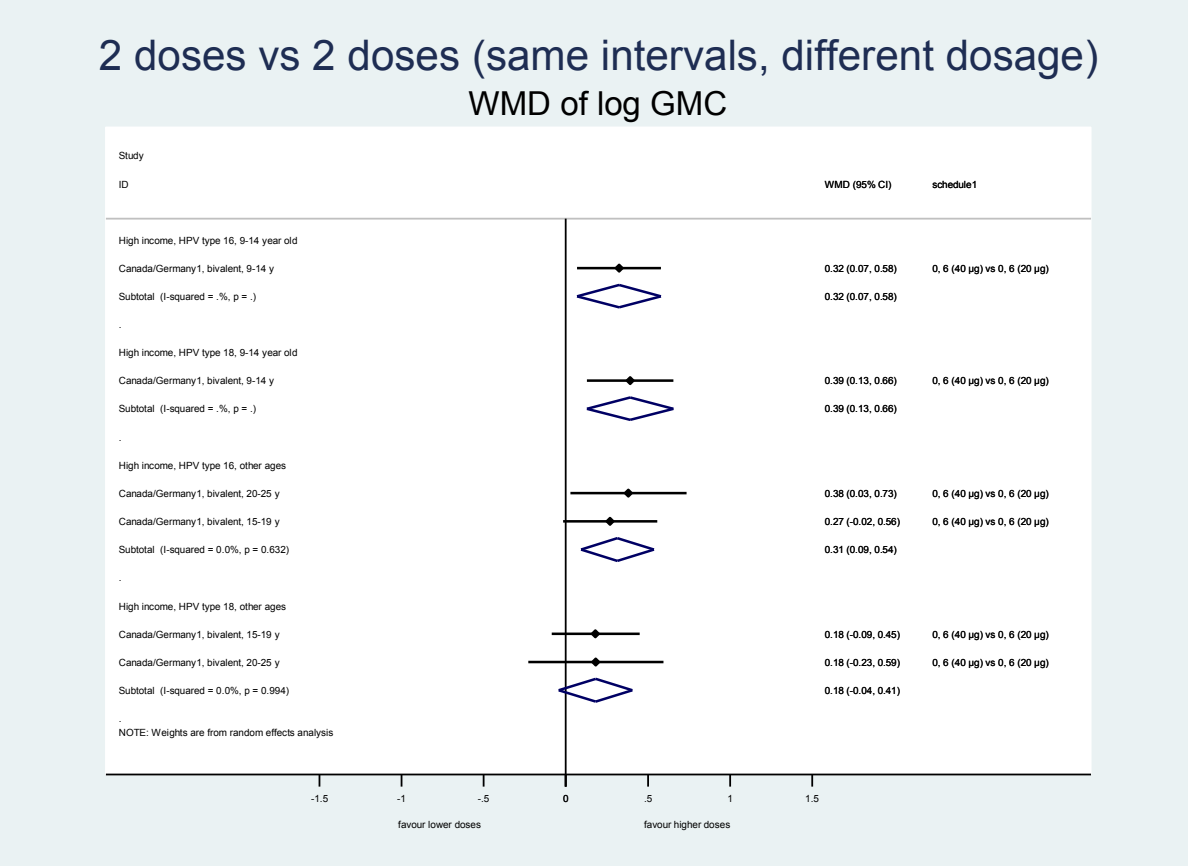

Figure 11. Forest plot, weighted mean difference between GMCs one month after the last vaccine dose in girls (9-14 years) and women at older ages (15-19 and 20-24 years) receiving two doses at 0, 6 months with participants receiving two doses at 0, 2 months.

Blue diamond shows the pooled average difference estimated from random effects meta-analysis. I-squared value is the percentage of heterogeneity between trials due to factors other than random variation. Non-inferiority margin not defined because neither schedule is current standard.

5 Additional tables

Table 5. Summary of RCTs with eligible data for any comparison, grouped together if from the same study.

Table 6. Randomised comparisons between 2-dose and 3-dose schedules, by study and types of outcome

Table 7. Available results for geometric mean concentrations and seropositivity in non-randomised comparisons of two doses in girls vs. three doses in women

Table 8. Comparisons between 2-dose vs. 2-dose schedules (different interval, same dosage)

Table 9. Comparisons between 2-dose vs. 2-dose schedules (different dosage, same interval)

Table 5. Summary of RCTs with eligible data for any comparison, grouped together if from the same study

Study name, vaccine, ref.	First author, year	Study design	Age group, years	Schedules, months	Outcomes reported	Timing of samples, available data, months (reported timing of samples)*	Comparison available	Comments
Canada1†; quadrivalent [3-5]	Dobson, 2013 Krajden, 2011 Sankaranarayanan, 2013	RCT	9-13	0, 6 0, 2, 6	GMC (mMU/mL) Seropositivity	0, 7, 18, 24, 36	2 vs 3 doses	
			9-13 16-26	0, 6 0, 2, 6	GMC (mMU/mL) Seropositivity	0, 7, 18, 24, 36	2 vs 3 doses, not randomised	Schedule assigned according to age no randomisation (2 doses for girls, 3 doses for women)
Canada, Germany1; bivalent [6-8, 13]	Romanowski, 2011 Romanowski, 2013 GSK, n110659, 2010 (HPV 048)	RCT	9-14	0, 6 (20µg) 0, 1, 6 (20µg) 0, 6 (40 µg) 0, 2 (40 µg)	GMC (EU/mL) seropositivity‡	0, 7, 24 (0, 3§, 7, 12, 18, 24)	2 vs 3 doses 2 vs 2 (different interval, same dose) 2 vs 2 (same interval, different dose)	
			15-19	0, 6 (20µg) 0, 1, 6 (20µg) 0, 6 (40 µg) 0, 2 (40 µg)	GMC (EU/mL) seropositivity‡	0, 7 (0, 3§, 7, 12, 18, 24)	2 vs 3 doses 2 vs 2 (different interval, same dose) 2 vs 2 (same interval, different dose)	
			20-25	0, 6 (20µg) 0, 1, 6 (20µg) 0, 6 (40 µg) 0, 2 (40 µg)	GMC (EU/mL) seropositivity‡	0, 7 (0, 3§, 7, 12, 18, 24)	2 vs 3 doses 2 vs 2 (different interval, same dose) 2 vs 2 (same interval, different dose)	
			9-14 15-25	0, 6 (20µg) 0, 1, 6 (20µg)	GMC (EU/mL) seropositivity‡	0, 7, 24 (0, 3§, 7, 12, 18, 24)	2 vs 3 doses, not randomised	Schedule assigned according to age no randomisation (2 doses for girls, 3 doses for women)
Canada2; quadrivalent [17-19]	Sauvageau, Gilca, 2013 Sauvageau, 2012 NCT02009800	RCT	9-10	0, 6 0, 6, 60	NR	NR	2 vs 3 doses	Results not available Study start date November 2013
Canada3;	Gilca, 2013	RCT	9-10	0, 6	NR	NR	2 vs 3 doses	Results not described in

quadrivalent [12, 18, 28-30]	Sauvageau, 2013 Sauvageau, Gilca, 2013			0, 6, 42				this report because comparison 2 vs. 3 was made in the same individuals
Europe; bivalent [11]	Esposito, 2011	RCT	15-25	0, 1, 6 0, 1, 12	GMC, Seroconversion rate, safety	0, 2, 7, 13	3 vs 3 doses	
			15-25	0, 1, 0, 1, 6	GMC, Seroconversion rate, safety	0, 2, 7	2 vs 3 doses	
			15-25	0, 1 0, 1, 12	GMC, Seroconversion rate, safety	0, 2, 13	2 vs 3 doses	
Europe1; quadrivalent (vs 9-valent) (ID 71)	Van Damme P, 2013	RCT	9-15	All given at 0, 2, 6 HPV16: 40 vs. 60µg/dose HPV18: 20 vs. 40µg/dose	GMC, Seroconversion rate	0, 7	3 vs 3 doses (different dosage, same interval)	
India; quadrivalent [5, 9] ‖	Sankaranarayanan R, 2013 Sankaranarayanan R, 2013	RCT	10-18	0, 6 0, 2, 6	FMI, GMC (mMU/mL), Seropositivity, Frequency of incident and persistent HPV 16/18/6/11 infection	0, 7, 18 (0, 7, 12, 18, 24, 36, 48)	2 vs 3 doses	Methods described based on meeting presentation and conference abstracts only.
Multinational2, bivalent [13, 15, 16]	GSK, n 114700, 2013 (HPV 070) Phutanakit, 2013	RCT	9-14	0, 6 0, 12	GMC (EU/mL), Seropositivity, Seroconversion, CMI	0, 7 (0, 7, 12, 18, 24, 36)	2 vs 2 dose, No data available	No GMC data available at month 13, only data at month 7 after first dose
			9-14 15-25	0, 6 0, 1, 6	GMC (EU/mL), Seropositivity, Seroconversion, CMI	0, 7 (0, 7, 12, 18, 24, 36)	2 vs 3 doses, not randomized	Schedule assigned according to age no randomization (2 doses for girls, 3 doses for women) Schedule assigned

			9-14 15-25	0, 12 0, 1, 6	GMC (EU/mL), Seropositivity, Seroconversion, CMI	0, 7 (0, 7, 12, 18, 24, 36)	2 vs 3 doses, not randomized; No data available	according to age no randomization (2 doses for girls, 3 doses for women). No data at month 13
Multinational4, [25, 26] (bivalent and quadrivalent)	NCT01462357 EUCTR2011-002035-26-SE	RCT	9-14	0, 6 bivalent 0, 6 0, 2, 6 quadrivalent	GMC, seroconversion	(0, 7, 12, 18, 24, 36)	2 vs 3 doses No data avaliable	Results not available
Peru; quadrivalent[32, 33]	Brown, 2012 NCT00925288	RCT	18-26	0, 2, 6 0, 3, 6	GMC	0, 7	3 vs 3 doses (different interval, same dosage)	
USA 2; quadrivalent [34]	Zimmermann, 2010	RCT	18-23	0, 2, 6 0, 2, 12	GMC, seropositivity¶	0, 7 0, 13	3 vs 3 doses (different interval, same dosage)	
USA; quadrivalent	Lin, 2014(ID1005)	RCT	18-25 (male)	0, 2, 6 0, 2, 12	GMC	0, 7 0, 13	3 vs 3 dose (different interval, same dosage)	
USA; quadrivalent	Villa, 2006 (ID1343)	RCT	16-23	0, 2, 6 (20 µg) 0, 2, 6 (40 µg) 0, 2, 6 (80 µg)	GMC	(0, 2, 7, 36)	3 vs 3 doses (same interval, different dosage), No data available	Data not available
Vietnam; quadrivalent [35, 36]	Neuzil, 2011 LaMontagne, 2013	RCT	11-13	0, 2, 6	GMC	6, 7, 35 (0, 6, 7, 35)	3 vs 3 doses (different interval, same dosage)	
				0, 3, 9		9, 10, 41 (0, 9, 10, 41)	3 vs 3 doses (different interval, same dosage)	
				0, 6, 12		12, 13, 44 (0, 12, 13, 44)	3 vs 3 doses (different interval, same dosage)	
				0, 12, 24		24, 25, 56 (0, 24, 25, 44, 56)	3 vs 3 doses (different interval, same dosage)	

Abbreviations: RCT, randomised controlled trial; GMC, Geometric mean concentration; GMCs, Geometric mean concentration ratio; MFI, mean fluorescence index (serum antibodies seems to be tested using a competitive Luminex immunoassay (cLIA)); CMI, specific T-cell and B-cell mediated immune responses; NR, not reported; EU/ml, ELISA units per millilitre; LU, Luminex units; mMU/ml, milli-Merck units per millilitre;

* Reported as time since first dose; months outside brackets are available data

† Designed as noninferiority immunogenicity study

‡ Seropositivity defined as ≥8 ELISA units [EU]/mL for HPV 16 antibodies and ≥7 EU/mL for HPV 18

§ Only for the 0, 2 months group

‖ Assumes that study reported in Eurogin abstract SS17-7 is the same trial as NCT00923702, and that text refers to results 1 month after the last dose;

¶ Seropositivity defined as anti-HPV serum cLIA (competitive Luminex immunoassay) levels ≥20 milliMerck (mM) units/mL for HPV types 6 and 16, ≥16mM units/mL for type 11, and ≥24mM units/mL for type 18

Table 6. Randomised comparisons between 2-dose and 3-dose schedules, by study and types of outcome

Study name; vaccine [refs]	Age, years	Schedule compared, months (dose 20µg unless stated)	GMC units	Timing of samples, available data in months (timing of samples, according to methods)*	HPV type	Results 2 doses	Results 3 doses	Ratio 2:3 dose	Additional data
Geometric mean concentrations						**2 doses, GMC (95% CI), 1 month after last vaccine dose, per protocol**	**3 doses, GMC (95% CI), 1 month after last vaccine dose, per protocol**	**2:3 dose GMC ratio (95% CI), 1 month after last vaccine dose, per protocol†**	**2:3 dose GMC ratio (95% CI), latest time point available, per protocol†**
Canada 1; quadrivalent [3-5]	9-13	0, 6	mMU/ mL	0, 7, 18, 24, 36	HPV 16	7457 (6388-8704)	7640 (6561-8896)	0.98 (0.75-1.27)	0.81 (0.55-1.20) ‡
		0, 2, 6			HPV 18	1207 (1054-1384)	1703 (1489-1946)	0.71 (0.56-0.89)	0.43 (0.26-0.73) ‡
Canada/Germany 1; bivalent [6-8]	9-14	0, 6	EU/mL	0, 7, 24	HPV 16	11067 (9190-13328)	22261 (18034-27480)	0.50 (0.38-0.66)	0.47 (0.34-0.65) §
		0, 1, 6		(0, 7, 12, 18, 24)	HPV 18	5510 (4646-6535)	7399 (6033-9073)	0.74 (0.57-0.97)	0.64 (0.45-0.90) §
	15-19	0, 6	EU/mL	0, 7	HPV 16	8442 (6895-10336)	12858 (9696-17051)	0.66 (0.46-0.93)	NR
		0, 1, 6		(0, 7, 12, 18, 24)	HPV 18	5142 (4354-6072)	4845 (3740-6277)	1.06 (0.78-1.45)	NR
	20-25	0, 6	EU/mL	0, 7	HPV 16	5673 (4377-7354)	7971 (5766-11020)	0.71 (0.47-1.07)	NR
		0, 1, 6		(0, 7, 12, 18, 24)	HPV 18	3523 (2514-4937)	3676 (2898-4664)	0.96 (0.63-1.45)	NR

Europe; bivalent [11]	15-25	0, 1	EU/mL	0, 2, 13	HPV 16	3117 (2874.8-3379.7)	11884 (10676.6-13229.6)	0.31 (0.27-0.35)	NR
		0, 1, 12			HPV 18	2271 (2080.6-2478.8)	4501.3 (4067.7-4981.1)	0.59 (0.52-0.68)	NR
	15-25	0, 1	EU/mL	0, 2, 7	HPV 16	3194.7 (2939-3472.6)	10311.9 (9390.2-11324.2)	0.26 (0.23-0.30)	NR
		0, 1, 6			HPV 18	2338.3 (2129.2-2567.9)	3963.6 (3589.4-4376.8)	0.51 (0.44-0.58)	NR
						Mean MFI	Mean MFI	MFI ratio (95% CI)	MFI ratio (95% CI)
India; quadrivalent [5, 9]	10-18	0, 6	mMU/ mL	0, 7, 18	HPV 16	6706.1	5806.8	1.2 (1.1-1.2)	0.6 (0.5-0.7) ‖
		0, 2, 6		(0, 7, 12, 18, 24, 36, 48)	HPV 18	3851.7	3445.7	1.1 (1.0-1-2)	0.5 (0.4-0.6) ‖
Seronconversion/seropositivity						**2 doses, Seroconversion/ seropositivity**	**3 doses, Seroconversion/ seropositivity**		
						7m after dose 1	7m after dose 1		
Canada 1; quadrivalent [3-5]	9-13	0, 6	mMU/ mL	0, 7, 18, 24, 36	HPV 16	243/243 (100%)	251/251 (100%)		
		0, 2, 6			HPV 18	243/243 (100%)	252/252 (100%)		
						24 months after dose 1	24 months after 1st dose		
					HPV 16	195/195 (100%)	186/186 (100%)		
					HPV 18	174/195 (89%)	176/187 (94%)		
						36 months after dose 1	36 months after dose 1		
					HPV 16	86/86 (100%)	83/83 (100%)		
					HPV 18	74/86 (86%)	79/83 (95%)		
						7m after dose 1	7m after dose 1		
Canada/Germany	9-13	0, 6	mMU/	0, 7, 18, 24, 36	HPV 16	65/65 (100%)	67/67 (100%)		

1; bivalent [6-8]		0, 2, 6	mL		HPV 18	64/64 (100%)	68/68 (100%)		
						24 months after dose 1	24 months after dose 1		
					HPV 16	64/64 (100%)	61/61 (100%)		
					HPV 18	63/63 (100%)	64/64 (100%)		
						1 month after last dose	1 month after last dose		
Europe; bivalent [11]	15-25	0, 1	EU/mL	0, 2	HPV 16	(100%) ¶	337/337 (100%)		
		0, 1, 12		0, 2, 13	HPV 18	(100%) ¶	346/345 (99.7%)		
	15-25	0, 1	EU/mL	0, 2	HPV 16	(100%) ¶	342/342 (100%)		
		0, 1, 6		0, 2, 7	HPV 18	(100%) ¶	346/346 (100%)		
Clinical						**2 doses, clinical outcome**	**3 doses, clinical outcome**	**Clinical outcome**	**Clinical outcome**
India; quadrivalent [5, 9]	10-18	0, 6	mMU/ mL	0, 7, 12, 24, 36, 48	All HPV type	Frequency of HPV incident infection	Frequency of HPV incident infection		
		0, 2, 6				6/36 (17%)	1/44 (2%)		

Abbreviations: GMC, Geometric mean concentration; GMCs, Geometric mean concentration ratio; FMI, mean fluorescence index (serum antibodies seems to be tested using a competitive Luminex immunoassay (cLIA)); NR, not reported; EU/ml, ELISA units per millilitre; mMU/ml, milli-Merck units per millilitre;

* Reported as time since first dose; months outside brackets are available data

† If GMC ratio not reported in text, point estimate has been calculated from reported GMCs

‡ latest time point available, month 36

§ latest time point available, month 24

‖ latest time point available, month 18

¶ Number of individuals with blood sample at this time point not reported, in forest plots we have used the denominator for month 7 per protocol data (for group 0, 1 vs 0, 1, 12 we used HPV16= 342 and HPV18=346; for group 0, 1 vs 0, 1, 6 we used HPV16= 337 and HPV18=346)

Table 7. Available results for geometric mean concentrations and seropositivity in non-randomised comparisons of two doses in girls vs. three doses in women

Study name; vaccine [refs]	Age, years	Schedule compared, months (dose 20µg unless stated)	GMC units	Timing of samples, available data in months (timing of samples, according to methods)*	HPV type	Results 2 doses	Results 3 doses	Ratio 2:3 dose	Additional ratio 2:3 dose
Immunogenicity, GMC						**2 doses, GMC (95% CI), 1 month after last vaccine dose, per protocol**	**3 doses, GMC (95% CI), 1 month after last vaccine dose, per protocol**	**2:3 dose GMC ratio (95% CI), 1 month after last vaccine dose, per protocol†**	**2:3 dose GMC ratio (95% CI), latest time point available, per protocol†**
Canada1; quadrivalent [3-5]	9-13	0, 6	mMU/mL	0, 7, 18, 24, 36	HPV 16	7457 (6388-8704)	3574 (3065-4169)	2.10 (1.68-2.59)	1.70 (1.16-2.49) ‡
	16-26	0, 2, 6			HPV 18	1207 (1054-1384)	661 (580-754)	1.82 (1.51-2.20)	1.46 (0.88-2.41) ‡
Canada/Germany1; bivalent [6-8]	9-14	0, 6 (20 µg)	EU/mL	0, 7, 24	HPV 16	11067 (9190-13328)	10322 (8329-12792)	1.07 (0.81-1.42)	0.91 (0.69-1.21) §
	15-25	0, 1, 6 (20 µg)		(0, 7, 12, 18, 24)	HPV 18	5510 (4646-6535)	4262 (3572-5084)	1.30 (1.01-1.65)	0.96 (0.71-1.31) §
Mexico, Lazcano-Ponce 2013 [23] ‖	9-10	0, 6	EU/mL	0, 7, 21	HPV 16	10442 (9894-11020)	6991 (6333-7717)	1.49 (1.34-1.67)	1.37 (1.26-1.52) ¶
	18-24	0, 1, 6		(7, 21, 60, 72, 120)	HPV 18	5837 (5517-6175)	3483 (3164-3834)	1.68 (1.49-1.88)	1.37 (1.26-1.58) ¶
Multinational2, GSK, n 114700, 2013 Phutanakit, 2013[15, 16]	9-14	0, 6	EU/mL	0, 7	HPV 16	9400 (8818.3-10020.4)	10234 (9258.3-11313.6)	0.91 (0.82-1.03)	NR
	15-25	0, 1, 6		(0, 7, 12, 18, 24, 36)	HPV 18	5909.1 (5508-6338)	5002.6 (4572-5473.1)	1.18 (1.05-1.32)	NR

Uganda, Safaeian 2012, [34] **	12-20	< 3 doses vs 3 doses	NR	NR	HPV 16	NR	NR	NR	0.51 (0.37-0.69)
					HPV 18	NR	NR	NR	0.69 (0.5-0.96)

Seropositivity						**2 doses, Seropositivity/ Seroconversion**	**3 doses, Seropositivity/ Seroconversion**	**2 doses – 3 doses, difference in proportions (95% CI)**
						7 months after 1 dose	7 months after 1 dose	
Canada1; quadrivalent [3-5]	9-13	0, 6	mMU/ mL	0, 7, 18, 24, 36	HPV 16	243/243 (100%)	246/246 (100%)	To follow
	16-26	0, 2, 6			HPV 18	243/243 (100%)	264/264 (100%)	
						24 months after 1 dose	24 months after 1 dose	
					HPV 16	195/195 (100%)	189/189 (100%)	To follow
					HPV 18	174/195 (89%)	168/202 (83%)	
						36 months after 1 dose	36 months after 1 dose	
					HPV 16	86/86 (100%)	86/86 (100%)	To follow
					HPV 18	74/86 (86%)	76/96 (79%)	
						1 month after last dose	1 month after last dose	
Canada/Germany1 ; bivalent [6-8]	9-14	0, 6 (20 µg)	EU/mL	0, 7, 12, 24	HPV 16	65/65 (100%)	111/111 (100%)	To follow
	15-25	0, 1, 6 (20 µg)		(0, 7, 12, 18, 24)	HPV 18	64/64 (100%)	114/114 (100%)	
						24 months after 1 dose	24 months after 1 dose	
					HPV 16	64/64 (100%)	101/101 (100%)	To follow
					HPV 18			

						63/63 (100%)	103/103 (100%)
						7 months after 1 dose	7 months after 1 dose
Mexico, Lazcano-Ponce 2013 [14]	9-10	0, 6	EU/mL	0, 7, 21	HPV 16	1016/1016 (100%)	317/317 (100%)
	18-24	0, 1, 6			HPV 18	1016/1016 (100%)	317/317 (100%)
						21 months after 1 dose	21 months after 1 dose
					HPV 16	976/976 (100%)	298/298 (100%)
					HPV 18	976/976 (100%)	317/317 (100%)
						1 month after last dose	1 month after last dose
Multinational2, GSK, n 114700, 2013 Phutanakit, 2013[15, 16]	9-14	0, 6	EU/mL	0, 7	HPV 16	540/540 (100%)	432/432 (100%)
	15-25	0, 1, 6		(0, 7, 12, 18, 24, 36)	HPV 18	536/536 (100%)	432/432 (100%)

Abbreviations: GMC, Geometric mean concentration; NR, not reported; EU/ml, ELISA units per millilitre; mMU/ml, milli-Merck units per millilitre;

* Reported as time since first dose; months outside brackets are available data

† If GMC ratio not reported in text, point estimate has been calculated from reported GMCs

‡ latest time point available, month 36

§ latest time point available, month 24

‖ This study is not a RCT; the data are included here because there is a comparison between 2 doses in girls and 3 doses in women. See table 8.

¶ latest time point available, month 21

** No numerical results for this study. Abstract only available. See table 2.

Table 8. Comparisons between 2-dose vs. 2-dose schedules (different interval, same dosage)

Study name; vaccine [refs]	Age, years	Schedule compared, months (dose 20µg unless stated)	GMC units	Timing of samples, available data in months (timing of samples, according to methods)*	HPV type	Schedule 1, GMC (95% CI), 1 month after last vaccine dose, per protocol	Schedule 2 (95% CI), 1 month after last vaccine dose, per protocol	Schedule 1:2 GMC ratio (95% CI), 1 month after last vaccine dose, per protocol†	Schedule 1:2 GMC ratio (95% CI), latest time point available, per protocol†
						Longer interval	*Shorter interval*	*Longer:shorter*	*Longer:shorter*
Canada/Germany 1; bivalent [6-8]	9-14	0, 6 (40 µg)	EU/mL	0, 7, 24 (0, 3,‡ 7, 12, 18, 24, 48)	HPV 16	15304 (12855-18221)	7,442 (6238-8878)	2.05 (1.60-2.64)	1.93 (1.43-2.64) §
		0, 2 (40 µg)			HPV 18	8155 (6671-9970)	5095 (4288-6140)	1.60 (1.22-2.10)	2.18 (1.54-3.10) §
	15-19	0, 6 (40 µg)	EU/mL	0, 7 (0, 3,‡ 7, 12, 18, 24, 48)	HPV 16	11061 (9035-13541)	5153 (4246-6254)	2.14 (1.62-2.83)	NR
		0, 2 (40 µg)			HPV 18	6162 (4996-7601)	2986 (2385-3740)	2.05 (1.52-2.80)	NR
	20-25	0, 6 (40 µg)	EU/mL	0, 7 (0, 3,‡ 7, 12, 18, 24, 48)	HPV 16	8307 (6533-10564)	4809 (3886-5952)	1.73 (1.26-2.39)	NR
		0, 2 (40 µg)			HPV 18	4230 (3346-5349)	2742 (2031-3701)	1.54 (1.05-2.25)	NR

Abbreviations: GMC, Geometric mean concentration; EU/ml, ELISA units per millilitre; LU, Luminex units; mMU/ml, milli-Merck units per millilitre; NR, not reported; RCT, randomised controlled trial;

* All reported time points, in months since first dose; months outside brackets are available data;

† If GMC ratio not reported in text, point estimate has been calculated from reported GMCs;

‡ Only for the 0, 2 months group

§ latest time point available, month 24

Table 9. Comparisons between 2-dose vs. 2-dose schedules (different dosage, same interval)

Study name; vaccine [refs]	Age, years	Dosage compared, months (dose 20µg unless stated)	GMC units	Timing of samples, available data in months (timing of samples, according to methods)*	HPV type	Dosage 1, GMC (95% CI), 1 month after last vaccine dose, per protocol	Dosage 2 (95% CI), 1 month after last vaccine dose, per protocol	Dosage 1:2 GMC ratio (95% CI), 1 month after last vaccine dose, per protocol†	Dosage 1:2 GMC ratio (95% CI), latest time point available, per protocol†
						Higher dose	*Standard dose*	*Higher:standard*	*Higher:standard*
Canada/Germany 1; bivalent [6-8]	9-14	0, 6 (40 µg)	EU/mL	0, 7, 24 (0, 7, 12, 18, 24, 48)	HPV 16	15304 (12855-18221)	11067 (9190-13328)	1.38 (1.07-1.79)	NR (1.4) ‡
		0, 6 (20 µg)			HPV 18	8155 (6671-9970)	5510 (4646-6535)	1. 48 (1.14-1.94)	NR (1.4) ‡
	15-19	0, 6 (40 µg)	EU/mL	0, 7 (0, 7, 12, 18, 24, 48)	HPV 16	11061 (9035-13541)	8442 (6895-10336)	1.31 (0.98-1.75)	NR
		0, 6 (20 µg)			HPV 18	6162 (4996-7601)	5142 (4354-6072)	1.20 (0.92-1.57)	NR
	20-25	0, 6 (40 µg)	EU/mL	0, 7 (0, 7, 12, 18, 24, 48)	HPV 16	8307 (6533-10564)	5673 (4377-7354)	1.46 (1.03-2.08)	NR
		0, 6 (20 µg)			HPV 18	4230 (3346-5349)	3523 (2514-4937)	1.20 (0.79-1.80)	NR

Abbreviations: GMC, Geometric mean concentration; EU/ml, ELISA units per millilitre; LU, Luminex units; mMU/ml, milli-Merck units per millilitre; NR, not reported; RCT, randomised controlled trial;

* All reported time points, in months since first dose; months outside brackets are available data;

† If GMC ratio not reported in text, point estimate has been calculated from reported GMCs;

‡ latest time point available, month 24

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Appendix 2:

Results from non-systematic review of the data from observational studies

Data available on schedule comparisons from observational studies in the literature and from studies presented at the WHO Ad-hoc Expert Consultation were summarized by the WHO Secretariat.

Contents

Evidence on the effect of fewer than 3 doses of HPV vaccine on important outcomes: Data from observational studies

Nine observational studies providing information on vaccine effectiveness among recipients of fewer than 3 doses were identified. Eight studies were conducted in industrialized countries and one was conducted in a low-income country. Table 1 provides an overview of the studies presented and identified.

Table 1. Overview of observational studies providing information on effect of fewer than 3 doses of HPV vaccines.

First author, year/ vaccine	Age group, year*	Comparisons	Outcomes reported
Gertig, 2013[2] Quadrivalent	≤ 17	unvaccinated vaccinated (unadjusted) vaccinated (adjusted) 1 dose 2 dose 1 or 2 doses complete	any high grade histological abnormalities
		unvaccinated vaccinated (unadjusted) vaccinated (adjusted) 1 dose 2 dose 1 or 2 doses complete	CIN3/AIS
		unvaccinated vaccinated (unadjusted) vaccinated (adjusted) 1 dose 2 dose 1 or 2 doses complete	CIN2
		unvaccinated vaccinated (unadjusted) vaccinated (adjusted) 1 dose 2 dose 1 or 2 doses complete	CIN1
		unvaccinated vaccinated (unadjusted) vaccinated (adjusted) 1 dose 2 dose 1 or 2 doses complete	any high grade cytological abnormalities
		unvaccinated vaccinated (unadjusted) vaccinated (adjusted) 1 dose	any low grade cytological abnormalities
Garland, 2013[4] Quadrivalent	born after 30 June 1981 (of vaccine eligible age ≤ 26 in 2007)	No doses + Vaccinated	CIN3+/AIS
	18-25		HPV infection
Blomberg, 2013[5] Quadrivalent	born 1995-1996 born 1993-1994 born 1991-1992 born 1989-1990	Vaccinated (at least one dose)	Risk of genital warts
Squarzon, 2013[1] Quadrivalent	11-13	3 doses	GMC
Pollock, 2013[11] Quadrivalent	Women attending first cervical smear		CIN3

[1] Squarzon, L. et al., Evaluation of neutralizing and cross-neutralizing antibodies induced by HPV prophylactic vaccines: an independent study. Eurogin 2013

First author, year/ vaccine	Age group, year*	Comparisons	Outcomes reported
Leval, 2013[5] Quadrivalent	<20 (10-44) 10-13 (14-16) (17-19) (20-22) (23-26) (>26) <20 (10-44) 10-13 (14-16) (17-19) (20-22) (23-26) (>26)	Vaccinated vs not fully vaccinated	Genital warts incidence
Herweijer, 2013[6 7] Quadrivalent	10-16 17-19 10-19 10-16 17-19 10-19	3 vs 2 doses	Genital warts incidence
Safaeian, 2012[10 9] Bivalent	18-25	1 vs 2 vs 3 doses	GMCs - HPV16
			GMCs- HPV18
Crowe, 2014[3] Quadrivalent	12-26 years (in 2007)	Vaccinated (1, 2, or 3 doses) vs unvaccinated	Exposure odds ratio Vaccine effectiveness

Quadrivalent vaccine

In Australia, this retrospective cohort linked data from the Victorian Cervical Cytology Registry (VCCR) and the National HPV Vaccination Program Register (NHVPR) and evaluated the effectiveness of the HPV vaccine against cervical abnormalities in a screening population of women eligible for vaccination in the school based cohorts (aged 17 or younger in 2007)[2]. The retrospective cohort was constructed of women aged 17 or younger in 2007 who had a Pap test recorded on the VCCR during the study period, 1 April 2007 (the date the HPV vaccination program commenced) to 31 December 2011. Women were counted as at risk of a diagnosis of a cervical abnormality from the time they commenced cervical screening, and were entered into the cohort at their first Pap test (or on 1 April 2007 if their first Pap test was prior to that time). Unvaccinated women were those who had no doses of HPV vaccine recorded on the NHVPR; vaccinated women were those who received any doses of HPV vaccine. Average follow up was 4.8 years. Women were 17 years or younger in 2007 and had a Pap test recorded during the study period (n=39,000). Censoring occurred at the date of outcome of interest, date of death, hysterectomy or end of study period. Vaccine effectiveness (VE) and hazard ratios (HR) for cervical abnormalities by vaccination status between 1 April 2007 and 31 December 2011 were calculated using proportional hazards regression. The analysis included 24,871women aged between 12 and 17 years who were vaccinated against HPV had commenced cervical screening. Of these women, 21,151 (85.0%) were completely vaccinated and 3,690 women had received one or two doses of vaccine. There were 14,085 unvaccinated women of the same age who had commenced cervical screening. The follow-up period was a maximum of 4.8 years with an average of 1.5 years for both vaccinated women and unvaccinated women. A lower risk of any histologically confirmed HG cervical abnormality was observed for vaccinated women (any dose) compared with unvaccinated women with a hazard ratio of 0.72 (95% CI 0.58 to 0.91), after adjusting for age at first screening, SES and remoteness. This effect was strongest for completely vaccinated women; there was no significant reduction among those partially vaccinated, but the number of outcomes was small. There was a reduced risk of LG cytological abnormalities for women who received one or two doses of vaccine HR 0.66 (95%

[2] Gertig, D.M., et al., Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. BMC Med, 2013. 11(1): p. 227

CI 0.60 to 0.72) compared with unvaccinated women. Vaccine effectiveness (VE), adjusted for remoteness, SES and age at first Pap test, was highest for CIN3/AIS at 47.5% (95% CI 22.7 to 64.4) for women who were completely vaccinated (compared to no doses), and was slightly lower for women who received any dose of vaccine 36.4% (95% CI 9.8 to 55.1). Methodological issues in relation to less than 3 doses may include misclassification of 2 doses (3?); assignment of dose status – time varying vs final dose; residual confounding – those who receive 2 doses in the real world may be different from those who complete the course and censoring of histological outcomes.

A case control study measured the effectiveness of the quadrivalent HPV vaccine against cervical abnormalities four years after implementation of a nationally funded vaccination programme in Queensland, Australia.[3] Participants were women eligible for free vaccination (aged 12-26 years in 2007) and attending for their first cervical smear test between April 2007 and March 2011. High grade cases were women with histologically confirmed high grade cervical abnormalities (n=1062) and "other cases" were women with any other abnormality at cytology or histology (n=10 887). Controls were women with normal cytology (n=96 404).The adjusted odds ratio for exposure to three doses of HPV vaccine compared with no vaccine was 0.54 (95% confidence interval 0.43 to 0.67) for high grade cases and 0.66 (95% CI 0.62 to 0.70) for other cases compared with controls with normal cytology, equating to vaccine effectiveness of 46% and 34%, respectively. The adjusted exposure odds ratios for two vaccine doses were 0.79 (95% CI 0.64 to 0.98) for high grade cases and 0.79 (95% CI 0.74 to 0.85) for other cases, equating to vaccine effectiveness of 21%.

A cross-sectional study -the Vaccine Against Cervical Cancer Impact and Effectiveness (VACCINE)- which focused on HPV vaccine-related infection and disease (CIN3) outcome, began in 2011, in Victoria, Australia.[4] VACCINE consisted of 2 sub-studies (A and B). Sub-study A involved Facebook recruitment of 1500 young women 18-25 years to undertake a questionnaire on line, and send a self-collected vaginal swab for HPV detection and genotyping. Sub-study B is recruiting 500 cases of CIN3/ACIS biopsies from women born after the 30th of June 1981 (of vaccine eligible age of ≤ 26 in 2007). Laser microdissection is being employed to attribute single HPV genotypes to separate CIN3 lesions. In an interim analysis of 395 subjects for sub-study A, the prevalence of HPV16 was only 1.6% (95%CI 0.6 to3.5%) and for any high risk HPV type was 14.4% (95% CI 11.0 to18.4%). No HPV18 was detected. Eighty one percent of the cohort was fully vaccinated.

Using individual-level data from the entire Swedish population a study assessed genital warts (GW) incidence after on-demand vaccination with quadrivalent HPV vaccine[5]. An open cohort of girls and women aged 10 to 44 years living in Sweden between 2006 and 2010 (N > 2.2 million) was linked to multiple population registers to identify incident GW in relation to HPV vaccination. For vaccine effectiveness, incidence rate ratios of GW were estimated using time-to-event analyses with adjustment for attained age and parental education level, stratifying on age at first vaccination. A total of 124 000 girls and women were vaccinated between 2006 and 2010. Girls and women with at least one university-educated parent were 15 times more likely to be vaccinated before age 20 years than girls and women whose parents did not complete high school (relative risk ratio = 15.45, 95% CI14.65 to 16.30). Among those aged older than 20 years, GW rates declined among the unvaccinated, suggesting that HPV vaccines were preferentially used by women at high risk of GW.

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[3] Crowe, E., et al. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. BMJ 2014; 348:g1458. doi: http://dx.doi.org/10.1136/bmj.g1458 (Published 4 March 2014).

[4] Garland, S.M., et al. Measures of vaccine effectiveness. Abstract no. SS 22-7 in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy

[5] Leval, A., et al., Quadrivalent human papillomavirus vaccine effectiveness: a Swedish national cohort study. J Natl Cancer Inst, 2013. 105(7): p. 469-74.

Vaccination effectiveness (VE) was 76% (95% CI 73 to 79) among those who received three doses of the vaccine with their first dose before age 20 years. Vaccine effectiveness was highest in girls vaccinated before age 14 years (VE 93%, 95% CI 73 to 98).

In Sweden, a population based study to examine the association between quadrivalent HPV vaccination and first occurrence of condyloma in relation to vaccine dose was conducted.[6, 7] An open cohort of all females aged 10 to 24 years living in Sweden (n = 1 045 165) was followed up between 2006 and 2010 for HPV vaccination and first occurrence of condyloma using the Swedish nationwide population-based health data registers. Incidence rate ratios (IRRs) and incidence rate differences (IRDs) of condyloma were estimated using Poisson regression with vaccine dose as a time-dependent exposure, adjusting for attained age and parental education, and stratified on age at first vaccination. To account for prevalent infections, models included a buffer period of delayed case counting. A total of 20 383 incident cases of condyloma were identified during follow-up, including 322 cases after receipt of at least 1 dose of the vaccine. For individuals aged 10 to 16 years at first vaccination, receipt of 3 doses was associated with an IRR of 0.18 (95%CI, 0.15 to 0.22) for condyloma, whereas receipt of 2 doses was associated with an IRR of 0.29 (95%CI, 0.21 to 0.40). One dose was associated with an IRR of 0.31 (95%CI, 0.20 to 0.49), which corresponds to an IRD of 384 cases (95%CI, 305 to 464) per 100 000 person-years, compared with no vaccination. The corresponding IRDs for 2 doses were 400 cases (95%CI, 346 to 454) and for 3 doses, 459 cases (95%CI, 437 to 482). The number of prevented cases between 3 and 2 doses was 59 (95%CI, 2 to117) per 100 000 person-years.

Although maximum reduction in condyloma risk was seen after receipt of 3 doses of quadrivalent HPV vaccine, receipt of 1 or 2 vaccine doses was also associated with a considerable reduction in condyloma risk. The implications of these findings for the relationship between number of vaccine doses and cervical cancer risk require further investigation, especially regarding the interval between the first and the 2nd dose. Substantial protection was found with less than three doses. The additional protection provided with the 3rd dose, especially in the 10-16 group, was limited and sensitive to buffer period length. Using a longer buffer period (>5 months) to account for prevalent infections resulted in no significant effectiveness differences between 2 and 3 doses. The study had limited power to assess dose effectiveness in girls first-vaccinated at ages 10-13.

A cohort study aiming to use individual information on HPV vaccination status to assess the effect on risk of GWs was conducted in Denmark.[8] Population-based registries were used to identify all girls in the birth cohorts 1989–1999 in Denmark, and information about HPV vaccination was obtained for the period 2006–2012. The cohort was linked to incident cases of GWs, and vaccinated and unvaccinated girls were compared using Cox proportional hazards models. A total of 248 403 girls were vaccinated. The relative risk of GWs among girls who had received at least 1 dose of vaccine compared with unvaccinated girls was 0.12, 0.22, 0.25, and 0.62 for those born in 1995–1996, 1993–1994, 1991–1992, and 1989–1990, respectively (*P* for trend <.0001). No GWs occurred among vaccinated girls in the youngest birth cohort (1997–1999).

[6] Herweijer, E., Association of Varying Number of Doses of Quadrivalent Human Papillomavirus Vaccine With Incidence of Condyloma. JAMA. 2014;311(6):597-603. doi:10.1001/jama.2014.95.

[7] Herweijer, E., et al. Dose effectiveness of quadrivalent human papillomavirus vaccine: A national cohort study. Abstract no. OC 6-6 in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

[8] Blomberg, M., et al., Strongly decreased risk of genital warts after vaccination against human papillomavirus: nationwide follow-up of vaccinated and unvaccinated girls in Denmark. Clin Infect Dis, 2013. 57(7): p. 929-34.

Bivalent vaccine

Young girls who participated in an HPV vaccine demonstration project in Uganda (2008-2009) were eligible for this study.[9,10] The study included all girls who had received one or two HPV vaccine doses (at whatever interval), and a subset from those who had received all three doses. In addition inclusion criteria required at least 24 months since receipt of their last vaccine dose (1 dose=37; 2 doses=144, 3 doses=195). HPV16 and HPV18 specific antibody levels were measured using an enzyme linked immunoassay (ELISA). Non-inferiority was assumed if the lower bound of the multiplicity-adjusted confidence interval (CI) of the type-specific geometric mean titer (GMT) ratio was greater than 0.5. The ratio of HPV16 and HPV18 GMTs comparing 2 dose to 3 dose groups were 0.51 (97.5%CI=0.37-0.69), and 0.69 (97.5%CI=0.50-0.96). HPV16 and HPV18 antibody GMTs were higher in all dose groups compared to naturally infected women from Costa Rica HPV Vaccine Trial (CVT) (HPV16 natural infection=37 vs. HPV16 1 dose=234, HPV16 2 doses=812, HPV16 3 doses=1608; p-value<0.001). Anti-HPV18 GMTs for 1, 2, 3, dose groups were 85, 274, and 396, respectively, compared to 19 among naturally infected (p-value for Uganda 1 dose vs. CVT<0.001).

An observational study using the data from a programme of longitudinal HPV surveillance was conducted in Scotland.[11] Key elements of surveillance were yearly sampling and HPV genotyping of women attending for their first smear and the monitoring of high-grade lesion prevalence through interrogation of national databases. As age at screening debut is currently 20 in Scotland, this data was used to determine the impact of a national immunisation programme on rates of HPV infection and HPV associated disease. Liquid-based cytology (LBC) samples from women attending their first cervical smear were genotyped for HPV and data linkage enabled HPV prevalence to be stratified by immunisation status. In addition, analysis included data from the National Colposcopy Clinical Information and Audit System (NCCIAS), a national colposcopy database that contains data on referral cytology, interventions and histology results associated with any colposcopy visit. While the vaccine was not associated with a reduction in low-grade cervical abnormalities, there was a statistically significant reduction in CIN3 diagnoses associated with vaccination status.

Summary of findings from observational studies providing information on effect of fewer than 3 doses of HPV vaccines

These observational studies reporting vaccine effectiveness after 2 versus 3 doses are based on a prime, prime, boost schedule. Contrastingly, a prime-boost alternative schedule may require a longer interval between doses. When interpreting effectiveness of 2 dose schedules, it is important to take into account that a 2-dose schedule must include at least 4 months before the 2nd dose to fulfill the criteria of a prime-boost (and not a prime-prime) schedule.

[9] http://www.childsurvival.net/?content=com_articles&artid=1666.

[10] Safaeien, M. Immunogenicity of the bivalent HPV vaccine among partially vaccinated young girls in Uganda. in 28th International Papillomavirus Conference & Clinical and Public Health Workshops, Abstract book page no. 326. 2012: San Juan, Puerto Rico.

[11] Pollock, K., et al. Early effect of the HPV bivalent vaccine on high-risk HPV prevalence and high-grade cervical abnormalities in Scotland. Abstract no. OC 6-2 in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

Table 2. Summary of findings from observational studies providing information on effect of fewer than 3 doses of HPV vaccines

Country	First author, year, ref	Comparison	Outcomes reported	Estimate type	Estimated Value	lower limit	upper limit
Australia	Gertig, 2013[2]	unvaccinated	any high grade histological abnormalities	Hazard Ratio	1		
		vaccinated (unadjusted)			0.76	0.61	0.95
		vaccinated (adjusted)			0.72	0.58	0.91
		1 dose			1.47	0.97	2.23
		2 dose			1.02	0.68	1.53
		1 or 2 doses			1.2	0.88	1.65
		complete			0.61	0.48	0.78
		unvaccinated	CIN3/AIS		1		
		vaccinated (unadjusted)			0.68	0.48	0.95
		vaccinated (adjusted)			0.64	0.45	0.9
		1 dose			1.4	0.75	2.61
		2 dose			0.87	0.46	1.67
		1 or 2 doses			1.09	0.67	1.76
		complete			0.53	0.36	0.77
		unvaccinated	CIN2		1		
		vaccinated (unadjusted)			0.81	0.61	1.06
		vaccinated (adjusted)			0.78	0.59	1.03
		1 dose			1.29	0.76	2.2
		2 dose			0.99	0.59	1.64
		1 or 2 doses			1.11	0.75	1.66
		complete			0.7	0.52	0.94
		unvaccinated	CIN1		1		
		vaccinated (unadjusted)			0.86	0.7	1.05
		vaccinated (adjusted)			0.83	0.68	1.02
		1 dose			0.89	0.56	1.41
		2 dose			0.9	0.61	1.33
		1 or 2 doses			0.9	0.65	1.23
		complete			0.82	0.66	1.01
		unvaccinated	any high grade cytological abnormalities		1		
		vaccinated (unadjusted)			0.77	0.67	0.89
		vaccinated (adjusted)			0.75	0.65	0.87
		1 dose			0.85	0.62	1.17
		2 dose			0.95	0.73	1.23
		1 or 2 doses			0.91	0.73	1.13
		complete			0.71	0.61	0.83
		unvaccinated	any low grade cytological abnormalities		1		
		vaccinated (unadjusted)			0.77	0.73	0.82
		vaccinated (adjusted)			0.76	0.72	0.8
		1 dose			0.67	0.59	0.76
Australia	Garland, 2013[4]	No doses	CIN3+/AIS HPV infection	Prevalence of HPV16	1.60%	0.6	3.5
		±Vaccinated		Prevalence of any risk HPV type	14.40%	11	18.4
Australia	Crowe 2014[3]	Vaccinated (1, 2, or 3 doses) vs unvaccinated	Cervical abnormalities – high grade cases	Exposure odds ratio 3 vs 0 doses	0.54	0.43	0.67
			Cervical abnormalities – other grade cases	Exposure odds ratio 3 vs 0 doses	0.66	0.62	0.70
			Cervical abnormalities – high grade cases	Exposure odds ratio 2 vs 0 doses	0.79	0.64	0.98
			Cervical abnormalities – other grade cases	Exposure odds ratio 2 vs 0 doses	0.79	0.74	0.85
Denmark[8]	Blomberg, 2013[8]	Vaccinated born 1995-1996	Risk of genital warts vaccinated (at least one dose) vs unvaccinated	relative risk of vaccinated vs unvaccinated	0.12		
		Vaccinated born 1993-1994			0.22		
		Vaccinated born 1991-1992			0.25		
		Vaccinated born 1989-1990			0.62		

Country	First author, year, ref	Comparison	Outcomes reported	Estimate type	Estimated Value	lower limit	upper limit
Sweden	Leval, 2013[5]	< 20 y	Genital warts incidence vaccinated vs not fully vaccinated	Incidence rate ratios	0.24	0.21	0.27
		10-44 y			0.27	0.24	0.3
		10-13 y			0.07	0.02	0.27
		14-16 y			0.2	0.17	0.25
		17-19 y			0.29	0.24	0.35
		20-22 y			0.52	0.35	0.78
		23-26 y			0.79	0.47	1.33
		≥ 27 y			2.32	0.87	6.18
		< 20 y		Effectiveness %	76	73	79
		10-44 y			73	70	76
		10-13 y			93	73	98
		14-16 y			80	75	83
		17-19 y			71	65	76
		20-22 y			48	22	65
		23-26 y			21	<0	53
		≥ 27 y			<0	<0	13
Sweden	Herweijer, 2013[6 7]	3 vs 2 d in 10-16 y	prevalence of HPV 16	Incidence rate ratios	0.63	0.43	0.93
		3 vs 2 d in 17-19 y			0.66	0.45	0.95
		3 vs 2 d in 10-19 y			0.63	0.48	0.82
		3 vs 2 d in 10-16 y		Incidence rate difference	59	2	117
		3 vs 2 d in 17-19 y			67	3	132
		3 vs 2 d in 10-19 y			66	23	109
Uganda	Safaeian, 2012[9 10]	2 vs 3 doses	GMCs - HPV16	GMT ratios	0.51	0.37	0.69
			GMCs- HPV18		0.69	0.5	0.96
* Age groups in brackets are outside range defined in PICO ; ± vaccinated schedule not reported assume licensed schedule							

WHO SAGE pertussis working group

Background paper

SAGE April 2014

14 March 2014

Composition of the Working Group:

- Elizabeth Miller (Working Group Chair until February 2014), Immunisation Department, Colindale, UK
- Claire-Anne Siegrist, (Working Group Chair since February 2014) Department of Pediatrics, University of Geneva, Switzerland
- Piyanit Tharmaphornpilas, National Immunization Program, Ministry of Public Health, Nonthaburi, Thailand
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- Gabriela Moreno, Departments of Epidemiology and Immunizations, Ministry of Health, Santiago, Chile
- Carl Heinz Wirsing von König, National reference laboratory for *Bordetella* infections, Krefeld, Germany

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- Philippe Duclos
- Ana-Maria Henao-Restrepo
- Melanie Schuster
- Cuauhtémoc Ruiz-Matus (replaced by Cristina Pedreira in February 2013)
- Mark Muscat

Contents

1. Introduction

In the light of the recent increase in reported pertussis cases from some countries, which were in some instances associated with an increase in infant deaths, SAGE and the WHO agreed that a new working group on pertussis would be established. This working group would first prepare for a SAGE review of the data and would then consider updating current pertussis vaccine recommendations as published in the 2010 pertussis vaccine position paper (http://www.who.int/wer/2010/wer8540.pdf). This also provided an opportunity to review newly available data on effectiveness of various vaccination strategies aimed at reducing infant mortality, as well as the pertussis-related outcomes of the vaccine schedule optimization project.

The terms of reference for the SAGE pertussis vaccines working group were:

1. Review epidemiological data on pertussis from selected countries using acellular pertussis (aP) and/or whole cell pertussis (wP) vaccines and evaluate the evidence for resurgence of pertussis, with an emphasis on severe pertussis in very young infants. In countries where the evidence supports resurgence, evaluate the evidence for the hypothesis that resurgence is due to shorter lived protection from aP relative to wP vaccines;
2. Review the evidence on effectiveness of 1 or 2 doses of pertussis vaccines against severe disease and death in young infants;
3. Review the evidence on effectiveness of three keys strategies aimed at reducing severe disease and death from pertussis in very young infants (cocooning, maternal immunization during pregnancy, and immunization of newborns);
4. Review the evidence for optimal primary vaccination scheduling and timing of booster dose(s);
5. Review the evidence that changes in circulating pertussis strains have had an adverse impact on the effectiveness of aP or wP vaccines;
6. Propose updated recommendations for SAGE consideration on the use of pertussis vaccines.

The working group has completed its review in relation with points 1, 2, 3, 5, of its terms of reference. The review of the optimal primary immunization schedules as per point 4 of the terms of reference is still ongoing and will be completed in the summer of 2014 and presented at the October 2014 SAGE meeting. This review entails a 4-component framework (epidemiology of the diseases, systematic review of the effectiveness and safety of the various schedules, operational considerations, and models & ICEA) following the model already applied to pneumococcal conjugate, rotavirus and *Haemophilus influenzae* type b (Hib) vaccines. Both combined diphtheria, tetanus toxoid and pertussis vaccine (DTP) and tetanus toxoid vaccine (TT) schedules will be reviewed by the pertussis working group in view of the impossibility of disentangling the primary vaccination schedule for pertussis from that of diphtheria and tetanus and the interrelation of the TT and DTP schedules. Point 6 of the terms of reference will only be fully completed after completion of point 4.

The 2010 pertussis position paper will be revisited only after the results of the review are available. In the meantime, a brief update to the position paper will be published, pending the decision made by SAGE at its April meeting.

2. Review of country specific information

Methods

A total of 21 countries (Argentina, Australia, Brazil, Canada, Chile, Colombia, Cuba, Denmark, Finland, France, Germany, Israel, Japan, Mexico, Norway, Portugal, Singapore, Sweden, Thailand, UK, and USA) were approached for detailed data collection. A standardized questionnaire developed by the working group (Annex 2) was used to capture information on pertussis incidence, vaccination coverage and schedule, surveillance methods, case definitions, and type of vaccine used. Relevant publications were also used to complete information from the questionnaire. The selected countries were not globally representative but were chosen on the basis that they were believed to have long-standing high vaccine coverage rates and effective disease control, and were able to provide high quality data on vaccine coverage and trends in pertussis disease burden over time. The countries selected were chosen to include representation from those with or without an apparent pertussis resurgence, those with wP or aP based programs, developing and industrialized countries, and different regions of the world.
The working group defined the term "resurgence" as a larger burden of disease than expected, given the periodic variability of naturally recurring pertussis disease, when compared to previous cycles in the same setting.

Results

The working group was presented with evidence derived from 19 countries (Figure 1 and Figure 2) on various measures of pertussis incidence, vaccination coverage and schedules in the context of the surveillance methods, case definitions and type of vaccine used. 15 countries were high income countries, 4 were upper middle income countries.[1] Two countries (Argentina and Colombia) did not return the completed questionnaire and insufficient information was available in published papers to allow for inclusion of data.

[1] World Bank List of Economies – as of Nov 19, 2013. www.worldbank_list_of_economies.com [accessed 19.11.13].

Figure 1: Total country populations

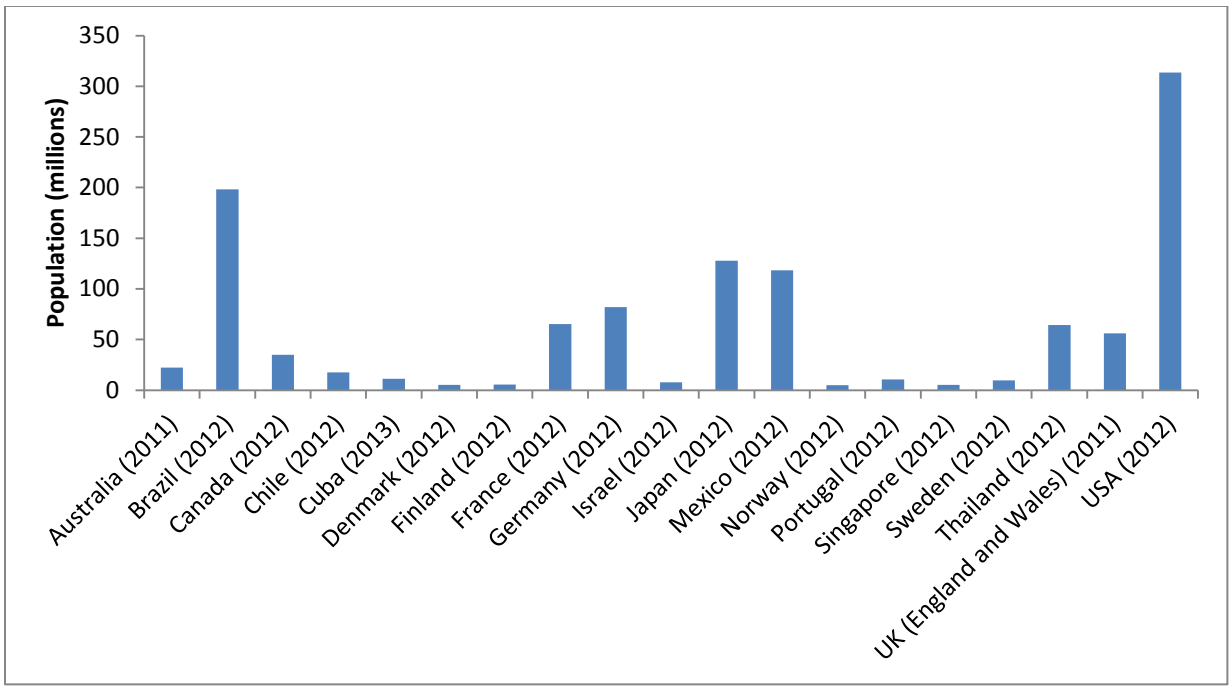
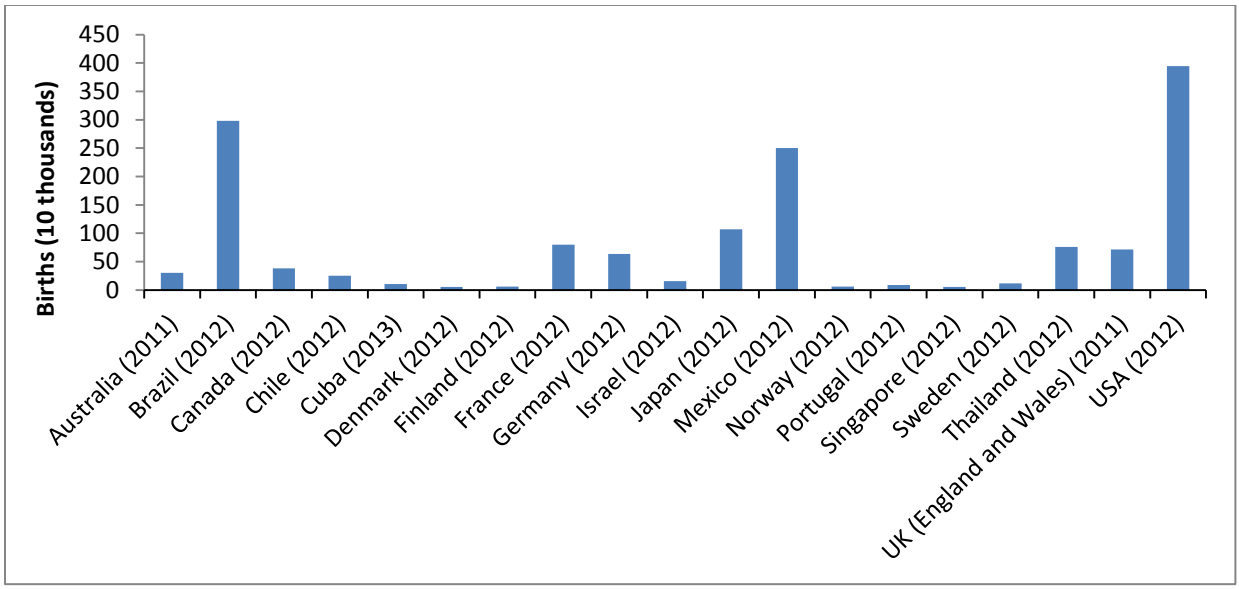


Figure 2: Total country births per year

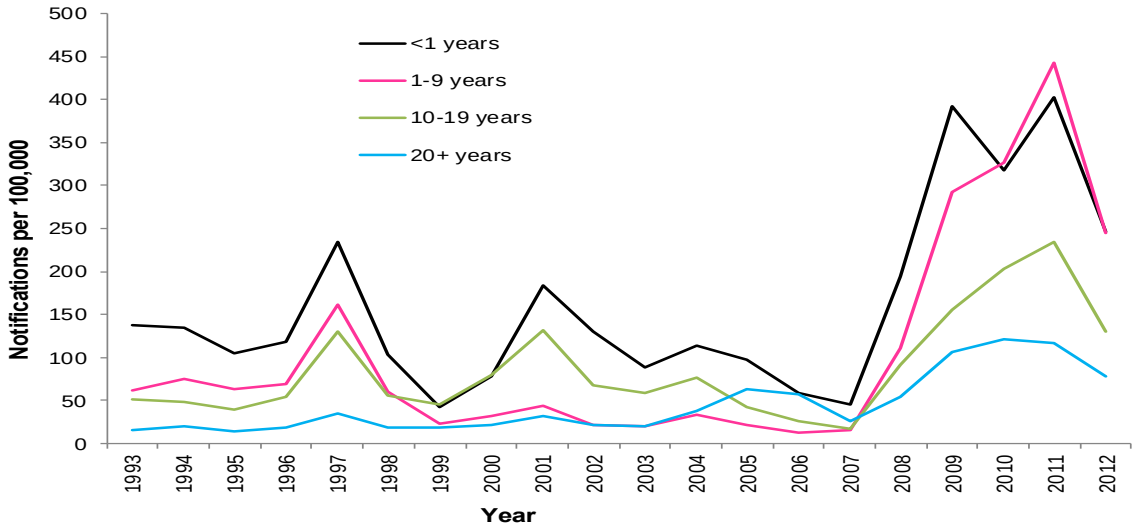


Australia (total population in 2012: 23.05 M)

Surveillance	Mandatory universal laboratory (public & private) reporting since 1993.
Laboratory confirmation	Culture (all years), immunofluorescence (from 1980s), serology (from 1990s) and PCR (from 2000, in hospitals). Reimbursement changes led to PCR tests being readily available in primary care from 2007, with an estimated 7 fold increase in use in this sector. All reports based on PCR or culture are deemed confirmed irrespective of clinical symptoms; individual follow up of cases is largely restricted to children under 5 years of age.
Vaccination coverage	95% for the full primary series (DPT3) at the age of 24 months at the national level, but there are pockets of low coverage (<85%), predominantly in alternate lifestyle regions outside capital cities.
Current vaccine in use	aP (3 component)
Vaccination recommendations	Australia used a locally manufactured wP from 1975 to 1996; a booster dose at 18 months was re-introduced in 1983 and a pre-school dose was introduced in 1995. Acellular pertussis vaccine (DTaP) has been used for booster doses since 1997 and exclusively since 1999. Until September 2003, the recommended primary schedule was 3 doses at 2, 4 and 6 months, with boosters at 18 months and 4 years. In 2003, the 18 month dose was removed in favour of an adolescent booster dose, which was given in schools at varying ages (11-17 years) from 2004. Recommendations for adults (Health Care Workers (HCW), those with contact with infants, child-care personal, pregnant women) exist but doses are not funded by the national immunization program. However, a number of Australian States have provided funding for free of charge adult vaccination in the context of “cocoon” programs during outbreaks from 2009.

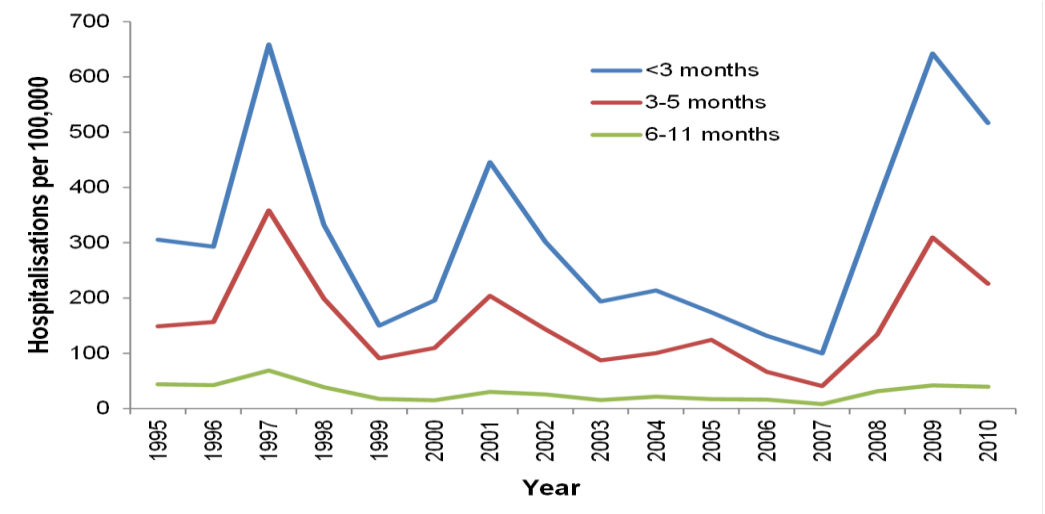
There has been a notable rise in pertussis incidence since 2008, with epidemic activity occurring at varying times in different areas of Australia (Figure 3). In contrast to previous epidemics in 2001 and 1997, the steepest increase was among children under 10 years. In children, the most notable increases in notified cases have been in 2 to 4 year olds and in 5 to 9 year olds. In persons over 15, the highest and most steeply increasing incidence of pertussis has been in those over 60 years of age.

Figure 3: Incidence of reported pertussis cases in Australia



In the era before PCR was widely available, more hospitalizations than notifications were recorded in infants less than 1 year; since 2000, notification rates exceeded hospitalization rates in this age group (Figure 4), as reporting relies more on PCR positives from laboratories than clinicians. Despite greatly increased use of PCR, hospitalization rates have not increased over historical levels, suggesting that most of the observed increase has been in less severe cases. Reported deaths from pertussis have decreased in the most recent epidemic period. Mortality per 1 million births was 7.5 (95% CI: 4.5-11.7) from 1993 to 2002, but declined to 4.3 (95% CI: 2.2-7.5) from 2003 to 2012, despite PCR being available to increase diagnostic test sensitivity.

Figure 4: Incidence of pertussis hospitalisations in Australia, infants aged <1 year



Key conclusions	• Data quality from Australia was judged to be good. • Resurgence of pertussis was seen from 2008-2012 in children less than 10 years of age, in particular in 2-4 year olds and 7 to 9 year olds. • Pertussis is a major public health issue in Australia, with a continuous increase observed over a long period of time, first in adults related to availability of serologic tests, then in adolescents related to low historical vaccine coverage, and most recently in younger children consistent with waning immunity in the context of increased test availability and use. No other country using acellular vaccines has seen such a major increase in 2 to 3 year old children; other countries have seen increased cases from 6 years of age, but these apparent increases have been magnified by testing. • Cessation of the 18 month booster dose appears to be an important contributor to resurgence in 2 to 4 year olds, with early waning immunity following the last acellular vaccine dose at 6 months. As in the US, large increases in cases over 6 years of age have been observed, and there are Australian data to support a shorter duration of immunity among children who have received aP vaccines than in those who received the Australian-manufactured wP. • The resurgence was not associated with any increase in infant pertussis deaths, which have remained similar or lower to that of previous pertussis epidemics in the past 2 decades despite more sensitive diagnostic tests.

Brazil (total population in 2012: 198.66 M)

Surveillance	Mandatory universal passive notification; hospitalization and mortality data are obtained through the reporting system and/or taken from hospital records (ICD coded).
Laboratory confirmation	In the past, laboratory confirmation was obtained using culture; in 2008 PCR was introduced and is currently being implemented nationwide. In 2012, 41% of the cases in 2012 were lab confirmed (PCR or culture), 47% were clinical and 11% were epi-clinically confirmed (1% not provided). Sensitivity of the surveillance system increased in 2011.
Vaccination coverage	From 2001-2011, national vaccination coverage in infants <1 year with DTP3 was high (>95%). In 2012, a decrease was observed due to supply issues. From 2006 to 2012, the number of municipalities with >95% DTP3 coverage decreased from 83% to 55% with non-homogenous coverage throughout the country. Causes for the decline were mainly operational issues as social acceptance of vaccination in Brazil is high.
Current vaccine in use	wP (private sector is using combination aP vaccines; this market targets around 10% of the population)
Vaccination recommendations	Brazil introduced a wP primary 3 dose schedule plus a booster at 15 months in 1977 (DTwP). A 2nd booster was introduced at age of 4-6 years in 2004. Pentavalent wP vaccine (Crucell; Serum Institute India) was introduced in 2012, with retention of DTwP for booster dose. Pentavalent vaccine is used as a 3-dose primary schedule at 2, 4, and 6 months of age; the booster doses of

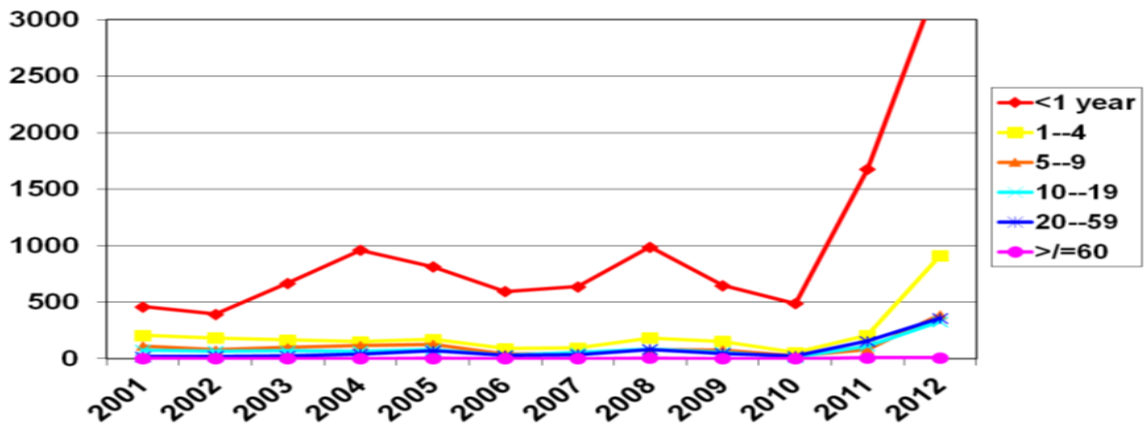
	DTwP (Butantan) are recommended at 15 months of age and 4 years of age (Sanofi Pasteur). The country will recommend Tdap in the routine immunization programme for pregnant women from 2014 onwards.

The number of pertussis cases increased from 2001- 2012 (Figure 5). In 2011 and 2012, there was an apparently large increase in morbidity and mortality among infants less than 1 year of age. In mid-2011, there was a sudden increase of the number of cases starting from the epidemiologic week 30, attributed to improvement in the sensitivity of the surveillance. Between 2007 and 2012, 51% of the reported pertussis cases under 6 months of age had not received any doses, 37% had received only one dose of pertussis vaccination, and 12% had received 2 or more doses. The majority of cases (75%) reported were from the South and South-East of the country, in states representing around 45% of the population. As the most recent hospitalization data available are from 2007, confirmation of this increase in reported cases through hospitalizations rates in infants under 1 is not possible. Within the Brazilian national notifiable diseases information system (SINAN), 25% of the notified hospitalized cases do not have any data on vaccination status. Of those hospitalized cases where information on the vaccination status is provided, approximately 50% have received a full primary series of pertussis vaccination. Generally outbreaks do not account for the majority of cases; the last outbreak reported in 2010 had fewer than 25 cases.

The accumulated number of deaths from 2000 to 2012 is reported by age-group. Of all deaths, 342 (97%) occurred in infants under 1 year. In older age groups, only 10 deaths are reported for this time period. Between 2008 and 2012, 185 pertussis-related deaths occurred in children less than 4 years of age: 125 had never been vaccinated, 20 had received one dose, 2 had received 2 doses, 1 case had received 3 doses, and 2 cases had received 3 doses plus the first booster. The immunization status was unknown for 35 of the deaths.

The increase in fatal cases among infants led the country to introduce aP in pregnant women and recommend a cocooning strategy. An increase in cases was observed in neighboring countries as well.

Figure 5: Pertussis cases by age group, Brazil, 2001 to 2012



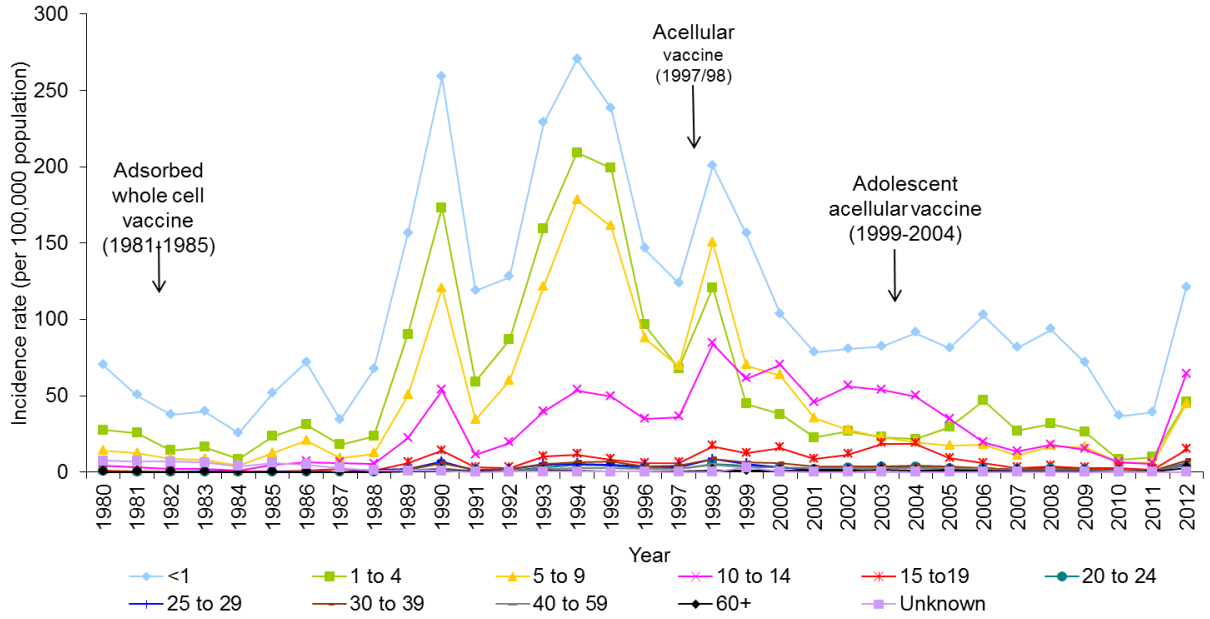
Key conclusions:	• Data quality is reasonable but could be improved. Reporting and testing has been suboptimal. • Evidence to confirm pertussis resurgence is limited. A recurrence of the natural cycle might be responsible for the observed trends as hardly any cases after 5 years of age were seen. A drop in coverage might have led to an increase in cases. The increase in laboratory testing and increased sensitivity of surveillance might have magnified the increase in reported disease, supported by the fact that the increase is seen in infants and not in older age-groups. • There is no evidence for waning immunity as it is predominantly infants too young to be immunized that have been affected.

Canada (total population in 2012: 34.84 M)

Surveillance	Mandatory universal passive notification as a statutory requirement for laboratory and clinicians plus active surveillance system: the pediatric tertiary care hospital active system (IMPACT). Data on hospitalization and deaths are obtained through ICD10 or IMPACT.
Laboratory confirmation	In the past, laboratory confirmation was obtained using culture; in 2000 PCR was introduced and is currently being implemented nationwide (91% of cases).
Vaccination coverage	Coverage is 99% for DTP3 at 24 months, 98% for the first booster at 2 years of age, 67% for the 7 year booster, and around 90% for the adolescent booster dose (varies by province).
Current vaccine in use	aP
Vaccination recommendations	wP was used until 1997-1998. In 1997, aP was introduced. The current vaccination schedule includes primary vaccination at 2, 4, 6, and 18 months using DTaP-IPV-Hib or DTaP-IPV-Hib-HepB, a booster dose using DTaP-IPV or TdaP-IPV at 4-6 years, an adolescent booster at 12-16 years (depending on the province) and an adult booster, both with Tdap. The adolescent booster dose was introduced in 2003. Cocooning or post-partum vaccination is recommended in 4 provinces if no adult booster has been received.

Over the last 30 years disease cycles have recurred periodically every 4 years, with the largest peaks observed in 1990, 1994, and 1998. During the last 10 years, several cycles had been missed. In 2012, a slight increase in cases was observed in comparison to the preceding years (Figure 6). The resurgence observed in the 1990s was likely due to a combination of factors, including the low efficacy of the whole-cell vaccine introduced between 1981 and 1985[1-3], as well as increased physician awareness, improved diagnostics, and improved reporting of pertussis infection[4] .

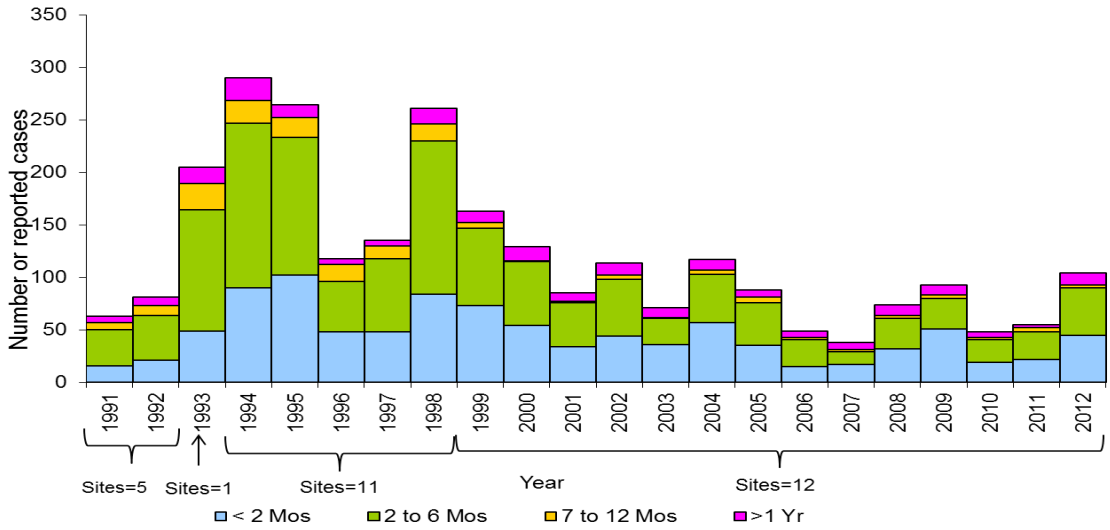
Figure 6: Incidence of pertussis in Canada by age group from 1980 to 2012



An increase in cases was generally limited to certain regions over discrete time periods. There were 3 outbreaks in the last few years, mainly related to religious or aboriginal communities with subsequent spread to neighboring provinces.

Hospitalization data from IMPACT sites suggest most admitted pediatric cases are restricted to infants less than 6 months of age (Figure 7).

Figure 7: Reported pertussis hospitalizations admitted to Canadian IMPACT sites by age group and year, 1990 to 2012



Annual death numbers are low; on average 1-4 cases occur per year with no change over time. In 2012, a total of 3 deaths were reported (7.9/1.000.000 births), all in infants less than 2 months of age.

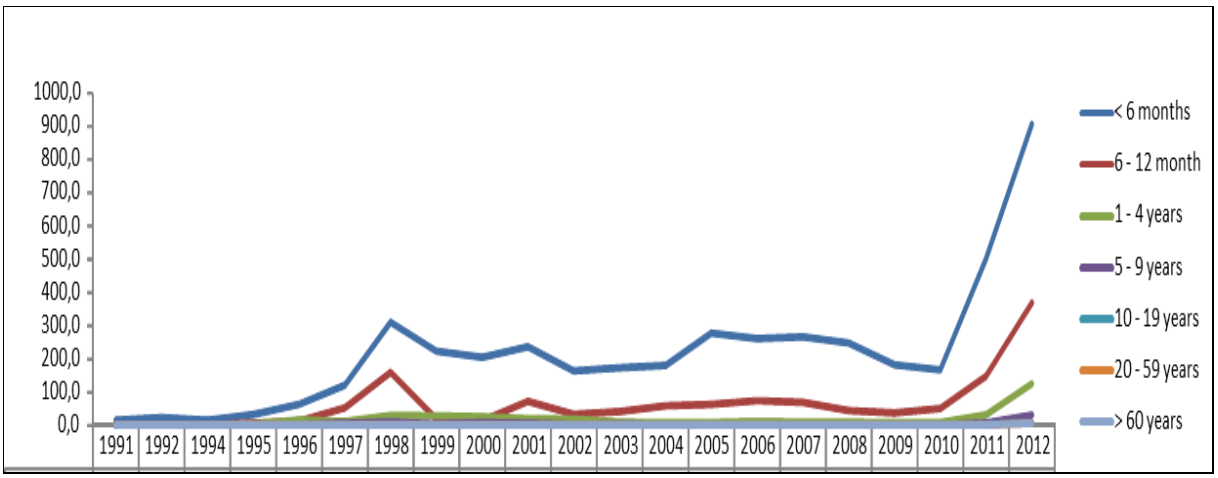
Key conclusions:	• Data quality is good but there are reporting gaps. • No resurgence was observed, but the periodic cycle had a higher peak in 2012 than the 2 cycles before. An increase in cases was mostly limited to certain regions over discrete time periods. • In general, the situation in the country is very heterogeneous with multiple causes of increase (low coverage, waning immunity, earlier wP vaccine with low vaccine effectiveness), yet there is no evidence that aP has contributed to the most recent increase in cases. • Data suggest some aP-induced waning of immunity before adolescent booster; hence, it is concluded that the timing of adolescent booster is important with 14 to 16 years of age being too late for the 3rd booster.

Chile (total population in 2012: 17.46 M)

Surveillance	Mandatory universal passive notification since 2000. A national system is in place to register hospitalization and death from pertussis.
Laboratory confirmation	Laboratory method used is direct immunofluorescence (DIF); PCR is not used in the whole country, only in 6 large hospitals. Only 0.5% of the cases were laboratory confirmed in 2012.
Vaccination coverage	In 2012, coverage was 92.8% (DPT3) for the full primary series at 24 months and 90.9% for the first booster dose. School entry coverage was 77.0% for the DTP pre-school booster at 4 years in 2011, and 57.9% for Tdap pre-school booster at 6 years in 2012.
Current vaccine in use	wP (multiple s used historically there have been several switches of vaccine, including those from Sanofi Pasteur, SII, GSK , Biosano, and Novartis products)
Vaccination recommendations	DTwP was used from 1952 to 1971 with a 3 dose primary schedule at 4, 6, and 18 months, and a pre-school booster at 4 years. From 1975-2011, DTwP was used with a 3 dose primary schedule at 2, 4, 6 months, a booster at 18 months, and a pre-school booster at 4 years. Since 2012, Tdap as a 3/5 component vaccine has been recommended, the pre-school booster was moved from 4 to 6 years, and cocooning was recommended for adults. In 2013, the pre-school booster was dropped and an adolescent booster (Adacel) at 13 years was introduced.

In 2011, an ongoing significant increase in notified cases over all age groups was observed. Children <6 months and <1 year of age were particularly affected (Figure 8). Vaccination coverage (full primary schedule) was 61.4% among the reported cases in 6-11 month old children.

Figure 8: Pertussis incidence per 100,000 population by age in Chile, 1991 to 2012



Vaccination coverage in recent years has substantially declined and could potentially be related to the current increase in pertussis cases (Table 1). This decline followed the health reform in 2005. The recent further drop in coverage in 2012 is probably related to a new monitoring system. The activity of anti-vaccination movements has also increased. Cohorts born around 2004 with lower coverage might have led to an increase in disease circulation, increasing the risk of transmission to infants too young to be vaccinated.

Table 1: Vaccination coverage with 2nd booster does estimated at school entry in Chile

Vaccine	Age	2005	2006	2007	2008	2009	2010	2011	2012
		Coverage (%)	Coverage (%)	Coverage (%)	Coverage (%)	Coverage (%)	Coverage (%)	Coverage (%)	Coverage (%)
DTwP	4 years	91.3	81.3	81.1	85.1	81.8	78.1	77.0	58.1
dtap	6 years								57.9

Hospitalizations and deaths have also increased, mainly in infants in <1 year. A substantial number of deaths were seen over a decade in young infants. The crude number of deaths in 2011 and 2012 was 16 and 13 respectively; 7 deaths occurred in each of 2010 and 2009. Mortality was highest in 2-3 month old infants in 2011 and 2012 (47.6 per 1, 000, 000 births in 2012). After a cocooning strategy was implemented in 2012, reported infant mortality has decreased.

Information on fatalities are obtained from the reporting system, hospital discharge data, and national death statistics; neither autopsy nor PCR confirmation are done. The actual increase in mortality may be overestimated as direct immunofluorescence (DIF) test is known to result in more false positives than PCR. As well, the potential overlap of respiratory syncytial virus (RSV) and pertussis cases might lead to false positive cases. There has also been some reluctance by physicians to report cases. The system captures severe hospitalized cases in infants, but a low proportion have mild symptoms, which might indicate low system sensitivity. Nevertheless the system has the capacity to detect outbreaks.

A hexavalent aP-containing vaccine is used in the private market but accounts for only 3.9% of the population. The overall quality of the wP vaccine used was good.

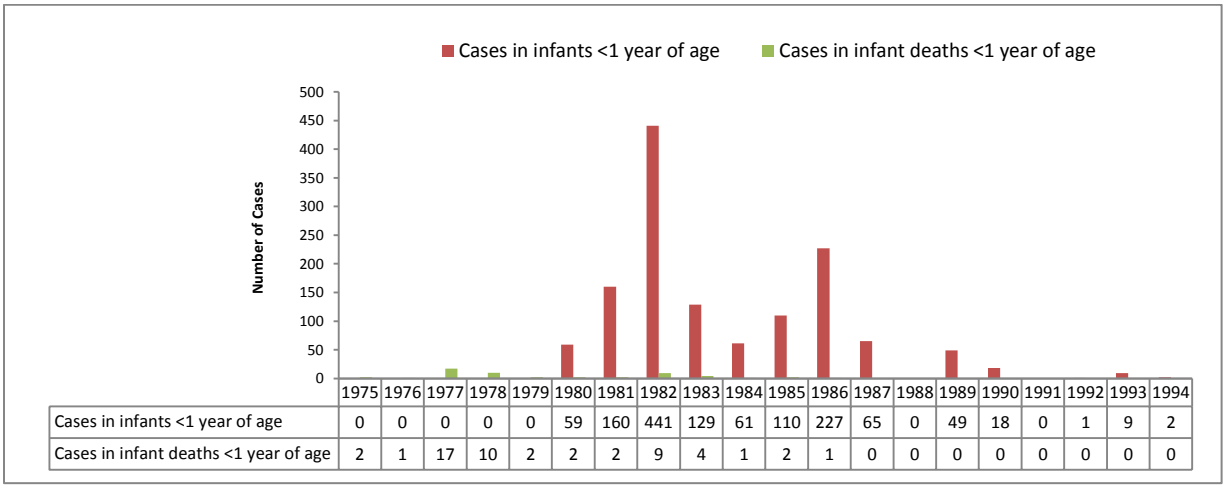
Key conclusions:	• Data quality greatly improved in 2012. Before 2012, the laboratory methods used were not ideal. Sensitivity and specificity of the laboratory methods may not be satisfactory (DIF related false-positive cases reported). • The resurgence of pertussis observed in 2011 and 2012 was preceded by a sustained drop in vaccine coverage and so might in part be linked with this drop in coverage.

Cuba (total population in 2012: 11.27 M)

Surveillance	Mandatory universal notification of clinical cases (all age groups). There is a sentinel surveillance system at the level of polyclinics notifying "Pertussis syndromes".
Laboratory confirmation	None since 1990
Vaccination coverage	Vaccination coverage of 100% of DTP3
Current vaccine in use	wP (Cuban manufacturers)
Vaccination recommendations	From 1962 to 1979, DTwP was recommended at 1, 2, and 3 months, along with a DTwP booster at 15months. In 2005, a tetravalent vaccine (DTwP--HepB) was introduced at 2, 4 and 6 months, moving the booster to 18 months. In 2006, the currently used pentavalent wP vaccine (DTwP-HepB-Hib) was introduced, using the pre-existing schedule.

Vaccination coverage is generally high for DTP3 at 12 months as well as for DTP3 plus the booster dose, with the exception of 2004 and 2007 (59% and 57%). Pertussis has been notifiable since 1962. From 1980 to 1990, laboratory culture was used in the country, but from 1990 to present, no laboratory confirmation is carried out. The last confirmed case of pertussis was reported in 1994 (Figure 9).

Figure 9: Infant (<1 year of age) pertussis cases and infant deaths by year, 1975-1994



	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
Cases in infants <1 year of age	0	0	0	0	0	59	160	441	129	61	110	227	65	0	49	18	0	1	9	2
Cases in infant deaths <1 year of age	2	1	17	10	2	2	2	9	4	1	2	1	0	0	0	0	0	0	0	0

No studies on vaccine effectiveness from Cuba are available. Data from the clinical reporting system has indicated an increase in cases for the last 5 years. It is unclear if this reflects a true increase in pertussis or related to the development of this surveillance system.

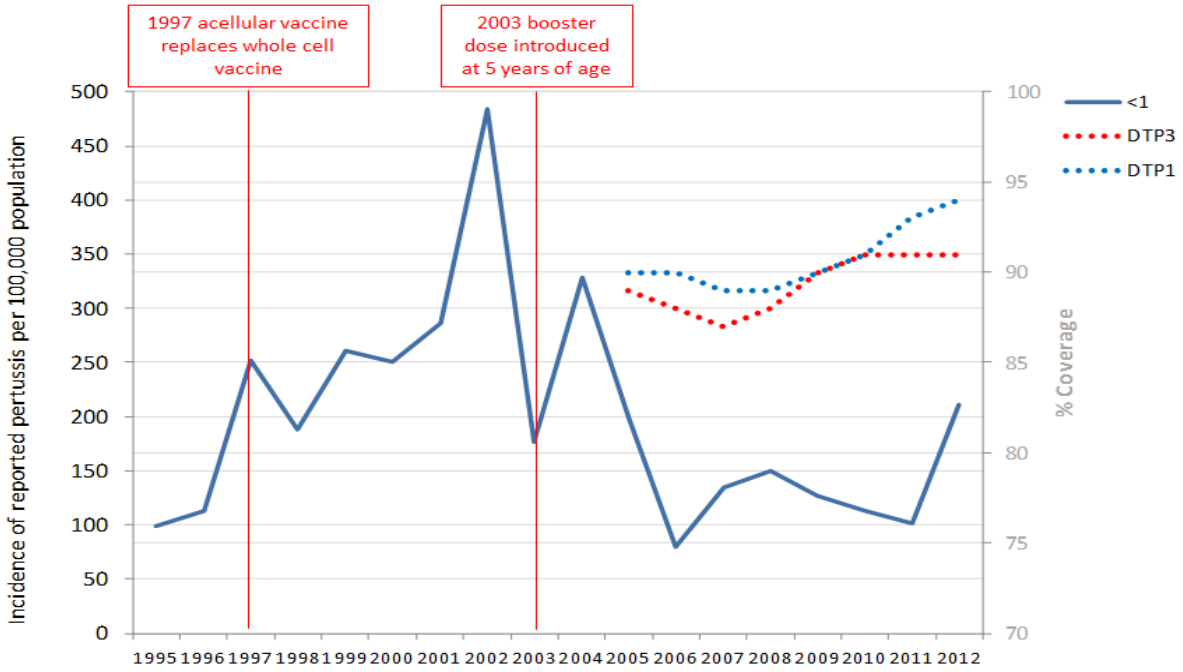
Key conclusions:	• Notification based on clinical definition only, no laboratory confirmation. Low sensitivity of surveillance system. • The working group concluded the data from Cuba are not comparable with data from other countries because of the lack of laboratory confirmation, limiting their utility.

Denmark (total population in 2012: 5.60 M)

Surveillance	Mandatory universal passive notification of cases by clinicians in children less than 2 years since 1994. Since 2007, all laboratory confirmed cases regardless of age are statutory notifiable by the diagnosing laboratory to the national reference laboratory. A national system is in place to register hospitalization and death from pertussis.
Laboratory confirmation	Historically, culture has been used for laboratory confirmation. In 1998, PCR was introduced. In 2012, about 73% of the cases were PCR confirmed. Serology has been used since 2010 (25% in 2012). In children <8 years and infants, PCR is commonly used (>95%), with the remaining cases confirmed by culture.
Vaccination coverage	Vaccination coverage in 2012 was 91% for the full primary schedule at 24 months. Since 2003, vaccination coverage with booster doses (DTP4) ranges from 81 to 84%.
Current vaccine in use	aP (monocomponent)
Vaccination recommendations	The vaccination schedule from 1961 to 1969 consisted of 5, 6, 7 and 15 month doses of a combined DTwP-IPV vaccine. From 1969 to 1997 wP was used as a single vaccine at 5 weeks, 9 weeks and 10 months of age. From 1997 onwards, monocomponent aP was used at 3, 5, and 12 months of age. In 2003, a pre-school booster dose was introduced at 5 years of age. Rational for the booster was to extend immunity as well as to provide indirect protection to infants.

Historically, pertussis incidence has been low. An outbreak-related increase in cases was observed in 2002 and again in 2004. In 2012, an increase in cases was reported, in part caused by increased use of serology (Figure 10). This trend was not sustained in 2013 and declined to pre-2012 levels.

Figure 10: Incidence of reported pertussis cases in infants under 1 year of age in Denmark, 1995 to 2012



Hospitalizations are reported for notified cases aged 2 years and under only. Deaths are reported through the disease reporting system. In general, deaths are rare with an average one fatality every 2 to 3 years, with the last fatal case being reported in 2010.

Key conclusions:	• Historically data quality was already good but is still improving. • No resurgence of pertussis. The situation in Denmark is stable, with an observed increase in cases occurring due to naturally recurrent cycles and an increased use of serology. • Denmark uses a monovalent PT vaccine and a unique schedule with the start of the primary immunization at age 3 months. Since 2004, the total number of reported cases has remained relatively stable since aP vaccine introduction. This is contrary to what has been reported from other countries with long-standing use of aP vaccines. Notably, Denmark stands out as the only country with exclusive use of monovalent PT vaccine, delivered according to the 3,5,12 month “Scandinavian” schedule of primary doses.

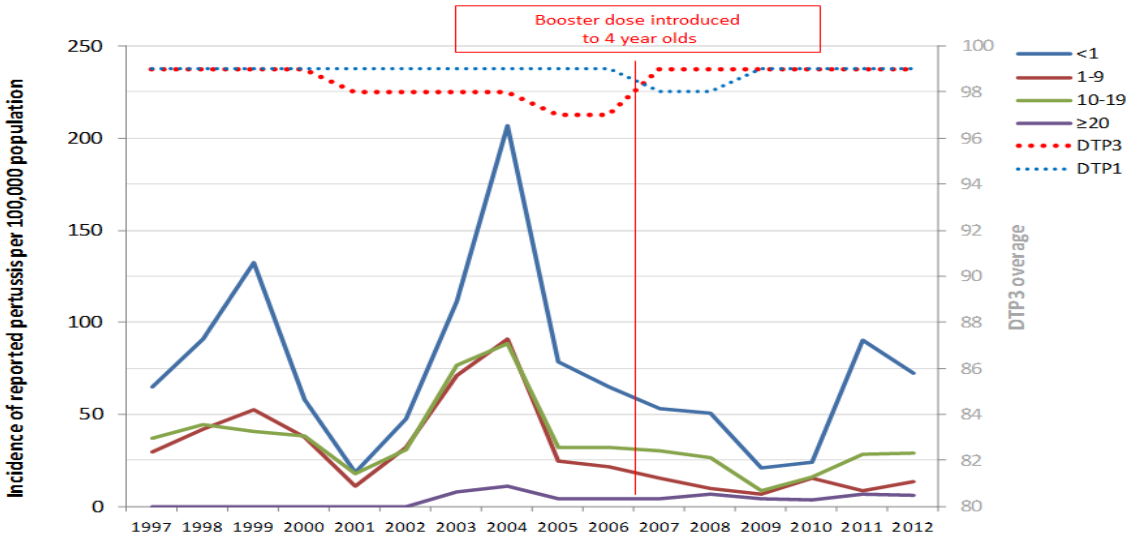
Finland (total population in 2012: 5.41 M)

Surveillance	Mandatory universal passive notification. Since 1995, only laboratory confirmed pertussis cases have been reported to the national infectious disease register.
Laboratory confirmation	Laboratory methods used in 2010 were PCR in 5% of cases, serology in 92% of cases, and culture in 3% of cases.
Vaccination coverage	Coverage before 2005 was 97% for the entire 3+1 schedule (3, 4 and 5 + booster at 20-24 months) based on 2003 birth cohort. Latest coverage for DTP3 was 99% based on 2007 birth cohort.
Current vaccine in use	aP (3 component)
Vaccination recommendations	The vaccine used from 1952 to 1957 was monovalent wP. From 1957 to 2004, DTwP-vaccine (National Public health Institute ((KTL)) was used. The 3+1 schedule, with 3, 4, 5 and 20-24 month doses, has been used since early in the beginning of the programme. Since 2005, new combination vaccines with an aP-component are being used: DTaP-IPV-Hib (Infanrix-Polio+Hib or Pentavac) is given at 3, 5 and 12 months, a booster DTaP-IPV (Tetravac or Infanrix-Polio) at 4 years, and a booster Tdap (Boostrix) for adolescents at 11-13 years (for those born before 1997) or 14-15 years (for those born 1997 or later).

Vaccination coverage data is based solely on a survey of 1000 children under 2 years of age which is conducted every second year. The results of the 2009 birth cohort coverage study are not available yet. Finland plans to establish a national immunization registry.

The incidence of pertussis increased from 1998 to 2000. Implementation of a booster with Tdap at 6 years of age in January 2003 was done to protect the children who were reaching the school age. The highest pertussis incidences were reported in 2003 and 2004. In 2005, the vaccines in the national program were changed to new combination vaccines containing aP-component; the vaccination schedule was changed at the same time and a Tdap booster for adolescents was added to prevent outbreaks of pertussis among school children. The aim of the changes was also to protect very young children. Another increase in incidence observed in 2011 and 2012 was mainly restricted to infants <1 year old, with older age-groups not greatly affected (Figure 11).

Figure 11: Incidence of reported pertussis cases in Finland, 1995 to 2012



Data on hospitalization and death were not provided. Hospitalization data are not yet linked to the national surveillance system or discharge database using ICD codes, and data on pertussis related deaths are not routinely collected by the national surveillance system.

Key conclusions:	• Data quality is good but could be improved. • The observed epidemiology is explained by the naturally recurrent cycles. In general the situation is stable; no statistically significant change in trends is identified after 2003-2004. Overall vaccination coverage is high. • aP was introduced in 2005, resulting in less time to potentially result in resurgence due to aP related waning of immunity. • In the future, the "real time" vaccination registry will provide an easier way to follow the coverage and will enable register linkage studies.

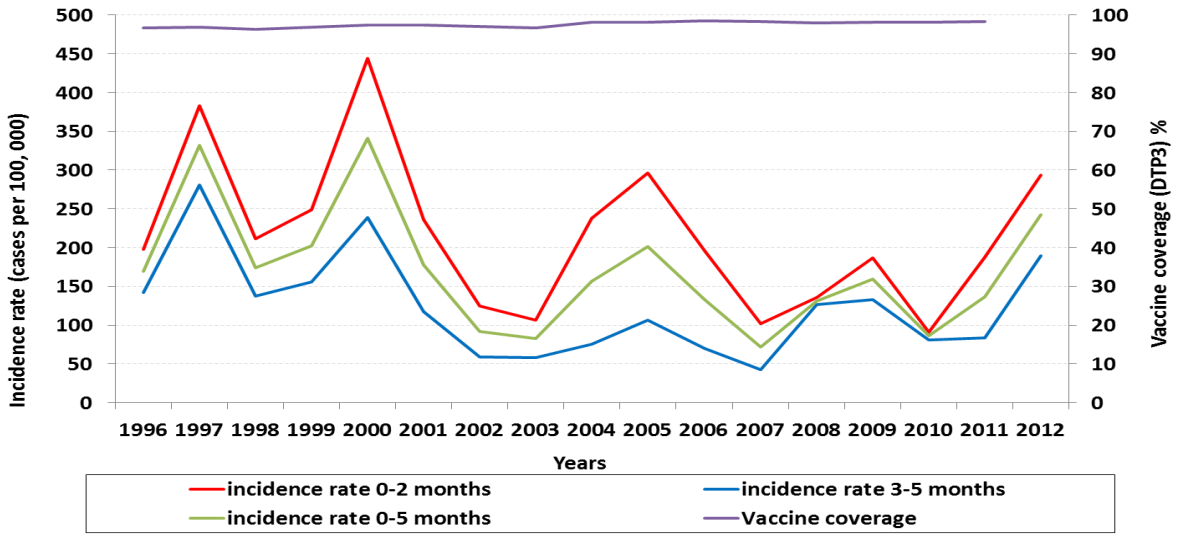
France (total population in 2012: 63.94 M)

Surveillance	Active voluntary hospital-based pediatric sentinel network of 42 hospitals has been in place since 1996, covering 30% of all pediatric admissions. Through this active surveillance (Renacoq), bacteriologists and pediatricians report cases in children. A detailed clinical form is filled in by pediatricians for cases in infants aged 0-5 months only. Information on pertussis deaths is obtained from national death certificates
Laboratory confirmation	PCR in 99% of cases. Only 1% of the cases are clinically confirmed.
Vaccination coverage	In 2011, 98.4 % for DTP3 at 24 months of age and 90.5% at the 18 month booster dose. Cocooning recommendations did not lead to high coverage among parents, with was estimated to be around 27% in mothers and 21% in fathers by a web-based survey.

Current vaccine in use	aP (3 components and 2 components for young children and adolescents ; 3 and 5 components for adults)
Vaccination recommendations	From 1990 to 2003, wP (DTwP-IPV-Hib) was used in a 2, 3, 4 and 18 months schedule. An additional booster at 11-13 years with aP containing vaccines was introduced in 1998. Progressive replacement of wP by aP (DTaP-IPV-Hib ± Hep B) took place in toddlers and infants from 1998 to 2003. After 2005, wP was no longer available. In 2004, aP vaccination was recommended for future parents along with a cocooning strategy for household members and health care workers (HCW) in charge of newborns and young infants. In 2008, an additional booster was added for adults at 26-28 years. In 2013, there was a change in the French immunization schedule to a slightly modified Scandinavian-like extended schedule with doses at 2, 4, and 11 months and the addition of a booster dose at 6 years.

Over the observation period from 1996 to 2012, a typical cyclic pattern of increases in pertussis incidence was observed every 3-4 years, with the most recent peak in 2012. The small peak observed in 2009 could also be due to the new PCR technique used (the end point PCR was replaced by RT-PCR which is 100 times more sensitive) (Figure 12).

Figure 12: Pertussis Incidence rate among infants aged 0-5 months and vaccine coverage against pertussis (3 doses at 24 months of age), 1996 to 2012



Pertussis incidence in France has always been highest for infants 0-2 months of age as compared to 3-5 months olds. The majority of reported cases (>90 %) under 3 months of age are unvaccinated. The crude number of deaths varies between 1-10 cases depending on the year of the cycle. There was only one fatal case in a vaccinated child during the last 15 years of surveillance (with 1 dose of vaccine), as high vaccination coverage has had a large impact on the prevention of infant deaths. Between 50 to 60 % of likely contaminators of hospitalized young infants are parents, with siblings identified as the likely source of infection in another 20 to 30 %.

Key conclusions:	• Data quality is good, yet limitations apply to the surveillance method used • No resurgence was observed, with only periodic increases in cases related to the natural recurrent cycle. • aP has been in use for 15 years and exclusively used for the last 10 years, with a highly effective wP program in place before that time. High population coverage was obtained. • Data suggest a recent increase in incidence in 5 to 10 years olds, which may reflect greater waning of protection in cohorts exclusively vaccinated with aP containing vaccines. • While other strategies such as the adult booster and cocooning have not had a big impact, their level of implementation remains low.

Germany (total population in 2012: 82.80 M)

Surveillance	Universal passive notification was only mandatory in 5 federal states of the former East Germany (FEW) during the period of 1991-2013. From 2013 onwards notification has been mandatory in all federal states, though data are not yet available.
Laboratory confirmation	The laboratory methods and frequency of testing including serology, PCR, and culture vary from states to states.
Vaccination coverage	Historically lower in former West Germany (FEW) (2-60% dependent on region. Mandatory vaccination in FEW (>95%). In 2011, vaccination coverage was 95.1% at school entry.
Current vaccine in use	aP (3/5 component)
Vaccination recommendations	wP was used from 1991-1997 with a 4 dose schedule (2, 3, 4 and 11-14 months). DTaP was used exclusively from 1997 onwards. A DTaP booster dose at 9-17 years was introduced in 2000. In addition, cocooning was recommended for child care and health care workers (2003), and for care-givers of infants (2004). From 2006 onwards, a pre-school booster was introduced at 5-6 years. From 2010, one dose of Tdap for universal adult vaccination was recommended.

The historical split in East Germany and West Germany resulted in differences in vaccination use, notification, and coverage until the time of unification. Vaccination was mandatory in the Former East Germany (FEG) but not recommended in the Former West Germany (FWG), hence vaccination coverage was high in FEG and low in FWG.

Incidence rates can only be assessed for FEG, as these are the only states requiring notification for notification for pertussis prior to 2013. Hospitalization data are available from all parts of Germany, with the highest rates among those <1 year of age (Figure 13). Incidence was highest in 2005/2006 and 2011 (Figure 14).

Figure 13: Incidence of notified pertussis disease and hospitalizations in Germany, 1947 to 2007[5]

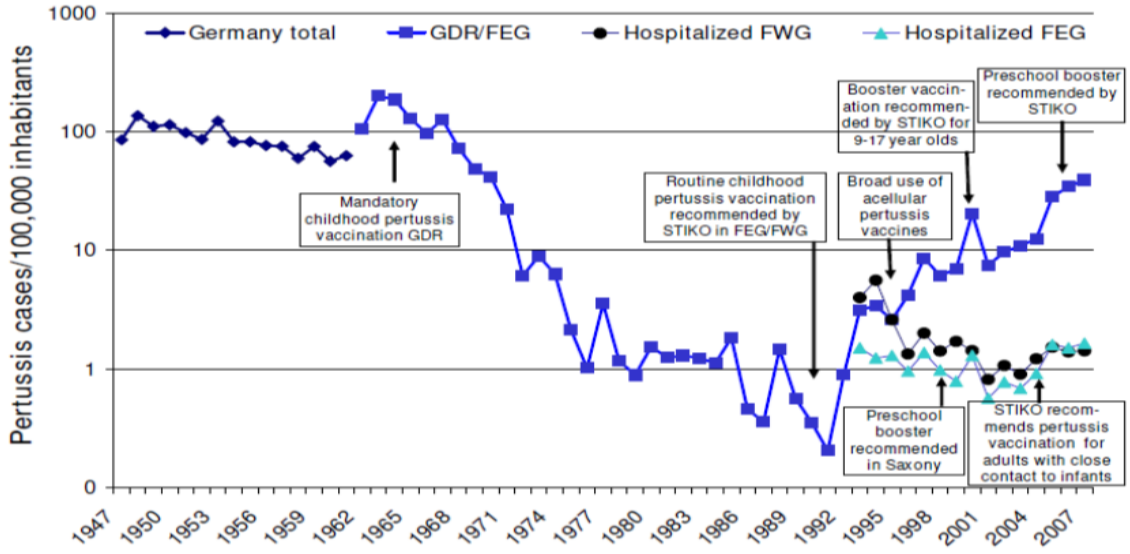
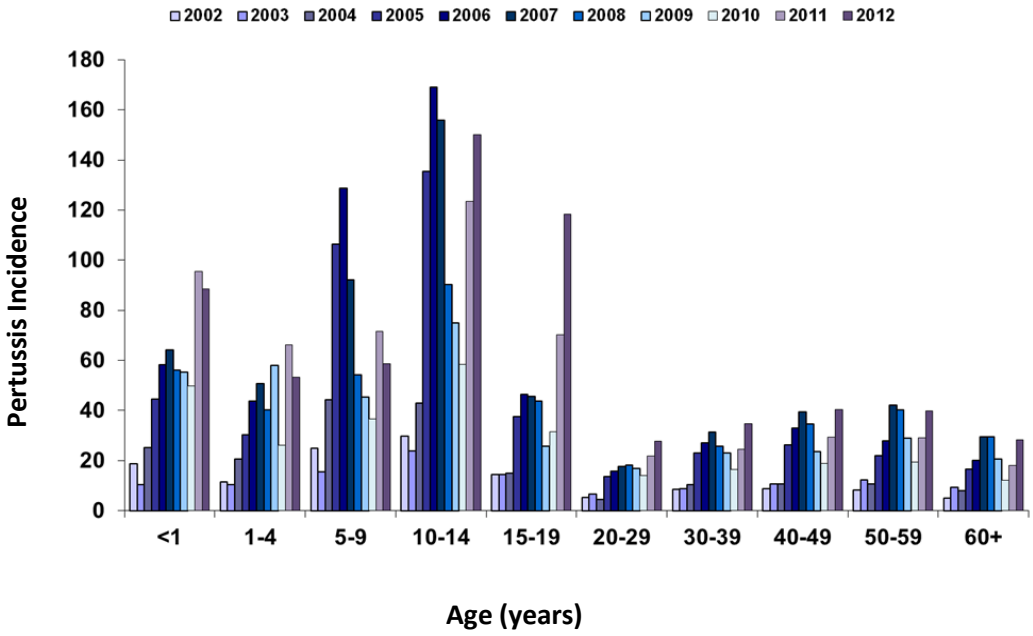


Figure 14: Age-specific pertussis incidence of pertussis in the FEG, 2002 to 2012



Only 2 deaths were reported from 1998-2011 based on notification data from Federal Statistics. However, based on death notifications from hospital statistics, 11 deaths were reported over the same time period. This discrepancy and possible underestimation will be assessed in a surveillance survey covering >90% of all pediatric hospitals.

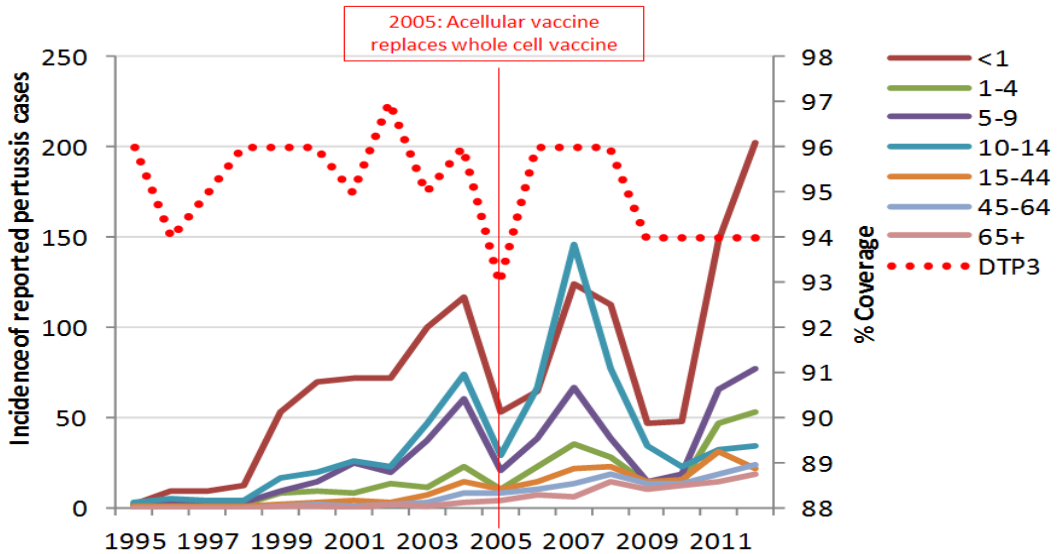
Key conclusions:	• Data quality is good, but has been regionally limited to FEG. • The presented data do not suggest a resurgence of pertussis in Germany. An overall low incidence (70/100,000 in infants <1year) and low number of hospitalizations are observed despite recurrent peak years. A magnification of the peaks may be due to an increase in serology testing in adolescents. A recent increase was observed in the last 2 years, yet in 2013 this number has already decreased significantly.

Israel (total population in 2012: 7.64 M)

Surveillance	Mandatory passive universal notification has been in place since 1950.
Laboratory confirmation	90% serology, followed by PCR with a small proportion of laboratory confirmation done using culture.
Vaccination coverage	Vaccination coverage was 94% for the complete primary series (DTP3) in 2012 at 24 months and 95% for the booster dose given at 7 years of age.
Current vaccine in use	aP (3/5 component)
Vaccination recommendations	wP was used as DTwP from 1957 to 2004 in a 2, 4, 6, 12 month schedule. Since 2005, aP (Infanrix-iPV+Hib (GSK) and Pediacel (Sanofi PasteurSP)) has been used, with 2 additional boosters doses recommended at 7 years (Tdap+IPV; Boostrix-Polio or Adacel Polio) and 13 years (Tdap; Boostrix or Adacel).

Review of the incidence suggests an increase in cases over the last few years. Historically, infants have had the highest incidence of any age group, although in 2007, the 10-14 year-old age group had a higher incidence. A sharp rise in the incidence rate among infants was observed between 2010 and 2012 that was not reflected in a parallel increase of adult cases (Figure 15).

Figure 15: Incidence of reported pertussis cases per 100,000 in Israel, 1995-2012



Hospitalization data are available from 2005 to 2011 through the national surveillance system. 80% of hospitalized pertussis cases during this period were <1 year of age. Information on deaths is derived from the national surveillance and not from death registries. For the period from 2005 to 2012, there were 9 deaths due to pertussis identified among infants (age <1). There were no deaths recorded in the other age groups.

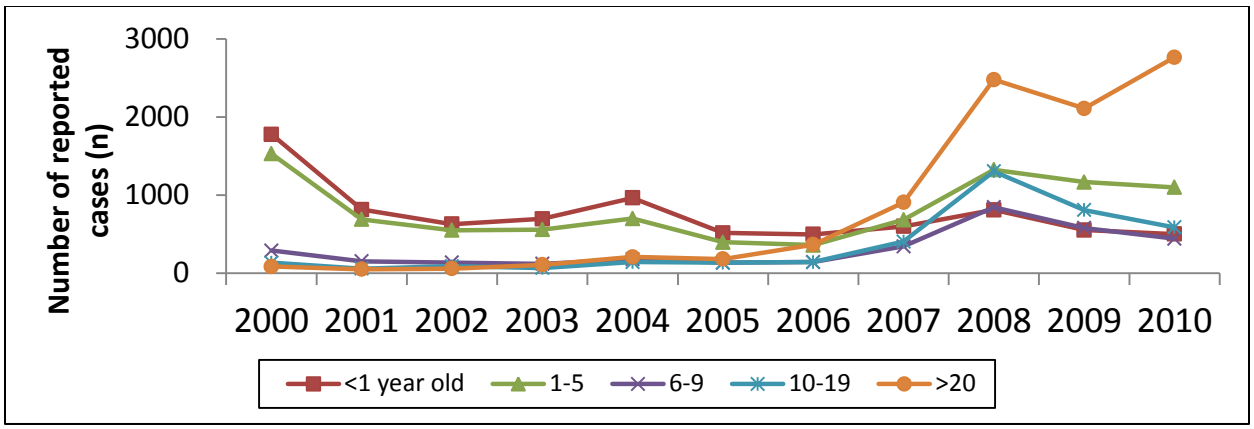
Key conclusions:	• Data quality is satisfactory with room for improvement. • Available data does not provide clear evidence about resurgence. No definite conclusion can be drawn on actual resurgence vs. an increase in cases related to the natural recurrent cycle. • Possible explanations for the increase in infant cases include a greater awareness of pertussis and the availability of better laboratory tests... • Overall vaccination coverage is high with aP (3/5 component), despite this vaccine having only be in use for 7 years.

Japan (total population in 2012: 127.25 M)

Surveillance	Universal passive sentinel-site notification by pediatricians
Laboratory confirmation	Laboratory tests used for case confirmation are PCR or culture; laboratory testing is done mainly during outbreaks
Vaccination coverage	Administrative data overestimates true vaccination coverage which is reported to be 101.8% for DTP3+ booster at 24 months. One study provided coverage estimates of 96.6% and 67.9% for the booster.
Current vaccine in use	aP (different vaccines from different manufacturers have been used with different purification processes and number of components)
Vaccination recommendations	Historically, the vaccination schedule was 3/5 component aP vaccine (DTaP) at 3, 4 and, 6 months plus a booster at 12-18 months. Since 2012, DTaP-IPV has been used with recommendation for pre-school booster pending.

Incidence data are not available as the sentinel surveillance reports only crude number of cases from the sentinel sites. Reported cases were highest in 2000 for children under 6 years of age. The most recent data from 2010 show an increase in cases in 2009 and 2010 in adults >20 years. This increase was not reflected in infants and only a small increase could be observed among older children (Figure 16). No data could be obtained on pertussis-related hospitalizations and deaths in Japan.

Figure 16: Number of reported pertussis cases in Japan by year



Key conclusions:	• Data quality could be better • No evidence for resurgence though data are limited.

Mexico (total population in 2012: 120.85 M)

Surveillance	Mandatory universal passive notification for all age-groups.
Laboratory confirmation	Culture only for 100% of probable cases. PCR has not been introduced systematically in the country but a pilot test has been conducted in 2011 with the support of the Centers for Disease Control and Prevention (CDC).
Vaccination coverage	National vaccination coverage in 2012 at 24 months with primary vaccination was 76.09%.
Current vaccine in use	aP (5 components)
Vaccination recommendations	From 1973-1997, Mexico used DTwP with a 3 dose primary schedule and 2 booster doses at 2 years and 4 years. From 1998-2006, DTwP was replaced by pentavalent whole-cell pertussis vaccine for the primary series, with retention of DTwP booster doses at 2 years and 4 years. Since 2007, Mexico has been using a primary schedule of 2, 4, 6, and 18 months doses with a pentavalent aP vaccine (Pentaxim) and a booster dose of DTP at 4 years of age

Vaccination coverage over the last 20 years ranged from 68% (1999) to 87% (2005). Yet a great variation between the different federal states was observed. 13 of 32 states have coverage below the national level and only 5 states have coverage levels above 90%.

An evaluation of the surveillance system (established in 1994) was conducted in 2010 with the help of a working group from the CDC. Strong surveillance infrastructure was in place but laboratory confirmation was only done by culture so there is limited sensitivity to recognize pertussis in children under 5 years of age. Further, sensitivity is further reduced due to inability of health care professionals to recognize cases. The overall number of reported cases since 1993 has varied substantially, with the vast majority of cases

being reported in infants (Figure 17). In 2012, an increase in total infant cases was observed, with 25.6% of these cases having received at least one vaccine dose.

This increase in identified cases was not associated with in an increase in infant mortality (Figure 18). No effectiveness studies are available from Mexico. The possibility was raised that ethnicity might explain the high mortality rate compared with that observed in other countries, considering US mortality rates are highest in Hispanic infants. It was also noted that mortality rates in Mexico tend to be higher in the first year of an epidemic cycle than in the second.

Figure 17: Number of reported cases in infants and in the entire population in Mexico by year, 1993 to 2012

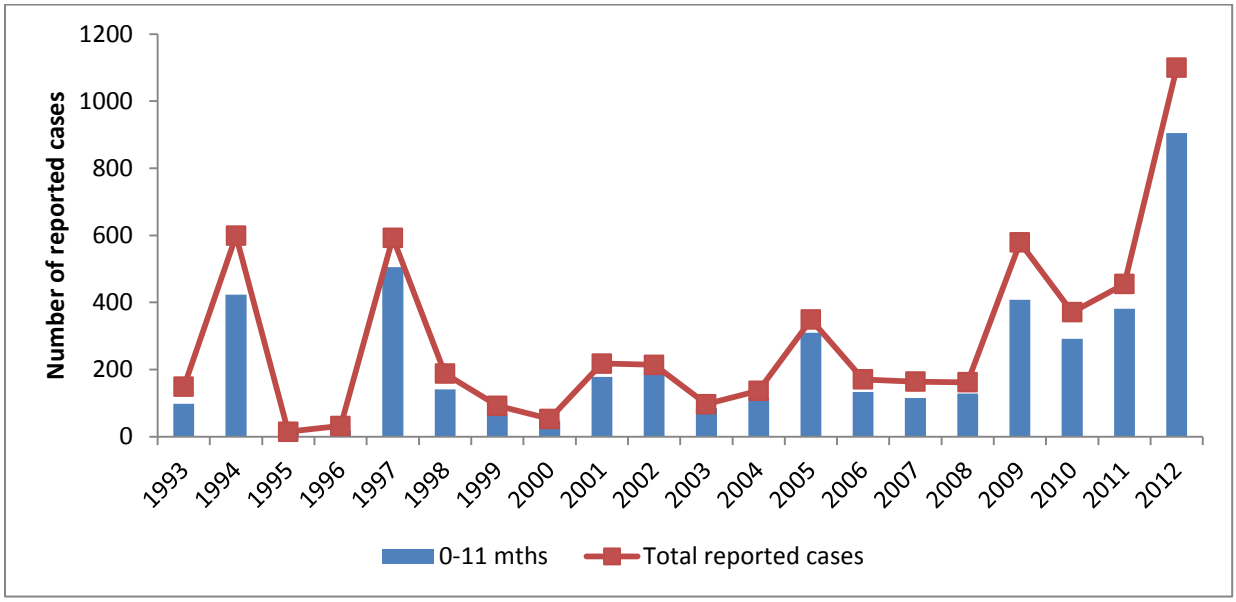
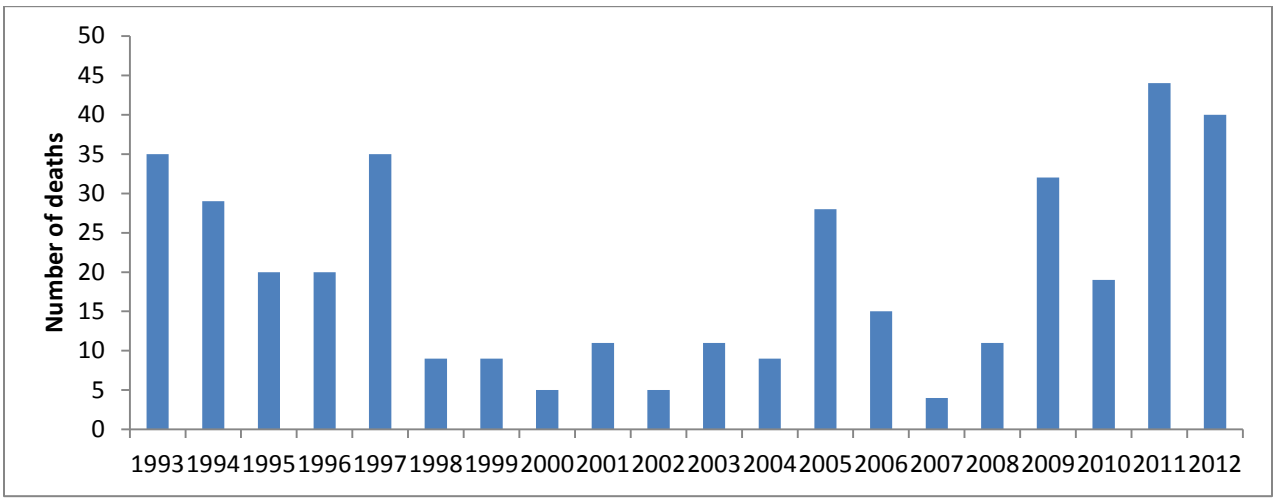


Figure 18: Number of infant deaths <12months in Mexico by year



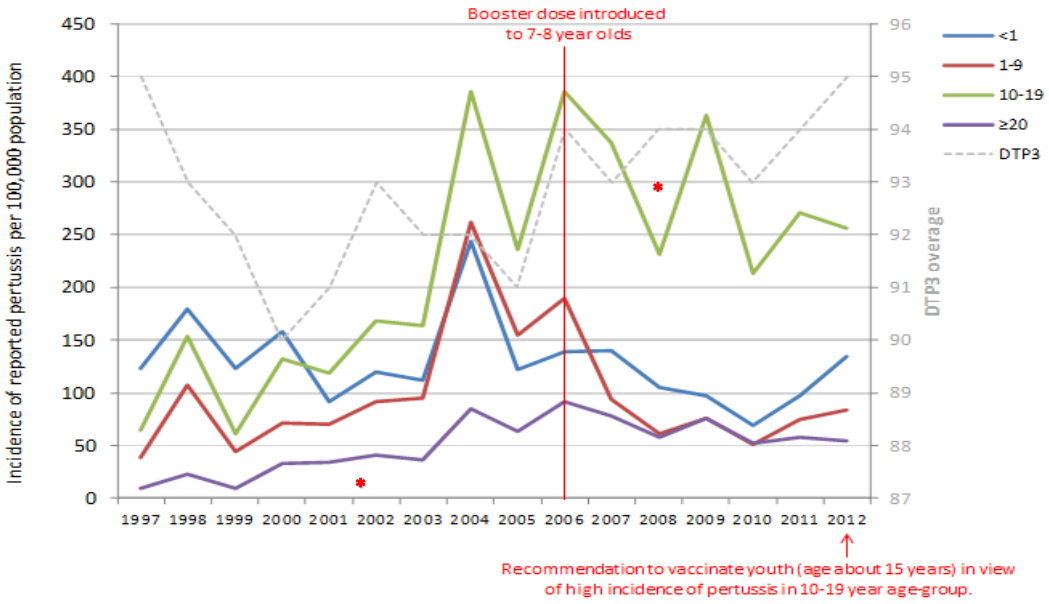
Key conclusions:	• Data quality suffers from serious limitations and there surveillance system sensitivity is low. • Data are not suggestive of a real resurgence. • Increase in cases might be related to low and heterogeneous vaccination coverage. • The use of a more sensitive laboratory method (PCR) might explain the recent rise in cases, an idea supported by the dissociation between total infant cases and infant mortality in 2012.

Norway (total population in 2012: 4.99 M)

Surveillance	Mandatory universal passive notification by laboratories and clinicians.
Laboratory confirmation	Performed laboratory tests consist of PCR (60%), serology (40%) and culture (<1%) in 2012.
Vaccination coverage	In 2012, vaccination coverage was 100% with DTP 1 and 95% with DTP3 at 24 months and for the booster at 7-8 years of age (at 9 years).
Current vaccine in use	aP (3 component)
Vaccination recommendations	wP was used until 1998 and was then replaced by a primary 3 component aP series (Infanrix) at 3, 5 and 10 months. In 2001, the schedule changed to consist of 3, 5 and 12 months doses using Infanrix-Polio. In 2006, a pre-school booster (Tetravac) was introduced at 7-8 years. In 2012, a teenage booster at 15 years of age (Boostrix polio) was recommended for those born after 1998, with the maintenance of adult booster every 10 years.

Pertussis incidence was highest for infants <1 year of age until 2001. From 2002, the highest incidence was reported in 10-19 year olds with a peak in 2005/2006. This led to the introduction of an adolescent booster dose. The incidence in the <1year olds (150/100,000) lies within global average (Figure 19).

Figure 19: Incidence of reported pertussis cases in Norway, 2003 to 2012



Hospitalization data are based on the number of cases reported as hospitalized to the national surveillance system for notifiable diseases. Data are not linked to hospital discharge database using ICD codes. Trends in hospitalization and notification of patterns for cases under 1 year of age are closely related. The highest incidence of hospitalized cases under 1 year was in 2004 with approximately 140/100,000 population. In total, 4 deaths have been reported since 1995, with the last death in 2004. No data on vaccination status are available for one fatal case in 1995, the other 3 deaths occurred in unvaccinated infants of 1 month of age.

Hypotheses concerning possible explications of the increase in infant cases include a greater awareness of pertussis, availability of better laboratory tests, and true increase in the incidence of pertussis resulting from reduced potency of pertussis vaccines, waning of vaccine-induced immunity, or genetic changes in *B. pertussis* strains.

Ongoing studies (unpublished data) in Norway suggest that a decreasing trend in disease-free duration in pertussis cases occurring after receiving 3 doses of vaccine seems to have stabilized in the past few years. In addition, the impact of the first booster dose at age 7-8 years (introduced in 2006) is currently being evaluated.

Key conclusions:	• Data quality is good. • Data do not support a resurgence as a stable cyclic situation for all age-groups was seen in the last several years. The exception is the ongoing increase in older age-group (10-19 years), which is higher than the 1-7 years prior to introduction of the booster at 7 years of age. • It is highlighted that Norway is a country which has been using an extended schedule over a long time. In regard to lab methods, application of serology might have magnified the effect of increased incidence.

Portugal (total population in 2012:10.60 M)

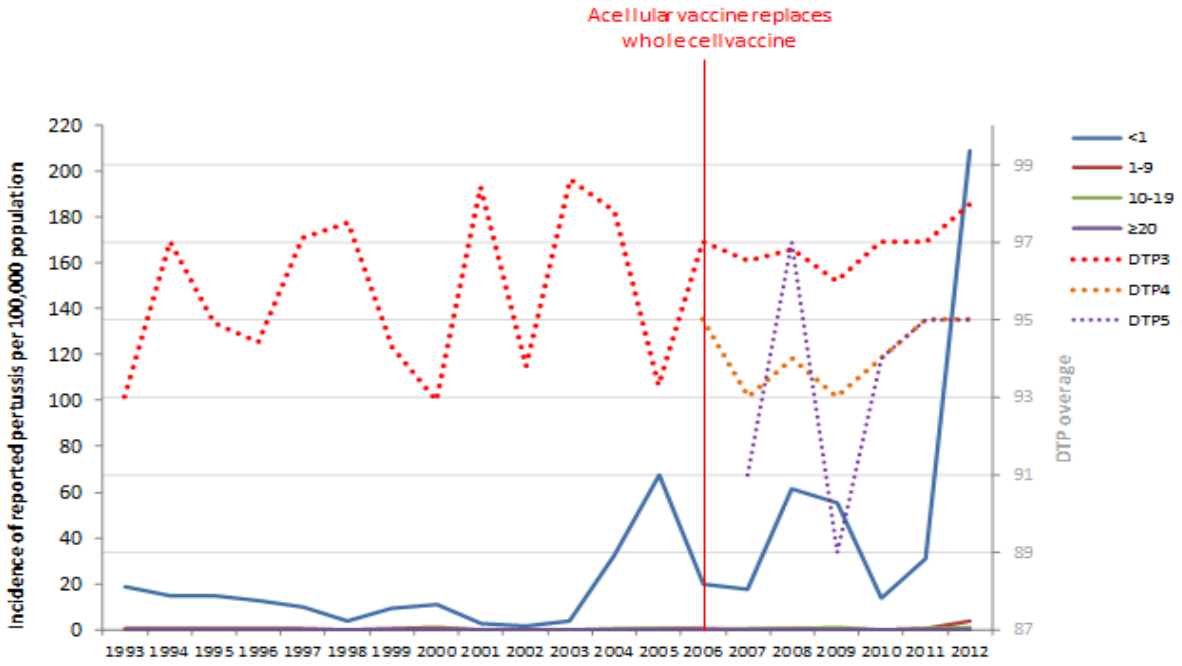
Surveillance	Mandatory universal passive notification by medical practitioners.
Laboratory confirmation	PCR and culture.
Vaccination coverage	National pertussis vaccination coverage for children aged 12 months of age with the third dose of pertussis-containing vaccine was estimated at 93%-98%. (1993 to 2012) For children aged 7 years, the vaccination coverage with the 5th dose of pertussis-containing vaccine was estimated at 89%-97% (2007-2012).
Current vaccine in use	aP (3/5 component)
Vaccination recommendations	wP vaccine was introduced in 1965 in the Portuguese immunisation schedule for children aged 3, 4, 5 months followed by a booster doses at 18 months and 5-7 years. Since the late 1980s, primary series doses were recommended to be given at 2, 4 and 6 months of age. The 4th dose was recommended for 18-24 months of age and the pre-school booster dose for 5-6 years of age. From 2000 onwards, the4th dose was recommended at 18 months of age. In 2006, acellular pertussis vaccine replaced the whole cell vaccine. In 2011-

	2013, Pentavac (Sanofi PasteurSP) was used for the primary series and Infanrix-Hib (GSK) was used for the4th dose. For the 5th dose, Infanrix Tetra (GSK) was used in 2011 and subsequently changed to Tetravac (Sanofi Pasteur) from 2012 onwards.

Despite the long standing immunization programme for pertussis, and generally high vaccination coverage, a cyclical pattern of disease occurrence has emerged in the 2000s with peaks every 3-4 years. However, a sharp rise in incidence in 2012 deserves particular attention. In the period from 1993 through the first 6 months of 2013, 788 cases of pertussis have been recorded in Portugal. Since 2000, a cyclic pattern of disease occurrence became noticeable with peaks in 2005, 2008-2009, and 2012. Between January 2011 and June 2013, 338 cases of pertussis were reported: 32 in 2011, 237 in 2012 and 69 for the first 6 months of 2013 (Figure 20).

Overall, 76% (n=258) of cases were below 6 months of age. In 2011, the proportion of cases < 6 months was 94% (n=30) declining to 79% (n=187) in 2012 and 59% (n=41) in 2013. The proportion of cases aged 10 years and older increased from 3% (n=1) in 2011 to 7% (n=17) in 2012 to 23% (n=16) in 2013. Of the total cases, 39% (n=132) were infants that had not reached the recommended age of 2 months to receive the first dose of pertussis vaccine.

Figure 20: Incidence of reported pertussis cases in Portugal, 1993 to 2012



Of the 258 cases below 6 months of age,108 (42%) were infants between the 2 months and 6 months old and therefore eligible for at least one dose of pertussis vaccine. Of these, 21 (19%) were unvaccinated, 73 (68%) had received one dose of pertussis vaccine, 11 (10%) had received 2 doses and in 3 cases the number of vaccine doses received was unknown. Of these 258 infants below 6 months of age, 247 (96%) were hospitalized.

Twelve pertussis-related deaths were reported for the period 2000-2013, with ages ranging from 2 to 57 weeks. With the exception of2 cases all were unvaccinated. The case fatality rate (CFR) varied between 1.4% in 2005 and 7.7% in 2000. For 2012 and the first 6 months of 2013, the CFR was 2.1% and 4.7%, respectively. The mortality rate per 1,000,000 infants (<1 year old) was highest in 2012 (45 per 1,000,000) relative to mortality rates in 2000, 2004, 2005 and 2008 (range 8-19 per 1,000,000).

Delayed vaccination may have contributed to a number of cases in infants and the high pertussis incidence observed. Similarly, 80% of the fatal infant cases from 2000-2012 had not received any observed (20% had received one dose).

Key conclusions:	• Data quality is acceptable. • In the 2012, a significant rise in incidence in infants <1 years of age was observed suggesting a true resurgence, though incidence may be magnified by increased PCR testing. Infant mortality was very high in 2012, while the mortality over period from 2000-2011 was similar to that in other countries. A possible underreporting in the older age groups is noted. • Whole cell vaccine was replaced by acellular vaccine in 2006.

Singapore (total population in 2012: 5.30 M)

Surveillance	Mandatory universal passive notification since 2008.
Laboratory confirmation	PCR from 2006 onwards, prior to which direct immunofluoresence and culture were used.
Vaccination coverage	98% for the first dose and 97% for full primary schedule (2012). In 2006, a serosurvey that found seroprevalence to be low in adolescents (~50%) and high in adults (~97%) was suggestive of natural infection of adults.
Current vaccine in use	aP (3 component)
Vaccination recommendations	wP (DTwP) in a 3, 4 and 5 months primary schedule, plus a wP booster at 18 months was recommended in 1982. In 2006, a switch to aP (DTaP-OPV) was recommended. In 2008, the 2nd Td booster dose at 6-7 years of age was moved to 10-11 years of age and switched to Tdap and the 3rd Td booster dose was discontinued. In June 2013, DTaP was replaced with DTaP-IPV-Hib. DTaP-IPV-Hib-HepB is also available through both public and private sector facilities. In 2010, an additional booster (Tdap) was recommended for HCWs.

The population size of Singapore greatly increased over the last several years but for the <1 year of age it remained stable. In the below cited surveys the demographics of the reported cases were in line with demographics of the general population.

From 2008-2012, reported pertussis cases occurring in vaccinated persons were generally low (1-3 cases) and predominantly in infants under one year having received only one dose of vaccine. In 2011 and 2012, a slight increase in disease activity was observed with 3 cases in 11-19 year olds and 6 (2011) and 8 (2012) cases in individuals over 20 years occurring after having received more than three doses of pertussis vaccination.

From 2008-2012, hospitalizations were reported mainly from infants under 1 year of age. There were 19 (2008), 5 (2009), 5 (2010),) 10 (2011), and 7 (2012) infant cases hospitalized. No pertussis related deaths have been reported.

A retrospective review of children diagnosed with pertussis from 2004 through 2007 in2 major hospitals (KK Women's and Children's Hospital (2006-2007) and Singapore General Hospital (2004-2006)) was performed.

An increase in incidence for infants <1 year of age was observed between 2007 and 2010. Incidence in 2006 rose from 4/100.000 to 75/100.000 (population) in 2007. Incidence decreased in 2010, but incidence increased again in 2011 to 59/100.000 population (Figure 21). Incidence was highest for infants under 6 months (Table 2).

Figure 21: Pertussis vaccine coverage and reported pertussis incidence

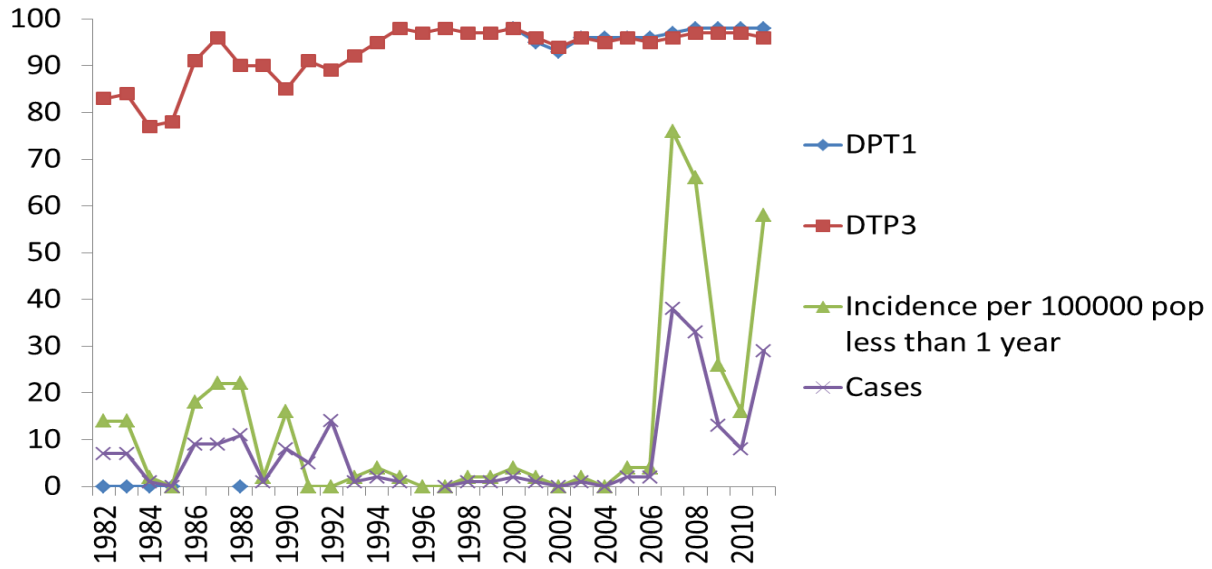


Table 2: Incidence of pertussis by year in infants <6 months and 6-12 months

Incidence of pertussis by year	2009	2010	2011	2012
Infants <6 months	52.1 /100.000	38.2 /100.000	88.2 /100.000	22.9 /100.000
Infants 6-12 months	5.2/100.000	0/100.000	5.5/100.000	0/100.000

In older age-groups over all years of reporting, incidence was ≤1/100,000 with the exception of 2012 where a slight increase in incidence could be observed in 10-14 year olds (1.4/100.000).

Since 1982, an average of 4 cases of pertussis per year have been reported among unimmunized or incompletely immunized children less <1 year. In 2007, a sharp increase in disease activity, with 38 reported cases, was observed.

There were 45 confirmed pertussis cases from 2004 through 2007. Most children (n=42) were <6 months with an age range from 13 days through 5.4 years, with mean age of 4.1 months. 77.8% of children were not vaccinated, 15.6% had received only one dose, 2.2% had received 2 doses, and 4.4% had received 3 doses.

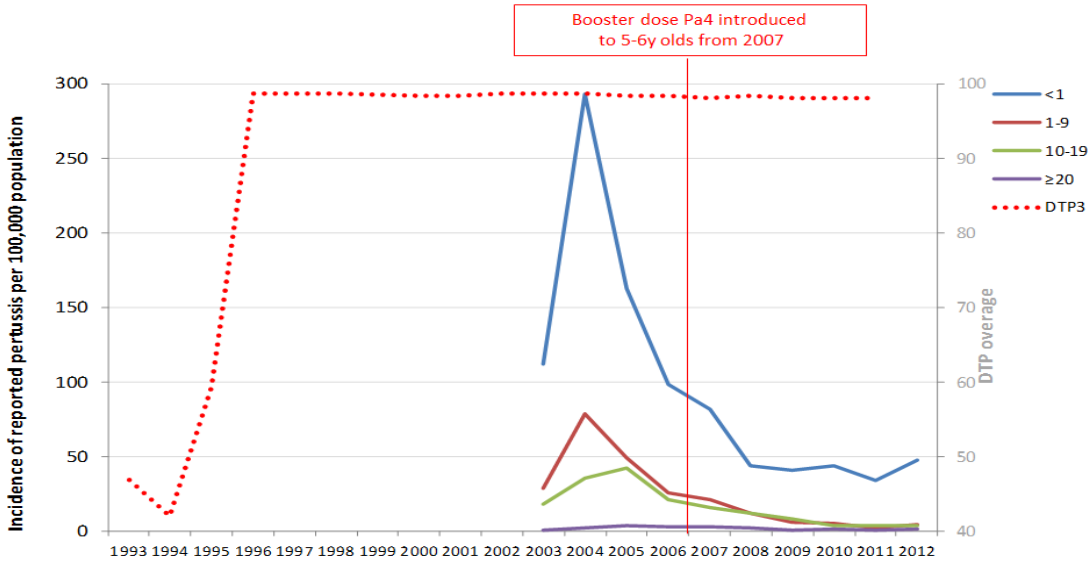
Key conclusions:	• Data quality is good. • No evidence for a resurgence of pertussis. • Data do not allow for any clear conclusions regarding the sudden increase of pertussis among unimmunized or incompletely immunized in 2007, which may have been due to the introduction of PCR, or was a real increase with a doubling of cases in 2007. It is recognized that despite the2 peaks in 2007 and 2011, overall incidence was low. • The recent increase in pertussis started soon after the switch from wP to aP in 2006.

Sweden (total population in 2012: 9.51 M)

Surveillance	Mandatory universal passive notification.
Laboratory confirmation	In 2012: PCR in 61%, serology in 32% and culture in 7% of cases over all age-groups. 97.4% of cases in infants of 0 to 12 weeks of age were PCR confirmed
Vaccination coverage	Vaccination coverage was 98.3% for the primary schedule (DTP3) at 24 months in 2012 and 96% for the booster doses.
Current vaccine in use	aP (3 or 5 component; previously 2 and 5 component)
Vaccination recommendations	wP was withdrawn in 1979. No vaccination was recommended until 1996, when a primary schedule using a 3-component aP vaccine (Infanrix, except in Gothenburg area where monocomponent DiTeKik was used) at 3, 5 and 12 months was introduced. In 2005, a booster dose at 10 years was introduced which was lowered to 5-6 years in 2007 along with a second booster at the age of 14-16 years for individuals born in 2002 and after.

The number of reported cases was highest in 2004 and 2005 and has since declined. No data on cases are available before 2003. Incidence was highest among infants <1year of age in 2003, yet overall incidence of reported pertussis cases in Sweden decreased greatly in 1997-2011 in comparison with 1986-95. Hospitalization data are based on an enhanced national surveillance system for pertussis that actively collects hospitalization records. Hospitalization of children <1year of age was highest in 2004 (75/100,000 population) and has declined in parallel to notified cases (Figure 22).

Figure 22: Incidence of reported pertussis cases in Sweden, 2003 to 2012



Nine pertussis-related deaths were reported since 1999, all in unvaccinated infants except one case in 2004 who had received a full primary series. No deaths have been reported since 2008. It is noted that the overall death rate is very low.

Hypotheses concerning low pertussis incidence include that low incidence was related to a highly immune general population, with high acquired immunity in populations as vaccination was re-introduced late in the mid-nineties. This scenario would have allowed adults to acquire natural immunity earlier in life and children to be protected by vaccination.

Key conclusions:	• Data quality is good. • No resurgence; a reduction in overall pertussis incidence can be observed since the re-introduction of pertussis vaccine after a 17-year period without use of vaccine. • Hospitalization in infants is potentially not well represented as no spread from children to infants was seen.

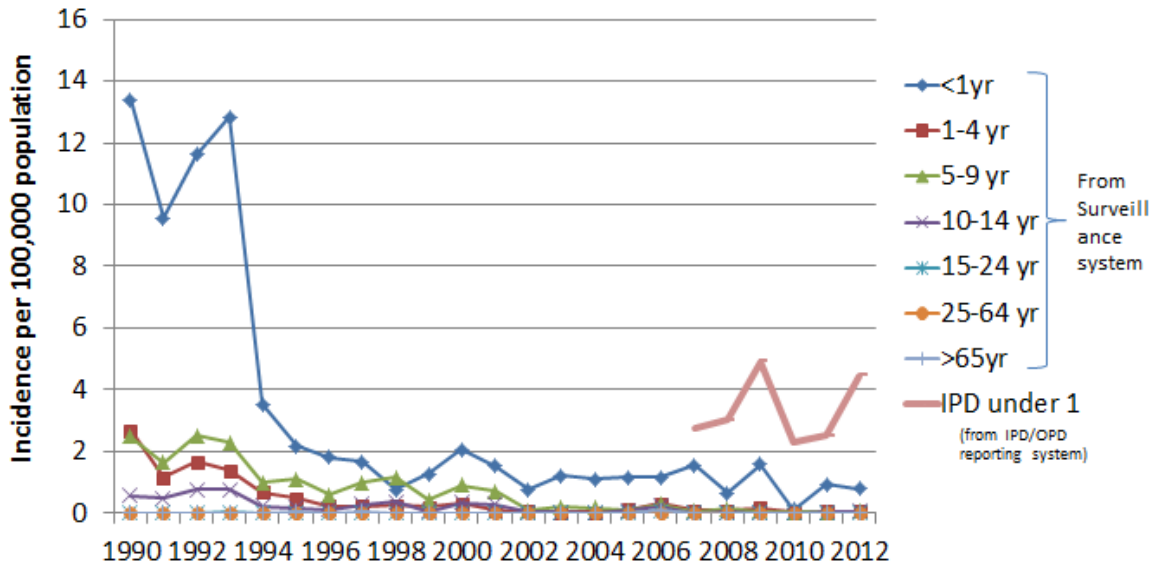
Thailand (total population in 2012: 66.79 M)

Surveillance	Mandatory universal passive notification
Laboratory confirmation	Infrequent use of PCR from 2005 onwards; culture was used previously.
Vaccination coverage	Vaccination coverage, derived from survey data, increased over time and reached 98% for complete primary series (DTP3) by 24 months in 2010.
Current vaccine in use	wP (before 2005, vaccine was locally produced; after 2005, use of DTwP produced by SII or Biofarma, and since 2008, DTPw-HB from GSK, SII or Biofarma. An exception was in 2009-2010, when the majority was produced by Shanta Biotech with local filling

Vaccination recommendations	wP vaccines have been used so far. From 1977 to 1981 at 2 and 4 months, vaccination was recommended for use in the Bangkok area only. From 1982 onwards, vaccination was recommended at 2, 4 and 6 months. In 1991, a booster dose was recommended at 18 months, and in 2000, an additional booster was recommended at 4 years of age.

No increase in cases has been observed in the recent years in infants <1year of age (Figure 23). Only 2 deaths were reported in the last 20 years in a 2 year old in 1999 and a less than 3 month old infant in 2003. In the last 10 years, only one outbreak was reported in a very remote area of the country (2006).

Figure 23: Pertussis incidence in Thailand by year, 1990 to 2012



Two additional studies were highlighted: the first, a mathematical modeling study, suggests that there is no evidence for resurgence (Blackwood et al., 2013). The second, a study in a large children's hospital, recruited 96 patients aged up to 18 years of age with cough >7 days + additional symptoms. 92% had received DPT and 18.8% were PCR positive for pertussis, yet there were only 8 reports through national reporting system and hospital management information system, suggesting substantial underreporting. Yet the case definition varies between the reporting system and the study conducted in the children's hospital (cough for >14 days vs 7 days)[6]

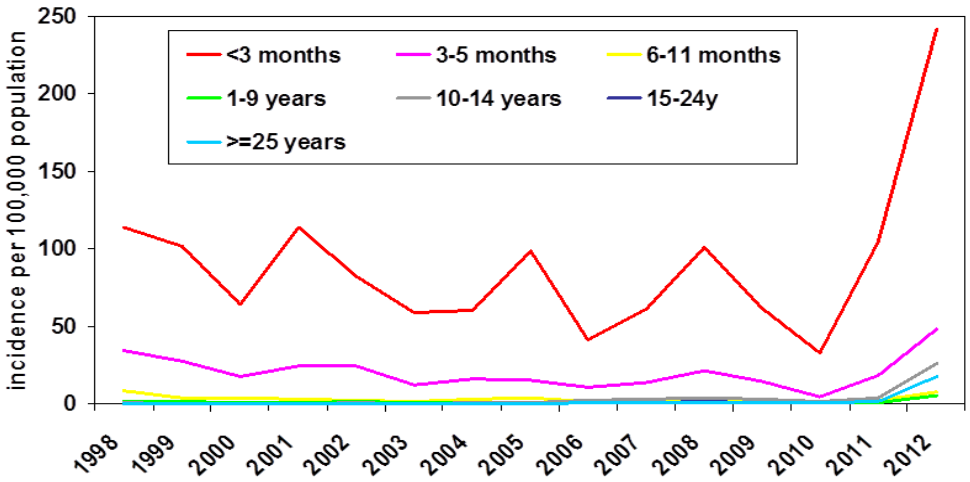
Key conclusions:	• Data quality is limited • Underreporting of cases. Sensitivity of surveillance system is low. No change of surveillance system since its start. • No evidence of pertussis resurgence • Thailand has used only whole cell pertussis vaccination as stand-alone DTwP until 2008, after which DTwP-HepB has been used for the primary schedule.

UK (England & Wales) (total population in 2012: 56.57 M)[2]

Surveillance	In the UK there are three national surveillance systems in place based on laboratory confirmed cases, hospital admissions, and national notification.
Laboratory confirmation	PCR is mainly used in hospitalized infants <1 year but is currently being trialed across all age groups. Serology was introduced in 2001. Oral fluid collection, a new method of serologic testing assessing IgG levels, was introduced in January 2013 to test 8-16 year olds in an effort to further improve ascertainment in these age groups. This test has proven to be highly specific test, yet sensitivity is not optimal.
Vaccination coverage	Vaccination coverage is 96.4% (by 24 months) for the primary schedule (DTP3) and 89.2 % for booster dose (by 5 years of age).
Current vaccine in use	aP (5 component)
Vaccination recommendations	From 1957-1990, wP (DTwP) was used as primary immunization. From 1990 until today, the primary doses are given at 2, 3 and 4 months. In 2001, a TdaP preschool booster was introduced (Infanrix or Repevax). wP was used until 2004 after that only aP (DTaP5) has been used. In 2012, a single dose of TdaP (Repevax) was recommended for pregnant women.

In 2012 lab-confirmed pertussis incidence was highest among infants in the <3 months and 3--5 month age groups. From 2011, incidence increased predominantly in children 10-14 years and infants <1 year of age, but all age-groups, except children 1-9 years of age, were affected (Figure 24).

Figure 24: Incidence of laboratory confirmed pertussis by age group, 1998 to 2012



[2]Office for National Statistics release - Population Estimates for England and Wales, Mid-2012: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-england-and-wales/mid-2012/index.html)

Hospitalization of infants <1 year increased in the last 2 years, particularly among infants <3 months of age. In 2012, 14 deaths from pertussis in infants <12 months were reported, with increasing mortality from an average of 4-5 per million per year to 19.7 per million per year.

It was hypothesized that the increase in pertussis cases was at least in part due to an aP induced waning of immunity and reduced acquisition of natural immunity, particularly in 10-14 year olds.

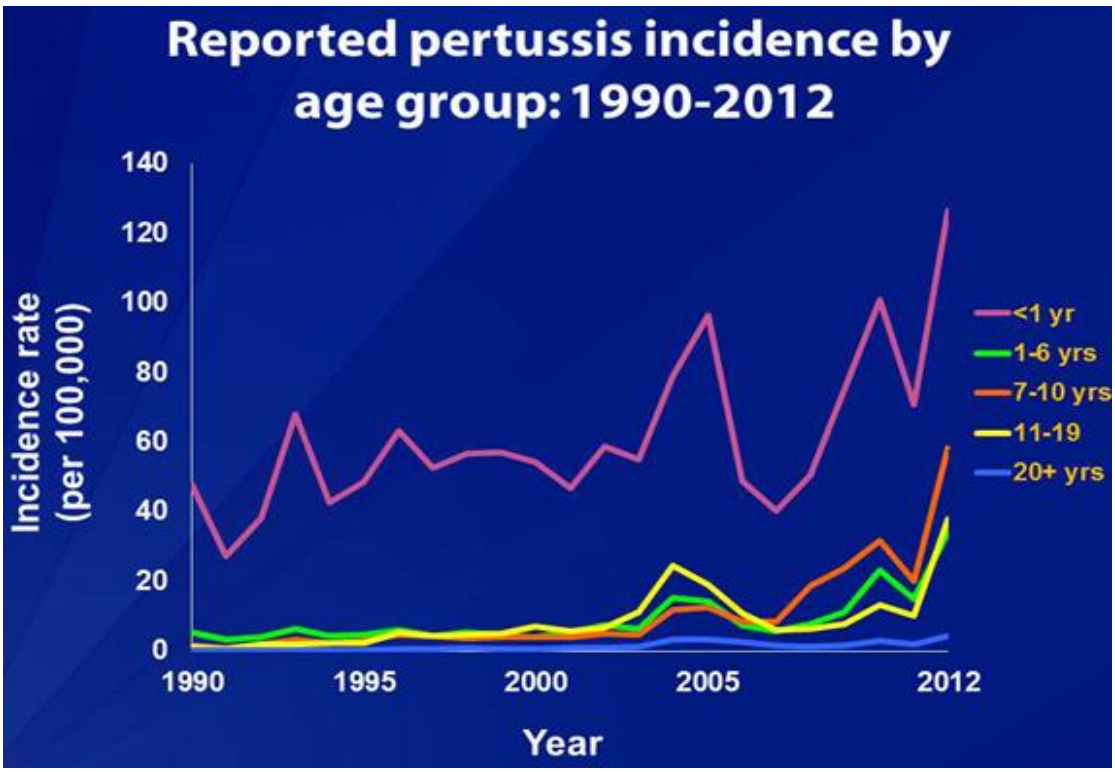
Key conclusions:	• Data quality is good. • Evidence suggests a resurgence of pertussis. • Although incidence has declined over the last 20 years, no interruption of natural 3-4 year epidemic cycle could be seen. A real increase over the natural cycle was observed in the infants <3 months in the years 2011 and 2012. An increase in notified cases, in hospitalization, and in the crude number of deaths could be observed. A real resurgence was registered 7 years after the introduction of aP vaccine, coinciding with the peak of the natural epidemic cycle.

USA (total population in 2012: 317.51 M)

Surveillance	Mandatory universal passive notification of pertussis disease. Hospitalization status is collected through national pertussis surveillance; however, ICD coded pertussis hospitalizations are also recorded through other hospital surveillance sources (National Immunization Survey (NIS), Kids' Inpatient Database (KID)). Death information is collected through national pertussis surveillance, and in addition, NCHS records pertussis deaths from death certificates.
Laboratory confirmation	Culture was historically used for lab confirmation, yet PCR is now widely used. 62% of the cases were confirmed by PCR in 2012.
Vaccination coverage	Vaccination coverage for completion of the primary schedule was 95.5% and was 84.6% for 4 or more doses.
Current vaccine in use	aP (3 and 5 component)
Vaccination recommendations	Early vaccination recommendations from 1992 included vaccination with wP primary schedule at 2, 4 and 6 months plus 2 aP (DTaP) booster doses at 15-18 months and 4-6 years. From 1997 onwards a switch to aP (DTaP) was recommended with no change in schedule. In 2005, additional booster doses were recommended at 11-12 years and in adults to replace the recommended dose of Td. In 2011, one dose was recommended for pregnant women; in 2012, this policy was extended to one dose recommended during each pregnancy.

In 2004, 2005, and 2012, an increase in cases was observed, mostly affecting infants <6 months and adolescents, but there was an increase in all age groups in 2011-2012 (Figure 25). This was reflected in an increase in hospitalizations, with the highest proportion of hospitalized cases in infants <3 months of age.

Figure 25: Reported pertussis incidence in the US from 1990 to 2012



From 2003 to 2012, an average of 10 to 35 deaths were reported per year. In 2012, the death rate was 4.1/1,000,000 births in infants under 1 year of age. The majority of infant pertussis deaths occurred among unvaccinated individuals. From 2000 to 2012, only 7 of 231 total infant pertussis case-patients who died had received any documented doses of pertussis-containing vaccine prior to cough onset. 6 cases had received one dose of DTaP, and 1 case received 3 doses of DTaP. All of these deaths occurred among infants less than 6 months of age.

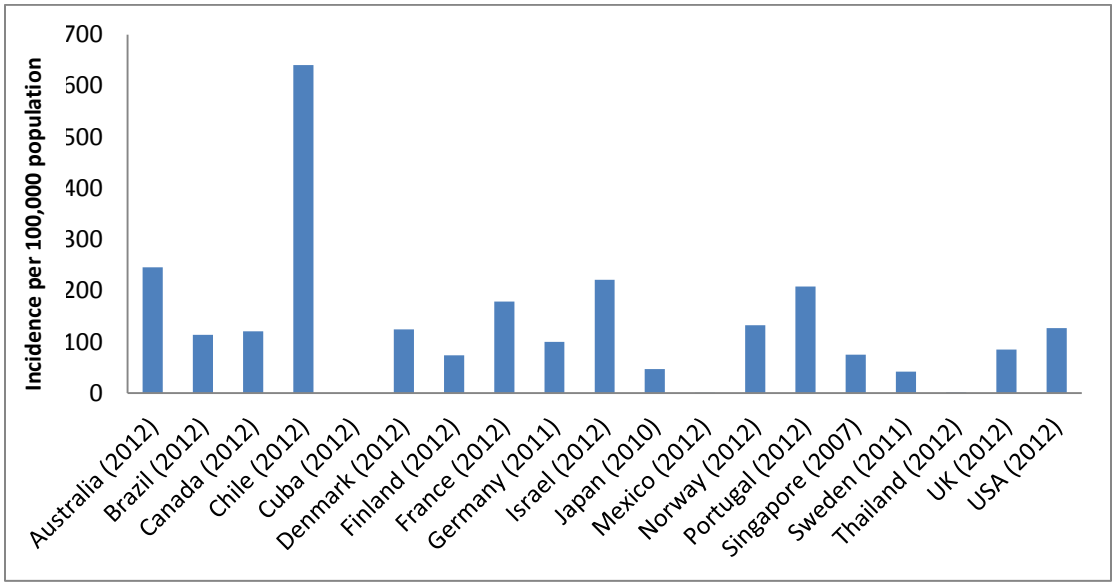
Regional differences of pertussis were noted, hospitalizations were lower in Washington compared to California, possibly related to ethnicity (Hispanic), as no differences in access or coverage of this population group could be observed, raising the point of genetic preposition or mixing patterns.

Key conclusions:	• Data quality is good. • Evidence suggests a resurgence of pertussis. • Since introduction of aP in 1997, despite stable coverage, an increase in incidence predominantly in older age-groups leading to high morbidity has been observed, suggesting a short protective effect of aP. Mortality and incidence under one has not (yet) been affected. • Ethnicity might have an influence on disease severity.

Conclusions and recommendations from country specific data

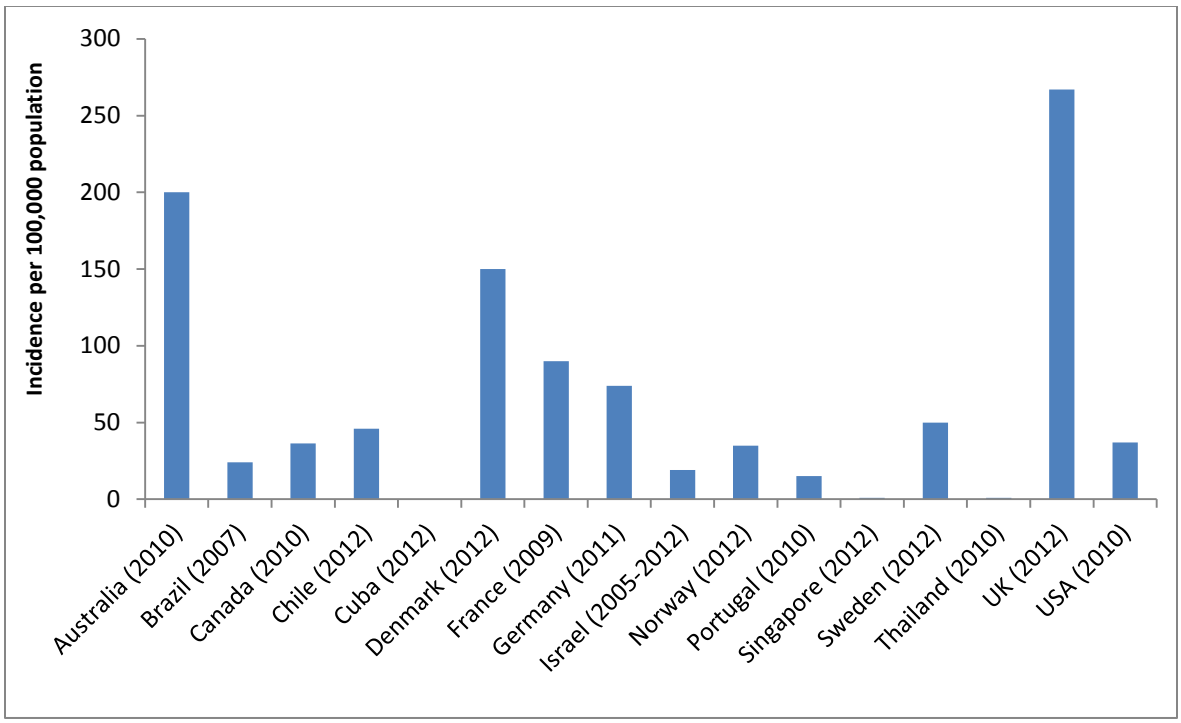
This review has several limitations. Assessment of the trends in the burden of pertussis is complex even at the country level, and especially so for between country and global comparisons. A number of factors relating to vaccines, populations in which they are used, and changes in surveillance over time, should be considered. With respect to vaccines, factors include the vaccine type in use (wP versus aP), differences in the composition and production of aP and wP vaccines, and differences in schedules over time, and duration of vaccine programs at various levels of coverage for the primary series and booster doses. With respect to populations, substantial changes may have occurred in age distribution (e.g. aging of populations and smaller ratio of birth cohort to the entire population) and mixing and transmission patterns over time. Finally , and most importantly, the nature and completeness of local surveillance is critical and highly variable. Changes in surveillance and diagnostic methods and performance (especially regarding laboratory confirmation of suspected cases) make it difficult, both within and especially between countries, to analyze and interpret epidemiological trends. However, the group concluded unanimously that this was nevertheless the best possible approach towards a greater understanding of pertussis epidemiology at the global level.

Figure 26: Incidence of infant (<1 year old) pertussis cases by year and country



***Raw data available only from selected countries. Estimates stem from provided graphs (Finland, Thailand). Denominator data may deviate from nominator data (Japan). Incidence only provided for cases 0-5 months (France). Data provided only for Eastern Federal States (Germany). Data from JRF (Norway).**

Figure 27: Incidence of infant pertussis hospitalizations by year and country



***No data available from Japan, Mexico and Finland. Brazil, data from 2007, denominator 2012. Crude data not available, estimate from graph (Denmark, Norway, Portugal, Sweden, Thailand). Data from 2009, denominator from 2012 (France). Average of Former Eastern and Western Federal states (Germany). Average from 2005-2012 (Israel). Two different incidence estimates: Incidence NNDSS: 36.92 in 2010, for NIS and KID: 79.37 (USA)**

Table 3: Summary of a decade of pertussis deaths (age < 12 months)

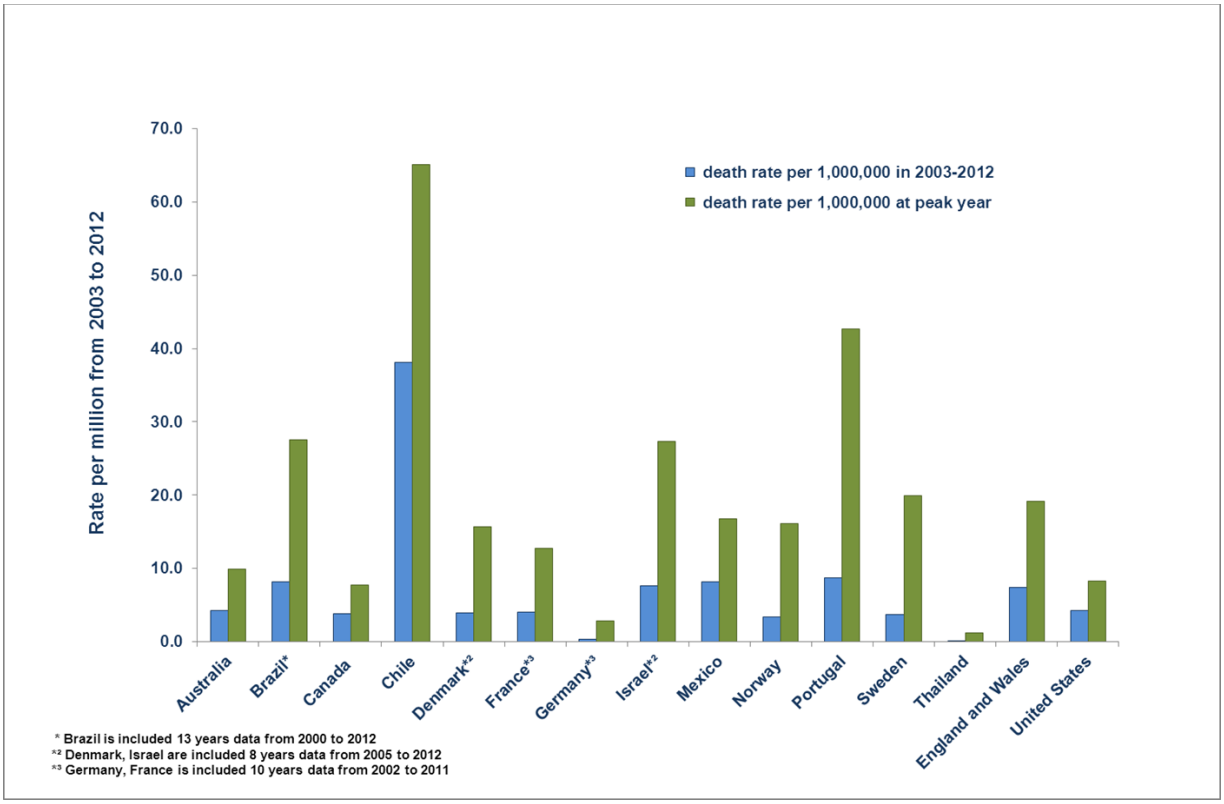
Name of country	Total deaths 2003-2012	Birth cohort average 2003-2012	Peak deaths (year)	Birth cohort at peak year	Death rate per million		Death rate per million	
					per decade	(95% CI)	at peak year	(95% CI)
Australia	12	283684	3 (2001)	302189	4.2	(2.2, 7.4)	9.9	(2.0, 29.0)
Brazil*	342	3204365	83 (2012)	3008538	8.2	(7.4, 9.1)	27.6	(22.0, 34.2)
Canada	14	363659	3 (2012)	390900	3.8	(2.1, 6.5)	7.7	(1.6, 22.4)
Chile	94	246578	16 (2011)	245672	38.1	(30.8, 46.7)	65.1	(37.2,105.8)
Denmark*²	2	64174	1 (2010)	63852	3.9	(0.5,14.1)	15.7	(0.4, 87.3)
France*³	32	786394	10 (2005)	782481	4.1	(2.8, 5.7)	12.8	(6.1, 23.5)
Germany*³	2	706277	2 (2011)	697040	0.3	(0.1, 0.9)	2.9	(0.3, 10.4)
Israel*²	9	147086	4 (2007)	146563	7.6	(3.5,14.5)	27.3	(7.4, 69.9)
Mexico	192	2354798	38 (2012)	2268950	8.2	(7.0, 9.4)	16.7	(11.9, 23.0)
Norway	2	59654	1 (2012)	62109	3.4	(0.4, 12.1)	16.1	(0.4, 89.7)
Portugal	9	102846	4 (2012)	93814	8.8	(4.0, 16.6)	42.6	(11.6, 109.2)
Sweden	4	107293	2 (2004)	100232	3.7	(1.0, 9.5)	20.0	(2.4, 72.1)
Thailand	1	778790	1 (2003)	858079	0.1	(0.0, 0.7)	1.2	(0.0, 6.5)
England and Wales	50	676402	14 (2012)	731996	7.4	(5.5, 9.7)	19.1	(10.5, 32.1)
United States	178	4220322	35 (2005)	4212276	4.2	(3.6,4.9)	8.3	(5.8, 11.6)

* Brazil is included 13 years data from 2000 to 2012

*² Denmark, Israel are included 8 years data from 2005 to 2012

*³ Germany, France is included 10years data from 2002 to 2011

Figure 28: Infant death rates per 1,000,000 per decade (2003-2012) and at peak year



Country specific data from 19 countries provided no evidence of a broad resurgence of pertussis at the global level. The increase in pertussis cases was attributed to cyclic patterns in the majority of countries where the increase was noted over the recent years, likely amplified by increase in disease awareness, increase in overall laboratory testing, and the enhanced sensitivity of the PCR diagnostic methods being used more widely. Natural recurring cycles might be more noticeable in countries where surveillance is more sensitive and where the control of the disease in recent years has generally been good.

Data from only 5 out of 19 countries (Australia, Chile, Portugal, USA and UK) supported the presence of a true resurgence in pertussis related morbidity in recent years relative to prior comparison periods. For Israel, the situation was unclear and more information is needed on the use of new diagnostic methods and other factors, such as increased awareness that might have recently improved case ascertainment.

Only one country using whole cell pertussis vaccination, Chile, reported a resurgence. For now it seems that the increase in cases could be attributed to a sustained decrease of vaccine coverage, variable coverage at the district level, changes in surveillance practices as well as problems with the specificity of diagnostic tests. The increase in infant cases was notable and associated with increased mortality, but as this was based on fluorescent antibody test data alone (known to have problems with specificity), more data on the characteristics of laboratory confirmation and cases were needed. Although reported data suggested a major recent increase in pertussis in Brazil, another country still using wP, it seems that the appearance of the increase was exaggerated due to changes in the surveillance system and that the change in disease activity is not in excess from what would be normally expected in epidemic cycles.

Data from Australia suggest a major increase in morbidity in children less than 10 years of age, including hospitalizations in infants <1 year but without an increase in mortality in this age group. It was considered that the resurgence was most likely related to cessation of the early childhood booster dose and aP-related waning of immunity among children before the 4 year booster was due.

Data from Portugal suggest that although increased testing with PCR may have contributed to the observed increase in incidence, the high proportion of affected infants <1 year of age and the high mortality rate from pertussis in this age group suggest a true resurgence of the disease.

Data from the US suggest waning of immunity following aP, but no impact on infant mortality was observed. The US data also clearly point to the more limited duration of protection from adolescent booster vaccination in individuals primed with aP vaccines compared to those who had at least one dose of wP.

An increase in notified cases, in hospitalizations, and in deaths in young infants was observed in England and Wales in 2011. The cause of this resurgence is still unclear and is being investigated.

Limited evidence suggests that ethnicity may be a potential risk factor for fatal disease, but it should be further investigated. Specifically it was noted that Hispanic children in the US have a greater mortality rate. Whether this is genetic based or related to access to care remains to be determined.

Evidence is not sufficient to assess a significant difference in vaccine effectiveness using different component aP vaccines; there is no conclusive data yet establishing the superiority of one aP vaccine versus another.

Pertussis vaccination has had a great impact in reducing the overall burden of disease. Cyclic recurrent patterns of pertussis can still be observed, but there has been an overall reduction of pertussis incidence, and in particular, a reduction in infant mortality. Both wP and aP are effective in reducing infant mortality, yet data highlight the importance of timely vaccination and high coverage, and point to the presence of an aP-related waning of immunity.

3. Acellular pertussis vaccine immunogenicity and efficacy studies in infants

With the development and testing of new aP vaccines in the 1980s and 1990s, assays to measure the humoral immune responses to the new vaccines were established [7]. In addition, the NIH supported a large comparative safety and immunogenicity trial of 13 aP and2 wP vaccines, combined with diphtheria and tetanus toxoids, and administered to infants at 2, 4, and 6 months of age [8, 9]. The trial was termed the Multicenter Acellular Pertussis Trial (MAPT). Serum samples were taken prior to and 1 month after the third vaccination, and enzyme-linked immunosorbent assays (ELISA) were performed to measure humoral responses to pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae (FIM). As shown in Table 1, the antibody responses to the acellular vaccines and the whole cell vaccines were compared[10]. The PT response to the wP vaccine was noted to be in the middle of the responses, while the PT antibody responses to the aP vaccines generally were comparable or higher than those noted after the whole cell vaccine, but with substantial variability in responses. The antibody responses to the other pertussis antigens are also shown in Table 4.

Following MAPT, several randomized pertussis vaccine efficacy studies were conducted in Europe and Africa in the late 1980s and early 1990s to compare the safety and efficacy of the aP with the wP vaccines for the prevention of laboratory-confirmed pertussis disease in infants [11-14, 15-19]. Although they provided pivotal safety and efficacy data needed for the replacement of DTP vaccines by DTaP vaccines, important differences in the study design, such as the inclusion of different whole-cell vaccines as the comparator arms, the number of aP components included in the DTaP vaccines, and different case definitions, made comparisons of the many different studies problematic. A detailed summary of the data derived from these pivotal efficacy studies are presented in Table 4. As noted in the table, vaccine efficacy varied among the different acellular vaccines, among the different whole cell vaccines, and between different whole cell and acellular products. What was remarkable was that the Connaught whole cell vaccine that served as the control in the Swedish and the Italian trials was very poorly immunogenic, stimulating very little antibody to PT, FHA, and pertactin. The efficacy of the Connaught wP vaccine was also lower than the included aP vaccines, and lower than the efficacy of the wP vaccines used in the other trials.

Another efficacy study, not cited in the table, was a trial comparing the efficacy of the 2, 3, and 5 component aP vaccines against a UK whole cell vaccine in 82,892 infants randomized to receive the vaccines in2 different schedules; at ages 3, 5, and 12 months, or at ages 2, 4, and 6 months. The primary case definition was culture-confirmed *B. pertussis* with at least 21 consecutive days of paroxysmal cough (typical pertussis), and the secondary definition was any culture confirmed *B. pertussis* with or without cough (pertussis infection). Although no significant difference was found in the efficacy of the whole-cell and the 5-component aP vaccine, the 3-component aP vaccine was less effective than either whole cell or the 5-component vaccine against culture-confirmed pertussis [20]

Overall conclusions from these efficacy studies were that multi-component acellular vaccines, defined as vaccines containing three or more pertussis antigens, were effective in preventing confirmed pertussis

infections and were associated with fewer adverse events than whole cell pertussis vaccines for the primary series. Multi-component acellular vaccines were more effective than low-efficacy whole-cell vaccines, but less effective than the highest-efficacy whole-cell vaccines.

Table 4: Antibody levels one month following the third dose of vaccine: results from the multicenter acellular pertussis trial and a follow-up trial.

		Geometric Mean Antibody Level (95% CI) Following Immunization at 2, 4, and 6 Months			
Manufacturer or Distributor	Vaccine†	PT	FHA	PRN	FIM
Sanofi Pasteur (Canada)	*Tripacel*	36 (32–41)	37 (32–42)	114 (93–139)	240 (204–282)
Sanofi Pasteur (Canada)	CLL-3F_2	38 (33–44)	36 (31–41)	3.4 (3.1–3.6)	230 (183–290)
Sanofi Pasteur (France)	*Triavax*	68 (60–76)	143 (126–161)	3.3 (3.1–3.6)	1.9 (1.6–2.1)
Sanofi Pasteur (USA)	*Tripedia*	127 (111–144)	84 (73–95)	3.5 (3.2–3.9)	2.0 (1.7–2.3)
Baxter Laboratories	*Certiva*	54 (41–71)	1.1 (1.0–1.2)	n/a	n/a
Biocine Sclavo	BSc-1	180 (163–200)	1.2 (1.1–1.4)	3.4 (3.1–3.7)	1.8 (1.7–2.0)
Chiron Vaccines	*Acelluvax*	99 (87–113)	21 (18–25)	65 (53–79)	1.9 (1.7–2.1)
GlaxoSmithKline	*Infanrix*	54 (46–64)	103 (88–120)	185 (148–231)	1.9 (1.7–2.2)
Massachusetts Public Health Biologic Labs	SSVI-1	99 (87–111)	1.2 (1.1–1.3)	3.4 (3.1–3.6)	2.1 (1.8–2.4)
Michigan Department of Public Health	Mich-2	66 (59–75)	237 (213–265)	3.2 (3.0–3.4)	2.0 (1.8–2.3)
SmithKline Beecham Biologicals	SKB-2	104 (94–116)	110 (99–122)	3.3 (3.1–3.5)	1.9 (1.7–2.1)
Speywood (Porton) Pharmaceuticals	Por-3F_2	29 (25–33)	20 (17–23)	3.0 (3.0–3.1)	361 (303–430)
Wyeth Lederle Vaccines and Pediatrics	LPB-3P	39 (32–48)	144 (127–163)	128 (109–150)	19 (13–27)
Wyeth Pharmaceuticals	*ACEL-IMUNE*	14 (12–17)	49 (45–54)	54 (47–62)	51 (41–63)
Wyeth Lederle Vaccines and Pediatrics	Whole-cell	67 (54–83)	3.0 (2.7–3.4)	63 (54–74)	191 (161–227)

CI, confidence interval; FHA, filamentous hemagglutinin; FIM, fimbrial proteins; MAPT, Multicenter Acellular Pertussis Trial; n/a, not available; PRN, pertactin; PT, pertussis toxin.

Table 5: Pertussis vaccine efficacy trials

Study	Study Design	Vaccine(s)	Absolute Vaccine efficacy % (95CI)	Antigens	Whole cell vaccine	Case Definition
Stockholm-Sweden (1986)[21]	Randomized, double-blinded, placebo-controlled study	JNIH-6 JNIH-7	81 (61-90) 75 (53-87)	**PT, FHA** **PT**	None	≥ 21 days cough + ≥ 9 coughing spasms on at least 1 day + positive culture
Stockholm (1992)[18]	Randomized, fully blinded, placebo-controlled study	SKB-2 *Tripacel* **Connaught-DPT**	59 (51-66) 85 (81-89) 48 (37-58)	**PT, FHA, DT, TT** **PT, FHA, PRN, FIM 2, FIM3, DT, TT**	Connaught-DPT	≥ 21 days paroxysmal cough + either: positive culture, confirmed by serologic assay or PCR; 2-fold PT or FHA IgG rise; or epidemiological link to culture-positive case
Italy (1992)[16]	Randomized, double-blinded, controlled, comparative study	*Infanrix* *Acelluvax* **Connaught-DPT**	84 (76-89) 84 (76-90) 36 (14-52)	**PT[1], FHA, PRN, DT, TT** **PT[2], FHA, PRN, DT, TT**	Connaught-DPT	≥ 21 days paroxysmal cough + either: positive culture, confirmed by serologic assay or PCR;
Goteborg-Sweden (1991)[15]	Randomized, fully blinded, controlled study	*Certiva*	71 (63-78	**PT, DT, TT**	None	≥ 21 days paroxysmal cough + either: positive culture confirmed by serologic assay or PCR; 3-fold PT or FHA IgG rise
Senegal (1990)[13]	Randomized, fully blinded, controlled study	*Triavax* **PMC-Fr DPT**	74 (51-86) 92 (81-97)	**PT, FHA, DT, TT**	PMC-Fr DPT	≥ 21 days paroxysmal cough + confirmation by culture, serology or epidemiological link
Erlangen-Germany (1991)[22]	Randomized, double-blinded, controlled study[3]	*ACEL-IMUNE* **Lederle DPT**	78 (60-88) 93 (83-97)	**PT, FHA, PRN, FIM 2, DT, TT**	Lederle DPT	≥ 21 days cough with paroxysm, whoop, or vomiting + confirmation
Mainz-Germany (1992)[23]	Passive monitoring for suspected household cases	*Infanrix* **Behring, SKB DPT**	89 (77-95) 98 (83-100)	**PT, FHA, PRN, DT, TT**	Behring, SKB DPT	≥ 21 days paroxysmal cough + either: positive culture, or serology in households
Munich (1993)[12]	Case-control study	*Tripedia* **Behring, DPT**	93 (63-99) 96 (71-100)	**PT, FHA, DT, TT**	Behring, DPT	≥ 21 days paroxysmal cough + either: positive culture or household contact with laboratory confirmation

Modified from Kathryn M. Edwards and Michael D. Decker. Pertussis vaccines. Vaccines. Plotkin and Orenstein. 4th ed.
CI, confidence interval; DTP, diphtheria and tetanus toxoids and whole-cell pertussis vaccine; FHA, filamentous hemagglutinin; FIM, fimbrial proteins; HCPDT, hybrid component pertussis-diphtheria-tetanus vaccine; PMC-Fr, Pasteur Merieux Connaught–France; PRN, pertactin; PT, pertussis toxin; SKB, SmithKline Beecham.
All results shown are for complete primary infant immunization series (3 doses, except Stockholm 1986, 2 doses); effects of booster dose not included.
[1] PT inactivated with formalin and glutaraldehyde.
[2] Genetically detoxified pertussis toxin.
[3] DTaP and DTP vaccines were administered in a double-blind, randomized design meanwhile DT vaccine was administered in an open arm of the study based on parental preference.

4. Baboon experimental model: comparison of aP and wP and proof of concept studies for neonatal and maternal vaccinations

Tod Merkel and his colleagues at the US Food and Drug Administration (FDA) in Bethesda, Maryland have developed a baboon model of pertussis that closely resembles human disease[24]. Recently they used that model to show that acellular pertussis vaccines protect against disease but are not fully effective in preventing infection and transmission of pertussis to other animals[25]. Their studies also show that the DTaP vaccines are much less effective at preventing infection than natural disease and are substantially less effective than DTwP vaccines[24]. Like for the nonhuman primates, asymptomatic transmission of *B. pertussis* to other humans may also occur in DTaP immunized humans and may drive pertussis outbreaks. The other notable finding in the baboon study is the role of both Th1 and Th17 cells in the immune response to natural infection and DTwP vaccine, but only Th2 immune responses after DTaP vaccines. It appears that both Th1 and Th17 memory responses are needed for sterilizing mucosal immunity. aP has therefore a reduced ability to prevent infection and reduce subsequent transmission relative to wP and natural infection.

Merkel et al. have also used the nonhuman primate model of pertussis to address the ability of neonatal and maternal vaccination to confer protection[26]. Neonate baboons were vaccinated with acellular pertussis (aP) vaccine at 2 days of age or at 2 and 28 days of age. To model maternal vaccination, adult female baboons that had been primed with aP vaccine were boosted at the beginning of their third trimester of pregnancy. Unvaccinated 5 week old baboons developed severe disease when challenged with *B. pertussis* at 5 weeks of age. Baboons receiving either 1 or2 doses of aP vaccine and infants born to mothers vaccinated at the beginning of their third trimester were protected. These studies clearly showed that neonatal and maternal vaccination confer protection in the baboon model and provide a proof-of-concept that supports further study of these strategies for protection of newborns from pertussis infection. The potential for evaluating alternative pertussis vaccine approaches in the nonhuman primate model is extremely attractive.

5. Pertussis modelling studies

Different country-specific mathematical pertussis models were presented from Australia, the UK and the US.

Australia

The existing 'Hethcote' model was adapted by Jodie McVernon et al. from the University of Melbourne and James Wood from the University of New South Wales to reflect Australian epidemiology. This new model allows incorporation of multiple national data resources, including recurrent national serosurveys of PT antibody distribution.

The research and policy questions driving this model were:

What are the relative contributions of natural and vaccine derived immunity on observed pertussis epidemiology?

How have the changes to the vaccine schedule and vaccine type influenced the patterns of disease and infection that we observe in Australia?

What are the likely public health impacts of suggested changes to the pertussis vaccine program in Australia?

Multiple data sources were consulted to inform the deterministic, age-structured, compartmental, dynamic model. Sub-categorization by immunologically naive and experienced (natural- or vaccine-acquired immunity) population was incorporated into the modelling. Assumptions were that all infections are infectious to some degree. Non-infectious boosting cycles were included in the model. Simulations were conducted for chosen parameters; the output was matched with key features of the Australian epidemiology. Alternative model assumptions were explicitly tested.

The key conclusion from the model was that natural immunity is the primary driver, with an influence over decades.

The model demonstrated a strong interaction between natural and vaccine immunity, and found that small changes in coverage could lead to loss of direct effects impacting on rates of pertussis infection decades later. The model explored the impact of different vaccination schedules and supports the assumption that additional doses are important for herd protection. The age at administration was less influential. Over the period of observation, aP inferred to have slightly shorter duration of protection than wP, but the period of observation for aP was much shorter and so may have under-estimated differences in duration of protection.

One potential role of the model is to explore long-term effects of vaccination and synthesize country-specific data. It models infection rather than disease, and suggests a role for serosurveillance in prediction, in that the Australian series of cross-sectional data over more than a decade found a low prevalence of elevated PT antibody titres prior to an epidemic year. The model predicts that small

changes in coverage or schedule can have a large subsequent impact on the resurgence of infection. In infants, unlike older age groups, infection would be expected to closely parallel disease. It was noted that the differences in model structures between groups can lead to differences in model outcomes.

The United States

Manoj Gambhir, currently at Monash University, Australia, described work he had done with collaborators while working at the US Centres for Disease Control and Prevention to construct a compartmental deterministic model simulating the natural history and population transmission of *B. pertussis* in the US. Infected individuals can be either primary infected or infected more than once. Several models were fitted to the available data with results based on the best-fitting model. Confidence intervals for model parameters had to be found. Ranges of plausible outcomes were chosen. Multiple data-sources fed into the model: Vaccination coverage obtained from National Immunization Surveys (NIS), U.S. demography, 'Polymod' age mixing matrix and National Notifiable Diseases Surveillance System (NNDSS) pertussis incidence counts.

Outputs of the model were the change in vaccine efficacy, the change in duration of protection, the infectiousness and susceptibility of secondary infections, the R0 and the reporting rate change. The known parameters are "fixed" and the unknowns vary. The model demonstrates the shift of disease to adolescents over time (1994-2012). The best-fitting model incorporates a drop in vaccine efficacy and a rise in the waning rate of protection from the wP to aP. The duration of whole-cell vaccine protection corresponds with natural infection.

England and Wales

Yoon Choi et al. (Public Health England, London, UK) developed a realistic-age-structured, compartmental deterministic model to describe the pertussis transmission dynamics.

The main questions to the model were:

Why did this resurgence occur and will it continue? Is an adolescent booster programme enough to control this resurgence? What would have happened if wP vaccine was not replaced with aP vaccine in the primary schedule? If there had been no dramatic decline in vaccine uptake in 1970s (associated with concerns about wP safety), would the continued use of wP still brought about the resurgence?

The model included 100 yearly age cohorts and a 52 weekly age structure in each annual age cohort. The model assumed the move to the compartment of non-susceptibility after natural infection. The model was parameterised using the pre-vaccination pertussis notification data and simulated with historical vaccine uptake and changes in vaccine programmes that occurred between 1956 and 2013 in England and Wales. The model was fitted to the 1956 age-stratified notification data as the pre-vaccine equilibrium year and simulated for 75 years between 1956 and 2030 with many transmission and vaccination scenarios to explore the uncertainty of model assumptions made. Comparing the simulation results with the annual notification data would inform plausible parameter scenarios to predict the impact of different intervention programmes. Yoon acknowledged that the mixing patterns have

changed over time. The parameters, duration of the natural immunity, reporting rate, mixing pattern, were varied in the simulations.

Simulation results showing the recent resurgence revealed that a shorter duration of aP than wP vaccine might be the cause of this resurgence. These scenarios predicted that elevated levels of pertussis would continue with the current vaccination programme and that while an adolescent booster programme could reduce the overall notifications marginally it would not prevent future resurgences as the highest future disease incidence was predicted to occur in individuals over 25 years of age.

Efficacious wP vaccines seem to induce a longer duration of protection than aP vaccines. Furthermore models with long durations of protection for aP [>10 years] did not fit the UK epidemiology. Protection afforded by aP against transmission was more difficult to assess given the short duration for which the vaccine had been used in the UK. Overall the model suggested that the drop of coverage in the 70s was not needed to generate the current resurgence, and that a resurgence may not have occurred with continued use of wP.

6. Prevention of early mortality

Review of effectiveness of 1 or 2 doses of pertussis vaccine against infant mortality

In 2009, SAGE addressed the protective effect of 1 or 2 doses of pertussis vaccine against death. At the time, the Working Group on Pertussis vaccines concluded that data were not sufficient to establish the existence or magnitude of a protective effect. In the context of the questionnaire distributed by the work group during 2013, countries were asked to provide data and results of observational studies on the effectiveness of 1 or 2 doses of pertussis containing vaccine. In view of limited specific effectiveness data against mortality, any pertussis disease, severe morbidity, and/or hospitalization, were also assessed. The data in the table were provided in responses to the surveys distributed to countries (Table 6). Further data might be added to the table, pending the results of the systematic review.

Table 6: Vaccine effectiveness against infant disease and hospitalization.

Country/ Vaccine	Single dose	Two doses	Full primary schedule
Australia[27] **aP**	VE hospitalization: 55% (95%CI: 43-65%)	VE hospitalization: 83% (95%CI: 70-90%)	VE hospitalization: 85% (95%CI: 75-91%)
England[28] **aP or wP**	VE against infant pertussis disease: 62% (95%CI: 53-69%)	VE against infant pertussis disease: 85% (95%CI: 77-91%)	VE against infant pertussis disease: 95% (95%CI: 86-99%)
France[29] **wP**	VE against infant pertussis disease: 58%[3]	VE against infant pertussis disease: 87%[4]	VE after 4 doses against infant pertussis disease: 84%- 100%
Germany[30] **aP**	VE hospitalization: 68.0% (95%CI: 45.6-81.1)	VE hospitalization: 91.8% (95%CI: 84.7-95.7)	
USA DTaP[31]**/ Tdap**[5]			VE after 5 doses of DTaP, approx. 98% in first year after vaccination but declining to approx. 75% >5years after vaccination. VE of Tdap: 75% in the first year declining to 40% after 2-4 years.
USA DTwP/DTaP[32]	VE against pertussis disease in ages 6-23mo: 50.5% (95% CI: -71.1-86.3)	VE in ages 6-23mo against pertussis disease: 80.1% (95% CI: 41.3-93.2)	

In general, incidence of pertussis peaks in the second month of life, prior to commencement of vaccination. Incidence declines rapidly as soon as 1 or 2 doses are received. This pattern was observed in data from the USA and Australia. For infants less than 1 year of age, disease is more likely to be severe than in older children, hence protection against any disease is expected to protect against severe

[3] Adjusted OR associated with risk of severe pertussis (ref: 0 dose) OR: 0.42 (95%CI: 0.19-0.91)
[4] Adjusted OR (2 or 3 doses) associated with risk of severe pertussis (ref: 0 dose) OR: 0.13(95%CI: 0.02-0.98)
[5] Unpublished data from CDC

outcomes including death and hospitalization. Further, observation of disease occurrence in the USA and Australia reveals a decline in hospitalization and deaths once the vaccination is initiated at age 2 months. Case-level data from Australia, France, the USA, and Canada indicate that hospitalizations and deaths predominate in the youngest ages (0-1 month), and that the majority of deaths occur in infants who received 0 or1 dose, while deaths are rare in those receiving2 or more doses.

Published and unpublished observational analyses of vaccine effectiveness were also reviewed. Australian data demonstrated that VE increases with the number of doses and age of the infant. VE for one dose is 55% (95% CI: 43-65%), 83% (95% CI: 70-90%) for 2 doses and is highest for a completed primary schedule (85% (95% CI: 75-91%) but rapid waning can be observed in the following three years. Effectiveness of pertussis vaccine against disease among infants aged 9 weeks to 6 months was assessed in England from 2002-2009. VE was 62% (95% CI: 53-69%) for one dose and 95% (95% CI: 86-99%) for three doses. Among infants aged 6-23 months, 1 and 2 dose VE were 50.5% (95% CI: -71.1-86.3) and 80.1% (95% CI: 41.3-93.2), respectively.

Among studies of hospitalization and severe disease, a Swedish study [33] suggests the risk of hospitalization decreases after receiving more vaccine doses [[61% (no doses), 36% (single dose) to 2.7% (2 doses)]. A French study calculated the odds ratio for severe pertussis to be reduced to 0.42 after 1 dose and to 0.13 after 2 and 3 doses, with the number of doses received more predictive for disease than was age of the infant.

One unpublished analysis of US data using multivariable regression found that one dose of vaccine reduced the risk of fatal cases. From 1991 through 2008, pertussis-related deaths occurred among 258 (0.57%) of 45,404 reported cases. All deaths occurred before age 34 weeks at illness onset. Receiving >1 dose of pertussis vaccine was protective against death (adjusted odds ratio [aOR] = 0.29, 95% CI: 0.12–0.69), hospitalization (aOR=0.64, 95% CI: 0.58–0.71), and pneumonia (aOR= 0.78, 95% CI: 0.67–0.91).

There is increasing and consistent evidence both from observational and analytical studies from a number of industrialized countries using aP and wP to show that a single dose of either pertussis vaccine in infancy has around 50% effectiveness in preventing severe disease, hospitalization, and death and that 2 doses of either pertussis vaccine offers higher protection (83%-87%). Evidence is not sufficient to assess a significant difference in vaccine effectiveness using different component aP vaccines; there is no evidence pointing to the superiority of one aP vaccine over another. While the assessment of effectiveness is preliminary and may change upon completion of the systematic review of vaccination schedules, the data are consistent and convergent across multiple studies.

The group concluded that timely delivery of the first dose is critical, but the age at which the first dose is recommended should depend on the local epidemiology and vaccine delivery system. While on-time vaccination is crucial regardless of the schedule, the group reinforced that 1 or2 doses are not sufficient and that completion of the entire recommended number of doses is needed to protect older age groups, which might not be at risk of death but still at risk for increased morbidity and who may contribute to transmission of the disease to unvaccinated young infants.

Maternal immunization

In October 2012, in response to a national outbreak of pertussis in the UK with an increasing number of deaths and hospital admissions in very young infants, a temporary pertussis vaccination program for pregnant women was introduced. Antenatal women were offered a 5-component aP containing vaccine (dTaP/IPV) between 28 and 38 weeks of pregnancy. Analysis of laboratory confirmed pertussis (January 2008-September 2013) and hospital admissions (January 2011-September 2013) was undertaken to investigate the impact of the program on infant disease. Vaccine effectiveness was calculated using a screening method based on follow up of confirmed infant cases for vaccination status and estimates of vaccine coverage for the antenatal population. Vaccine safety was also assessed by identifying pregnant women with a record for a pertussis-containing vaccination from beginning October 2012 to end March 2013 in the Clinical Practice Research Datalink, a large computerized data base of health care consultations for over 12.5 million National Health Service (NHS) patients registered at a representative subset of general practices in the UK. Stillbirth rates following vaccination were compared to published national background data. A matched cohort study was also conducted using historical unvaccinated controls and examining a range of pre-defined pregnancy-related adverse events.

Uptake of vaccination by mothers was good, around 70% at the start of the programme and leveling out at around 60% in 2013. No deaths occurred in the infants of vaccinated mothers since the start of the programme in October 2012. Two deaths in the infants of unvaccinated mothers had occurred in 2013. In contrast to all other age groups, laboratory confirmed cases in < 3 month olds were lower in the first 9 months of 2013 than in the same period in 2011 (around 40% lower) compared with an overall increase in all age groups of 503%. Vaccine effectiveness (VE), based on 82 confirmed cases followed up by September 2013 in infants aged less than 3 months whose mothers were vaccinated at least 7 days before birth, was 91% (95% CI: 84%-95%), and 38%(-95% to 80%) for those vaccinated within 7 days before or 1-13 days after birth. These results are consistent with high vaccine effectiveness and likely to reflect protection of the infant by both passive antibody and reduced maternal exposure. The results of a second case control study were also reported and gave similar results. Of the 30 infants with confirmed pertussis at aged 8 weeks or less at onset in the study, 7 of the mothers had been vaccinated during pregnancy. In comparison, 39 mothers of the 55 controls had been vaccinated during pregnancy. The VE (after adjustment for sex and birth period) was 0.90 (95% CI: 0.67-0.97). In the safety evaluation, data were available for over 20,000 vaccinated pregnant women.

The safety study showed no evidence of an increased risk of stillbirth in the 14 days immediately following vaccination, or later in pregnancy, compared to that in unvaccinated women. There was no evidence that vaccination accelerated the time to delivery or caused an increased risk of maternal or neonatal death, (pre-) eclampsia, haemorrhage, foetal distress, uterine rupture, placenta or vasa praevia, caesarean delivery, low birth weight, or severe events that can occur naturally later in pregnancy. This large study provides the first controlled data on the safety profile of pertussis vaccination in pregnancy.

Interim results of an immunogenicity study in 129 infants of vaccinated mothers that subsequently received the routine vaccines in the UK schedule at 2, 3, 4 months of age were also reported. Compared with immunogenicity data from historical controls, infants' Hib and tetanus antibody levels post primary were enhanced. There was some reduction in infants' post primary antibody levels to pertussis antigens,

diphtheria, meningococcal C conjugate and some pneumococcal serotypes. The clinical significance of these reductions is uncertain but it is reassuring that national surveillance of pertussis, invasive pneumococcal disease and serogroup C disease in the cohort of infants whose mothers would have been eligible for vaccination in pregnancy has shown no evidence of an increase in those aged 3-11 months. For pertussis, the number of cases in 2013 in this age group was similar to that before the resurgence in 2011.

Data from unpublished immunogenicity studies in Canada and the US using a 2, 4, 6 month schedule also showed evidence of a reduction in pertussis specific antibody responses post primary immunisation in infants whose mothers were vaccinated in pregnancy.

Key conclusions:	UK experience indicates a high impact of vaccination of pregnant women against infant pertussis with an overall reduction in infant mortality. This impact is likely due to the direct protective effectiveness in the infant via the transfer of maternal antibodies, and via impact on risk of transmission through protection of the mother. The vaccine is safe and effective to use in pregnant women. There is some evidence of a reduction in antibody responses to pertussis antigens in infants of vaccinated mothers. The clinical significance of this is uncertain, but to date there is no evidence of an increased risk of pertussis in infants aged 3-11 months. The evidence reviewed relates only to the use of aP vaccine in pregnancy, and the immunogenicity data are confined to infants vaccinated with aP containing vaccines. Conclusions on maternal immunization cannot therefore be extrapolated to wP vaccines without additional immunogenicity and safety data.

Immunization of newborns

During the whole cell only era, research on neonatal immunization largely ceased after a published study claimed to demonstrated immune tolerance in neonates to pertussis vaccine, but this was based on very limited evidence [34]. There have now been 4 additional small studies evaluating neonatal use of acellular vaccines, 1 using DTPa [35] and3 using acellular pertussis (aP) without D and T [36-38].

As well as vaccine used (DTPa vs aP and antigen content), study methods varied by timing of dose, timing of serology and concomitant vaccine antigens administered. Primary response to vaccination was measured by IgG antibody to pertussis antigens (PT, PRN, FHA), and in some cases data on maternal antibody at the time of birth were also reported.

There were important differences between study outcomes. All 3 studies where aP was used showed an increase in IgG antibody to pertussis antigens in birth dose recipients, but the study using DTaP did not. Both the Halasa study using DTPa and the Belloni study using Chiron-manufactured aP showed lower antibody levels in birth dose recipients at 7 months of age following completion of the primary series. The 2 studies using GSK-manufactured aP vaccine did not show any reduction in antibody levels at 7 months in birth dose recipients. No safety issues were reported, but the combined sample size of all trials was only around 300 subjects. The limited available data suggest that neonatal immunization is safe and can achieve good antibody responses early if aP rather than DTaP is used. Several limitations are flagged, including overall sample size being small and the lack of currently commercially available monovalent aP. A larger trial of 440 infants randomised to aP and Hep B or Hep B vaccine alone within 5

days of birth followed by DTaP-HepB-Hib-IPV vaccine at 6 weeks (including ~100 infants born to mothers who had received dTap within the previous 5 years) was completed in Australia in 2012 and should have immunogenicity data at 2, 4, 7 months available in 2014. Monovalent aP to the newborn could be an option if the mother has not received immunization and there could be potential to combine aP with hep B vaccine, which is recommended for newborn immunization in many settings.

Key conclusions:	• The presented data suggests the efficacy of neonatal immunization though cannot be generally recommended (yet) due to limited data on impact and safety and lack of availability of an aP alone vaccine. However, data demonstrating protection against severe pertussis disease in human and baboon infants after a single dose support continued evaluation of neonatal pertussis strategies alongside maternal vaccination.

Cocooning strategies

Cocooning strategies from various countries were assessed, with particular focus on the implementation and analysis of a cocooning strategy in Chile.

Cocooning was defined as a strategy to protect young infants who are too young to be protected by the receipt of their DTaP series and who are at substantial risk of severe disease, hospitalization, or death by exposure to *B.pertussis* by inducing protection through vaccination of most likely sources of infection i.e. individuals in close contact to the infant. Infants <2 months are at highest risk as too young to be vaccinated with parents, grandparents and siblings being the main source of infection. Various possibilities to implement this strategy exist. In Chile vaccination is recommended for mothers and persons >12 years that live with the newborn, caregivers that stay during the day with the newborn, as well as pediatric healthcare personnel.

Vaccination of post-partum women, antibody response is highest by day 10 for serum IgG and peaked between days 10-14 for breast milk IgA. Maternal antibodies against pertussis in breast milk do not interfere with the infant immune response to vaccines.

Experience in Chile, which implemented cocooning in 2011 in critical regions following an increase in infant deaths, was positive. Families, excluding the pregnant mother, were vaccinated 2 weeks before childbirth. The strategy was only implemented in regions with high infant morbidity and mortality. High coverage was reached in mothers (92% in 2012, 82% in 2013). Coverage among household contacts was 59% in 2012 and 55% in 2013. Multivariate analysis suggested a significant impact of cocooning with 84% reduction of infant mortality comparing cocooning against no measures (unpublished data). No impact was observed on the overall number cases, but a reduction in infant deaths in the first 6 months of age was seen. Yet more evidence is needed to confirm the impact of the cocooning strategy.

Data on the impact of cocooning strategies from further research studies and modeling were assessed. With respect to research, unpublished data from an Australian case control study to evaluate a funded

cocoon program with coverage of > 75% for adults in contact with infants under the age of one year in an epidemic between 2009 and 2011, suggested a significant decline in the risk of early onset pertussis if both parents had received a dose of dTap at least 4 weeks before disease onset. Most benefit appeared to accrue from maternal vaccination more than 4 weeks prior to disease onset, with relatively minor independent contribution from vaccination of the father. The findings highlighted the importance of timing of vaccination and suggested that a post natal vaccine dose delivered to the mother in the previous pregnancy may deliver persisting benefit in the next. This is an important consideration for future research as it has implications with respect to the risks and benefits of dTap in every pregnancy with respect to spacing of pregnancies.

Modeling suggests a 70% decrease in <3 months infection if parents in the US (mothers and close household contacts before postpartum hospital discharge) are vaccinated. The number needed to treat is 605 adults to prevent one infant case [39]. Coudeville et al. 2008 found that in the US a combination of cocoon strategy (vaccination of adult household contacts) plus a single dose for all adults and a decennial routine adult vaccination (40% coverage) could be highly effective in reducing pertussis in infants, adolescents and adults[40]. In the US across sectional study suggests difference in length of hospitalization and number of deaths due to post-partum vaccination of all care-givers[41]. Several studies were published to assess cost-effectiveness of the strategy. Westra et al. 2010 compared 3 different strategies (Immunization of infants at birth, cocooning, and maternal immunization). Findings suggest cocooning and maternal immunization to be cost-effective[42]. Scuffham et al. 2004 also compared three strategies (Immunization of infants at birth, at one month of age and parental immunization) of which parental vaccination at birth was the most cost-effective[43]. Coudeville et al. 2012 suggests an 80% incidence reduction through cocooning compared to childhood vaccination only[44]. Terranella et al. 2013 compared pregnancy vs post-partum vaccination. Pregnancy vaccination was superior over post-partum vaccination, even when post-partum vaccination was combined with additional cocooning doses[45].

Key conclusions:	• "Cocoon" doses may be able to reduce severe infant morbidity but timing is crucial and overall impact and cost-effectiveness might vary over countries and settings. • Advantages of cocooning are better acceptability of vaccination in the post-partum period than during pregnancy, the accessibility to the whole family and the opportunity to educate. • Disadvantages are the slow response to produce immunity to protect the newborn and the logistic and economic issues. In addition, challenges to implement cocooning strategies include parental refusal, low political commitment, logistical issues and cultural issues. • The cost-effectiveness of cocooning is likely to be substantially lower than maternal immunization, as the latter requires only one dose whereas cocooning requires doses for both parents at minimum.

Vaccination of health care workers

In many countries, vaccination with aP-containing vaccines of health care workers (HCW) is recommended. This may include either all HCWs or special groups of HCWs for whom a more intensive

contact to pregnant women, newborns and infants is assumed, such as pediatricians or obstetricians. No evidence for the effect of vaccination of HCWs in protecting transmission to newborns and/or infants has been documented; however, many case reports and outbreak reports have demonstrated the role of HCW in the transmission of nosocomial pertussis. Transmission has also been documented from HCWs with documented dTap in the previous 3 years, so it is an only partially effective preventive measure.

In many countries, vaccination of HCWs is also recommended to fulfil legal requirements for minimizing potential exposure of patients to infectious agents. As it is unclear to what extent aP vaccines protect against infection, the relative role of vaccination and antibiotic prophylaxis in minimizing pertussis transmission should be revisited.

In countries where vaccination of adults, either universal or for special groups, is recommended, HCW should be of highest priority to be vaccinated. In countries where no adult program exists, the implementation of such program would be logistically difficult.[46]

Summary of strategies aimed at the prevention of early mortality and key conclusions

When applied with high coverage, there is evidence of impact for cocooning strategies (Australia and Chile), but the degree of effect will vary depending on the setting and coverage rates and will likely require a substantial number of vaccinations per child protected.

Although the previous wisdom held that immunization at birth was detrimental as it was associated with immune tolerance, this point of view has been challenged by more recent data for aP vaccines and by data from infant baboon challenge studies. However, neonatal immunization cannot be recommended yet due to limited data on immune response and safety, especially over the longer term, and lack of availability of an aP alone vaccine. If data supporting immunogenicity, presumptive protection and safety become available, neonatal immunization could have a role in consort with other strategies.

The UK experience indicates a high impact of vaccination of pregnant women against infant pertussis with an overall reduction in infant mortality. This impact is due to the direct protective effectiveness in the infant via the transfer of maternal antibodies and via impact on risk of transmission through protection of the mother.

Evidence on the effectiveness of 1 or 2 doses of pertussis vaccine against mortality highlights the importance of timely vaccination and of starting DPT vaccination at 6 weeks where infant mortality remains a problem in the very young. Where vaccination of adults with TdaP is implemented, priority should be given to vaccination of health care workers to further reduce the risk of mortality/severe pertussis in infants.

7. Review of pertussis surveillance, vaccine quality, immunogenicity and strain selection

Surveillance

Variation in country-specific pertussis incidence raises the issue of discrepancies likely related to differences in surveillance. The question was raised whether countries like China and India, where a steep decline in reported cases is seen since the 1980s following implementation of the Expanded Program on Immunization (EPI), have had a true decrease or if there has been a fall in reporting of cases following introduction of pertussis vaccines into routine immunization. This was noted as key issue for low income countries, where clinically manifest pertussis, rather than laboratory positives, accounted for all reported cases.

DPT3 coverage differs over WHO regions (AFR 72%, AMR 92%, EMR 82%, EUR 95%, SEAR 72% and WPR 95%). The number and proportion of laboratory-confirmed cases differs widely between WHO regions (0 countries in AFR, 23 in EUR). In total, 43 (22%) countries reported lab-confirmed cases. Data on a pertussis outbreak in a remote Indian area with total susceptibility suggests high incidence and mortality, leading to the conclusion that the overall impact of pertussis vaccination on morbidity and mortality in unimmunized communities with poor access to health care was likely underestimated.

Development of laboratory capacity for pertussis surveillance may be financially challenging for countries, yet it was considered as crucial by the Working Group to enhance pertussis surveillance. First priority should be to better capitalize on existing sentinel networks e.g. potentially use existing influenza disease surveillance networks for pertussis surveillance, given that both are primarily respiratory diseases and both use PCR as one diagnostic tool. Further suggestions to enhance surveillance were to include pertussis surveillance in the invasive bacterial disease sentinel site network or the pneumonia and meningitis laboratory network. If financially feasible, hospital sentinel site surveillance should be established, with the aim of establishing sentinel sites in every region.

The WHO laboratory manual written in 2004, and modified in 2007, has been updated by the working group in 2014. This laboratory manual describes in details the “state of the art” assays which are requested for a proper pertussis biological diagnosis, as recommended after consensus meetings.

The document includes direct diagnosis, such as culture or RT-PCR on nasopharyngeal aspirates or swabs sampled during the3 first weeks when the subject is coughing. Culture, the golden standard method, is important in order to follow the evolution of the pathogen but also its antibiotic sensitivity. RT-PCR is more sensitive and faster than culture (1-2 days vs. 7 days). Culture is the diagnosis of choice, using infant’s nasopharyngeal aspirates, in countries where reagents for RT-PCR cannot be obtained easily[47, 48]. Laboratories performing RT-PCR needs to perform EQA regularly.

The measurement of anti-*B. pertussis* antibodies using ELISA technique and purified pertussis toxin in the serum of a suspected case, coughing since more than3 weeks, is an indirect diagnosis useful, in particular for adults and adolescents coming late after the beginning of the cough[49,50].

Key conclusions:	• Despite the existence of various guidance documents and initiatives conducted in some regions and in particular in Europe and in the Americas, the current global surveillance and diagnostic capacity should be enhanced. • There is a need for improved epidemiological data. Surveillance of the disease in infants is crucial and an etiology should be sought on any infant that dies. • More solid laboratory data are needed. Laboratory methods should focus on enhanced specificity and cultures of the organisms should be retained so that the molecular characteristics can be assessed. Samples could be frozen to be sent for assessment in national or regional reference laboratories. • First priority should be to better capitalize on existing influenza sentinel networks which could be used for pertussis surveillance as both are primarily respiratory diseases and both use PCR as one diagnostic tool. Challenges include insufficient collaborations between virologists and bacteriologists and the nature of the samples collected by the various networks. • Hospital sentinel site surveillance may be an option with sentinel sites in every region. • Pertussis surveillance may be included in the invasive bacterial disease sentinel site network or the pneumonia and meningitis lab network.

Vaccine quality control and immunogenicity

An update on the formulation of whole cell pertussis vaccines and the antigens in acellular vaccines was provided. The whole cell pertussis vaccine is composed of formalin-inactivated whole cell *B. pertussis*. For the acellular pertussis vaccine, many types of antigens are used including pertussis toxoid (PT/PTxd) , filamentous hemagglutinin (FHA), fimbrial proteins, type 2 and 3 (Fim2, Fim3, Fim2-Fim3) and pertactin (PRN).From the experiences of vaccines registered in Thailand, the amount of bacterial content of whole cell pertussis component vaccines varied from 12 to 16 international units (IUI) per dose and there are 3 types of aP component vaccines with different components including 2 components (PT and FHA), 3 components (PT, FHA and PRN), and 5 components (PT, FHA, PRN, Fim2 and Fim3). The amount of each component varies from one vaccine to another, for example, one dose of 3 component-DTaP vaccine contains 25 µg of PT, 25 µg of FHA and 8µg of PRN whereas TdaP contains 8 µg of PT, 8 µg of FHA and 2.5µg of PRN. Moreover, one dose of 5 component-DTaP vaccine contains 20 µg of PT, 20 µg of FHA, 3µg of PRN, and 5 µg of Fim 2 & 3 and for TdaP are 2.5 µg of PT, 5 µg of FHA, 3µg of PRN, and 5 µg of Fim 2 & 3.

Quality control according to WHO recommendations includes a long list of control items such as identity, sterility, specific toxicity, innocuity test, adjuvant, and potency, among others, and final containers are inspected. The residual pertussis toxin activities, especially Histamine Sensitizing Factor (HSF), is determined[51, 52]

To estimate the potency of wP vaccines, the Kendrick test is used by vaccinating mice, and directly challenging the animals 14 days after with *B. pertussis.* ED50 of the vaccine sample is compared with

that of standard vaccine at day 28 and the potency is calculated in international units. According to WHO recommendations, the potency of wP should not be less than 4.0 IU/dose[52]

Two potency tests are used to evaluate aP vaccine. Most manufacturers use immunogenicity tests in mice (MIT) or Guinea-pigs to evaluate antibody responses, and the potency is justified by relative comparison between the immune response of the groups immunized by the vaccine sample to those of the group immunized by reference vaccine. Modified Intracerebral Mouse Protection Assay (MICA) is used by some manufacturers and the potency can be calculated in IU/dose[51]. P immunogenicity in clinical trials is tested using ELISA or agglutination test. The method to estimate aP immunogenicity in clinical trials is ELISA with cut-off values varying according to kit[53].

Several constraints were highlighted when comparing vaccine efficacy evaluations and immunogenicity evaluations. It was noted that different case definitions may lead to different outcome of efficacy evaluations. It is also hard to evaluate protective efficacy as there is low incidence rate of pertussis and it is not possible to compare the efficacy of aP to wP by using the immunogenicity evaluation because there is no standard methodology for determination of antibody titers. Protective antibody levels have not been defined and no immune response correlated with vaccine protective efficacy is defined.

WHO has developed a standard reagent for pertussis antiserum. Nevertheless there are still issues with standardization despite international standards. New vaccines are licensed on comparative immunogenicity levels and it is stressed that companies need to measure serological bridging. Good surveillance systems are necessary to evaluate efficacy, and at a later stage, effectiveness of the vaccine. Different regulatory systems in different countries complicate the situation.

Key conclusions:	• To date, there is not an adequate test correlate for vaccine effectiveness and duration of protection. Tests used for vaccine control only monitor consistency of production. As a result, in the systematic review of the various schedules, immunogenicity data may be of more limited value.

Variation of bacterial strains according to vaccination strategies: consequences for strain selection

Various methods for characterizing bacterial isolates can be used, generating different data sets very much depending on the primary question to be studied.

On a phenotypic level, these can be morphology (i.e., Gram stain), biochemical activity, and proteome analysis by MALDI-TOF, antibiotic sensitivity profiles, serotyping (i.e., fimbrial typing) or production of virulence factors measuring activity of these factors or using specific polyclonal antisera.

On the genomic level, methods can be distinguished whether they target the whole genome or limited parts of it. Genome-sequencing, SNP analysis or PFGE (Pulsed-field gel electrophoresis) are methods targeting the whole genome. It is also possible to target it by microarrays, whereas multi-locus sequence typing (MLST), PCR-based fingerprinting, and Multiple-Locus variable number tandem repeat analysis (MLVA) only study limited portions of the genome. The advantages and disadvantages of these methods may be summarized as follows (adapted from Huber et al. [54]). Genome sequencing produces accurate

and reproducible data with high discriminatory power, although bioinformatics expertise is needed. Phylogenetic relationship can be studied by SNP analysis, and these methods are cost-and labor-intensive. Microarrays can analyze the genomic content and also the gene expression; they can detect phylogenetic relationships, but are quite costly. PFGE has a high discriminatory power and it is cheap, but it is laborious and results are not readily comparable between laboratories. MLST produces stable and transferable data at high costs. PCR-based fingerprinting has limited discriminatory power. As an alternative, MLVA has rather high resolution power, it can detect phylogenetic relationships, but it is cost- and labor-intensive. Generally, it is important to realize that the genome of all bacteria adapts over time, whereby bacteria can acquire or lose genomic material, and can activate or inactivate genes. *B. pertussis* seems to be among the most monomorphic human pathogens. Phylogenetic analysis suggests that *B. pertussis* is a rather recently evolved human pathogen. Mainly due to its repetitive elements, the overall genomic structure of *B. pertussis* is rather fluid.

Concerning *B. pertussis* isolates, it is important to bear in mind that in most countries no standardized method of collection of isolates has been established. Thus, continuous data about isolate variability are available mainly from Europe, the US, Argentina, Australia, Russia (St Petersburg region) and Japan, whereas limited data can be obtained from other WHO regions. Furthermore, there may be a limited or skewed regional distribution of collected isolates in some countries. Available isolates often stem from young infants, although they are probably representative of circulating isolates. From children, adolescents and adults, isolates are collected more or less by chance.

On a phenotypic level, resistance to macrolides in *B. pertussis* so far is relatively rare but recent publications may indicate differences between countries (i.e. China) [55-58]. Macrolide resistance seems to depend on1 mutation until now, and these isolates have been circulating for at least 25 years[59]. Fimbrial typing can distinguish between types Fim 2 and/or Fim 3, and fimbrial subtypes, and for many years, a large variation in production and circulation of fimbrial types has been observed. However, no consensus exists about the role of fimbrial variation in regard to the vaccination coverage or the type of vaccine used[60] .

Concerning the production of other virulence factors, isolates have been collected that are deficient in vaccine antigens. So far, PT-negative and FHA-negative isolates rarely occur. PRN-negative isolates rarely occurred until 2007, but since then have been increasing in several countries[61-66] and making up a substantial proportion of all isolates. Concerning non-vaccine antigens, AC-Hly-negative isolates occur extremely rarely, if ever, and the structure of the LPS has not changed over time[67]. The prevalence of PRN-negative isolates varies according to region. In France, the prevalence reached 14% in 2012 and was still 14% in 2013, whereas it reached more than 60% in some North American countries using aP vaccines. However, none have been reported in the Saint Petersburg region (Russia) where aP vaccine is not used[68]. A preliminary study indicated that these isolates were as virulent in infants less than 6 months old and as transmissible as PRN-negative isolates[69].

It can be suggested that every epidemic cycle is characterized by the emergence of a change in the isolates. For example, during the 1996-1997 cycles, isolates producing prn 3 emerged and then disappeared[70, 71], and during the 2011-2012 cycle, PRN-negative isolates could increasingly be found[61]

but the increase of their prevalence seemed to have reached a maximum. "Directly linking epidemiology and strain typing is tempting but may lead to inaccurate conclusions with unwanted side-effects" [72], but the surveillance of the prevalence of these PRN-negative isolates needs to be pursued in different regions, which underlines the importance to continue culture as biological diagnosis and not rely only on the use of real time PCR. This surveillance is important since the circulation of such isolates can affect the duration of vaccine induced immunity. During the period of wP vaccines use in North America or Western Europe, change of the bacterial population was also observed, but vaccine effectiveness and duration of wP vaccine induced immunity remained unchanged [73].

Key conclusions:	○ Data indicate that *B. pertussis* strains have evolved over time, with isolates differing in the pre- and post-vaccination era. Yet the evolution of the strains observed does not always correlate with changes in vaccine programme or epidemiology. ○ Nevertheless it remains important to continue collecting and analyzing isolates from many countries in order to follow future evolution of *B. pertussis* and to pursue the determination of aP-induced vaccine immunity. ○ There is no evidence to date for diminished effectiveness of vaccines against different allelic variants. In countries with a recently observed increase in cases, targeted vaccination intervention strategies were effective in providing additional evidence that the observed increase was not related to diminished effectiveness against currently circulating strains. ○ There is no evidence of emergence of *B. parapertussis* in aP or wP using countries.

8. Proposed recommendations

The main aim of pertussis vaccination is to reduce the risk of severe pertussis in infants. All children worldwide should be immunized against pertussis, and every country should seek to achieve early and timely vaccination (initiated no later than at 8 weeks of age) and maintain high levels of coverage (≥90%) with at least 3 doses of assured quality pertussis vaccine in infants. Evidence suggests that high coverage with highly efficacious vaccines leads to high levels of protection in children in the <5 year age group. In contrast, even minor reductions in overall coverage can lead to an increase in cases.

Consequently, all countries should consider starting their primary vaccination schedule as early as possible, ≥6 weeks of age. There is substantial and consistent evidence both from observational and analytical studies from a number of countries using aP and wP to show that a single dose of pertussis vaccine in infancy has significant effectiveness (around 50%) in preventing severe disease and that 2 doses of pertussis vaccination offers high protection (80% or more).

Choice of vaccines

Pertussis vaccination is highly effective in reducing disease from *B. pertussis*, with a drastic decline in overall global incidence and mortality seen compared with the pre-vaccination era. Protection against severe or fatal pertussis in infancy and early childhood can be obtained after a primary series of vaccination with either wP or aP vaccine.

Comparing the characteristics of aP and wP vaccines indicates that licensed aP vaccines have lower initial efficacy, faster waning of immunity, and possibly a reduced impact on transmission relative to currently internationally available wP vaccines. This is likely ascribed to the fact that aP vaccines induce a different type of immune response (higher Th2-promoting antibody responses but lower Th1 and Th17 responses), which is less effective at clearing mucosal infections.

When considering a switch from wP to aP vaccines, countries need to consider the overall goal of their immunization program; disease-related mortality in the first year of life can be significantly reduced using a primary series of either wP or aP vaccination, whereas the protection of older children or adult requires repeat boosting with the less reactogenic acellular vaccines.

Countries where only a limited number of pertussis doses are used / affordable should use wP vaccines for primary pertussis early infant vaccination. Surveillance and modeling data suggests that the use of aP vaccines will result in a resurgence of pertussis after a number of years and this resurgence might also lead to an increased risk of death in those too young to be vaccinated. The magnitude and delay for this resurgence to occur are difficult to predict considering the many factors that intervene such as vaccine coverage, natural immunity, vaccine type, schedules, and so on. Thus, the use of aP vaccines should only be considered if large numbers of doses (including several boosters) may be included in the national immunization schedules, which has huge implications in terms of costs given the much higher cost of aP vaccines and higher number of doses required.

Supplemental strategies to reduce infant mortality

Vaccination of pregnant women and household contacts

Vaccination of pregnant women is likely to be the most cost-effective complementary strategy and appears to be more effective and favorable than cocooning and neonatal immunization. The working group recommends considering the immunization of pregnant women with TdaP (1 dose in the 2nd or 3rd trimester at least1 week prior to delivery) as an effective complementary strategy to routine primary infant pertussis vaccination in countries or settings with high infant mortality from pertussis. This will require surveillance studies assessing early infant disease burden in various country settings, as death from pertussis may easily be overlooked. The continued value of this strategy will need to be assessed in women that were primed with aP vaccines, as data from Germany suggests lower immune responses to Tdap in aP primed adolescents.

Boosters of pertussis vaccine in adolescents and adults

No evidence could be observed of an impact of a booster dose in adolescence or adulthood on infant disease, hence an adolescent booster is not generally recommended to control infant disease (although it has been shown to decrease disease in adolescents). If countries wish to introduce a an adolescent and/or adult boosters they should have carefully assessed local epidemiology, tried to estimate the contribution of adolescents as source of infections of young infants or selected adolescents and/or adults as a target groups for protection.

Vaccination of Health Care Workers

When a country has implemented a pertussis adult immunization programme, HCWs should be prioritized as a group to receive pertussis vaccine. There is some evidence of transmission in hospital settings, but no evidence yet on the effectiveness of vaccinating HCWs as a strategy to prevent the acquisition and transmission of pertussis. Nevertheless, vaccinating health-care workers may be used as a strategy to prevent nosocomial transmission to infants within health care settings if high coverage rates can be obtained. Selected groups with direct contact with pregnant mothers and infant patients, such as staff working in maternities or involved in neonatal and infant care, may be considered as priority groups for pertussis immunization. This recommendation will need to be revisited in the future to assess the impact in those primed with aP only.

Surveillance

Careful epidemiological surveillance of pertussis, particularly laboratory-confirmed disease, is to be encouraged worldwide to monitor the disease burden and the impact of immunization. Of particular interest are surveys comparing age-specific incidences of pertussis in countries with different policies on vaccine booster doses. In case of limited capacity or resources, the monitoring of pertussis incidence should focus on infants <1 year of age, possibly through hospital-based surveillance and with an evaluation of all deaths. Outbreak studies may also offer valuable information and should be encouraged.

More solid laboratory data are needed. Laboratory methods should focus on enhanced specificity, and cultures of the organisms should be retained so that there molecular characteristics can be assessed. Samples may be frozen to be sent for assessment in national or regional reference laboratories.

Research questions

The working group recommends the comparison of age-specific incidence rates of pertussis in countries with different policies on booster doses. There would be interest in applying the country data to the models in order to (a) validate the models and (b) evaluate strategies and understand the impact of specific programs.

The specific questions that could be explored with the models are:

1) What are the circumstances under which a resurgence should be expected?

2) What is the impact of different potential boosting strategies to avoid resurgence?

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10. Annex

Annex 1: Lexicon

DTaP - Tetanus, diphtheria, acellular pertussis vaccine (childhood formulation)

- Infanrix® - GlaxoSmithKline (3 component)
- Ditekik® - Staten Serum Insitut of Denmark (1 component)

TdaP - Tetanus, diphtheria, acellular pertussis vaccine (adolescent/adult formulation)

- Adacel® - Sanofi Pasteur (5 component)
- Boostrix® - GlaxoSmithKline (3 component)

DTaP-IPV – diphtheria, tetanus, acellular pertussis, inactivated polio vaccine

- Tetravac® - Sanofi Pasteur (2 component)

TdaP-IPV - tetanus, diphtheria, acellular pertussis, inactivated polio vaccine (adolescent/adult formulation)

- Adacel-Polio® - Sanofi Pasteur (5 component)
- Boostrix-IPV® - GlaxoSmithKline (3 component)

DTaP-IPV-Hib - diphtheria, tetanus, acellular pertussis, inactivated polio, *H. influenza* type B vaccine

- Pediacel® - Sanofi Pasteur (5 component)
- Pentavac® - Sanofi Pasteur (2 component)
- Pentaxim® - Sanofi Pasteur (2 component)
- Infanrix®-IPV/Hib – GlaxoSmithKline (3 component)

DTaP-IPV-HebB - diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B vaccine

- Pediarix® - GlaxoSmithKline (3 component)

DTaP-IPV-Hib-HepB - diphtheria, tetanus, acellular pertussis, inactivated polio, *H. influenza* type B, hepatitis B vaccine

- Infanrix hexa® - GlaxoSmithKline (3 component)

Systematic Review of the Non-specific Immunological Effects of Selected Routine Childhood Immunizations

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Abbreviations

BCG	Bacillus Calmette–Guérin
CD	cluster of differentiation
CI	Confidence interval
CSF	Colony-stimulating factor
CVL	Central Veterinary Laboratory
DTP	diptheria-tetanus-pertussis
EGF	Epidermal growth factor
E-Z	Edmonston Zagreb
FGF	fibroblast growth factor
Flt-3L	Flt3-ligand
GM	geometric mean
GMR	geometric mean ratio
GRO	GRO protein (cytokine)
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IPP	isopentenyl pyrophosphate
IQR	Inter-quartile range
LPS	Lipopolysaccharides
MCP	Monocyte chemoattractant protein
MDC	Monocyte depleted mononuclear cells
MFI	Mean fluorescence index
MIP	Macrophage inflammatory protein
MMR	Measles mumps and rubella
NSIE	Non-specific immunological effects
PBMC	Peripheral blood mononucleated cell
PDGF	Platelet-derived growth factor
pg	Picograms
PHA	Phytohaemagglutinin
PMA	phorbol myristate acetate
PPD	Purified protein derivitive
RCT	Randomized controlled trial
RPMI	Roswell Park Memorial Institute medium
SAGE	Strategic advisory group of experts
SEB	Staphylococcal enterotoxin B
SK/SD	Streptokinase/Streptodornase
SSI	Staten Serum Institut
TLR	Toll-like receptors
TNF	Tumor necrosis factor
TT	Tetanus toxoid
UCL	University College London
UK	United Kingdom
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

Executive Summary

There is clear scientific evidence that exposure to infectious agents and vaccines results in non-specific inflammatory and innate immunological responses that subsequently direct "acquired" specific immunity through T cells and antibody, that recognise antigenic epitopes on the organism or vaccine. This concept underpins modern immunology and vaccinology. Agents, including infectious diseases, which modify these early non-specific signals might have important effects on the response that develop to a subsequent heterogenous stimulus. Despite widespread acceptance amongst immunologists that such non-specific immunological effects occur, there are no systematic studies which have summarised the literature in humans to provide a framework for understanding the circumstances under which such effects can be documented, when such responses occur, or for how long they are present or, most importantly, their biological significance.

In this review, conducted at the request of WHO, we have systematically searched the scientific literature to identify available data concerning non-specific effects which might be measured after immunisation with the main vaccine antigens that are including in the expanded programme of immunisation for children, namely, BCG, measles, diphtheria, tetanus and pertussis.

The review demonstrates that there are a substantial number of studies which contain data of relevance to the assessment, but the vast majority were not conducted to investigate this phenomenon, though they did report data which could be extracted. There were few studies with similar methodology or endpoints which could be formally meta-analysed and therefore data are presented in summary figures and tables for each vaccine. The reviewed studies were highly heterogeneous and the risk of bias was high or unclear in the majority. While some significant findings were present, the lack of replication of the findings and the low quality of the majority of studies, indicates that such findings should be interpreted with caution.

While these findings do not exclude the possibility of important non-specific immunological effects of vaccines, the published literature dose not provide confidence in the presence, quality, quantity, kinetics or impact of any non-specific immunological effects in young children after vaccination. It is, therefore, not currently possible to provide any guidance from the human data on expected effects or when/how to measure them.

Future studies using systems biology to capture the functional genomic, genetic, epigenetic and immunological effects of vaccines, might be applied to explore this biological phenomenon and to provide data on the timing, duration, quality and magnitude of such effects and to identify signals which might be used in large scale studies with relevant epidemiological endpoints.

Background

A growing number of published reports have suggested that several vaccines routinely administered to infants around the world may have "heterologous" or "non-specific" effects on mortality unrelated to prevention of illness and deaths caused by the specific diseases against which the vaccines have been formulated. For example, studies have suggested that receipt of both the Bacillus Calmette–Guérin (BCG) and measles vaccine are associated with a reduced risk of death (i.e. all cause mortality), while receipt of diphtheria-tetanus-pertussis (DTP) vaccine is associated with an increased risk of death, at least among female infants.[1,2] The vast majority of the studies demonstrating these effects have been observational in nature, rather than randomised controlled trials with non-specific effects as the primary outcome, and as a result, poorly-controlled or uncontrolled confounding and various types of selection and information bias have been suggested as alternative explanations for these findings.[3,4]

The biological plausibility of one or more vaccines having heterologous effects, either detrimental or beneficial, is supported by a number of studies in animals (for example mice) and observations in humans.[5-8] Nevertheless, the biological mechanisms and immune pathways that would underlie and explain such effects remain largely unspecified and open to question. At the same time, the possible implications of any such heterologous vaccine effects for the formulation or re-formulation of the infant immunization schedule remain unclear, but it has been suggested that if such effects can be established beyond a reasonable doubt, the infant immunization schedule might need to be re-configured.[9] However, prior reviews of this subject, including periodic assessments by the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety, have concluded that any such effects remain unproven and are therefore not a justification for altering the current schedule.[10]

The WHO Strategic Advisory Group of Experts (SAGE) has requested the WHO Secretariat to review the evidence surrounding the possible non-specific/heterologous effects of vaccines included in the routine infant immunization schedule.[9] Overall, our aim is to determine whether the current evidence is sufficiently sound to warrant further scientific investigation; and if so, to define the path towards obtaining unequivocal evidence on these issues that would support future robust, evidence-based adjustments in immunization policies, if warranted. Preparatory to such a review of the evidence by SAGE at its April, 2013 meeting, it is necessary to assemble the available evidence, both published and unpublished, and subject that evidence to a systematic review.

Thus the objective of this review is to systematically identify, assemble, review and critically appraise all available studies with immunological endpoints describing the possible non-specific or heterologous effects of BCG, diphtheria, pertussis, tetanus and measles containing vaccines.

Methods

Definitions

Specific immunological effects:- The effect on an immunological parameter in response to an antigen derived from the vaccines target pathogen.

Non-specific immunological effects: - The effect on an immunological parameter that is not in response to an antigen derived from the vaccines target pathogen.

General Approach

All available evidence (published and unpublished) that addressed possible non-specific effects of vaccines when given was identified and critically appraised, with a focus on the effects of vaccines on the child's immune system and the development of the immune system. Included in the review are randomized controlled trials (RCTs), quasi-randomized control trials, clinical trials, cohort studies, case-control studies, case series and case reports. The vaccines examined included live attenuated vaccines (BCG and measles containing vaccines), inactivated vaccines and toxoids (all diphtheria and tetanus toxoids, and *Bordetella pertussis* containing vaccines). The target population was infants under five years of age, however inclusion of studies was not limited to this age group. Gender, age at vaccination, and co-administration of vitamin A were examined as possible effect measure modifiers.

Search Strategy

Embase.com, which includes all records from MEDLINE, was searched from 1947 onwards, through to December 2012. Complementary, less extensive searches of the PubMed library, the Cochrane library, and the trip database, were performed in order to detect any articles missed by the search on Embase.com. A list of search entries used is displayed in Appendix A. In addition, the reference lists of all included articles found and all relevant review articles were manually searched to identify studies not included in the previously described search. Experts in the field were asked if they are aware of any unpublished reports of studies possibly meeting the inclusion criteria. Full text of all articles identified were sought, using internet downloads, interlibrary loans, and contacting of authors. Articles in any language were sought. A further limited search from December 2012 to January 2014 was performed in the PubMed library using the same search terms to provide an update. Experts in the field were also asked to review the initial search results and identify any further studies that should also be included. Fourteen additional papers were identified that had been missed in the search.

Selection of Eligible Studies

Each full text article was examined by two independent reviewers and a list of studies considered eligible for inclusion was made. Studies identified by both reviewers as being eligible for inclusion and having adequate data for extraction were included in the review. For studies where non-specific immunological data were generated but not reported, a request for provision of the data was sent to the authors. Where there were discrepancies, the reasons for these were discussed and a decision about inclusion was reached by consensus. If there was no agreement, a further independent reviewer adjudicated to make a final decision about eligibility.

Exclusion criteria

Ecological, animal and *in vitro* studies were excluded. Studies utilising recombinant vaccines or no vaccine at all were excluded. Those studies only reporting/generating study vaccine specific immunological endpoints were excluded.

Data Extraction

Acquisition of consistent data from studies, such as participants, methodology, potential confounders and background data was performed by the utilisation of specifically created data extraction forms using DistillerSR software. All relevant data were extracted from articles meeting inclusion criteria and entered into a database.

Data Analysis

Descriptive tables summarizing information about study design, study quality, and results of all included studies were generated. Data on non-specific immunological effects were extracted from papers which reported summary statistics in tabular form. Where results were presented in figures, data were extracted wherever possible using GetData Graph Digitizer version 2.26.0.20. Due to the heterogeneity of the study methodology, data presented and analysed using non-parametric statistics and substantial differences in reporting of outcomes it was not possible to meta-analyse any outcomes from different studies. Where at least two papers reported results from the same assay, descriptive figures demonstrating non-specific immunological outcomes were generated, with comparable assays clustered according to vaccine type.

Description of included studies

Completion of the search process resulted in a total of 77 studies meeting the eligibility criteria for the review (Figure 1). The composition of the studies is summarily described in Table 1 and extensively described in Appendix B. Relatively equal proportions of RCTs, cohort and case-controls studies were identified. There was a wide range (3-2345) of total study participants involved across the studies. The majority of studies (48%) utilised BCG as the study vaccine intervention, whilst 68% were exclusively conducted in a paediatric population. The final time-point of outcome measurement was primarily performed (70%) between one and 12 months after vaccination.

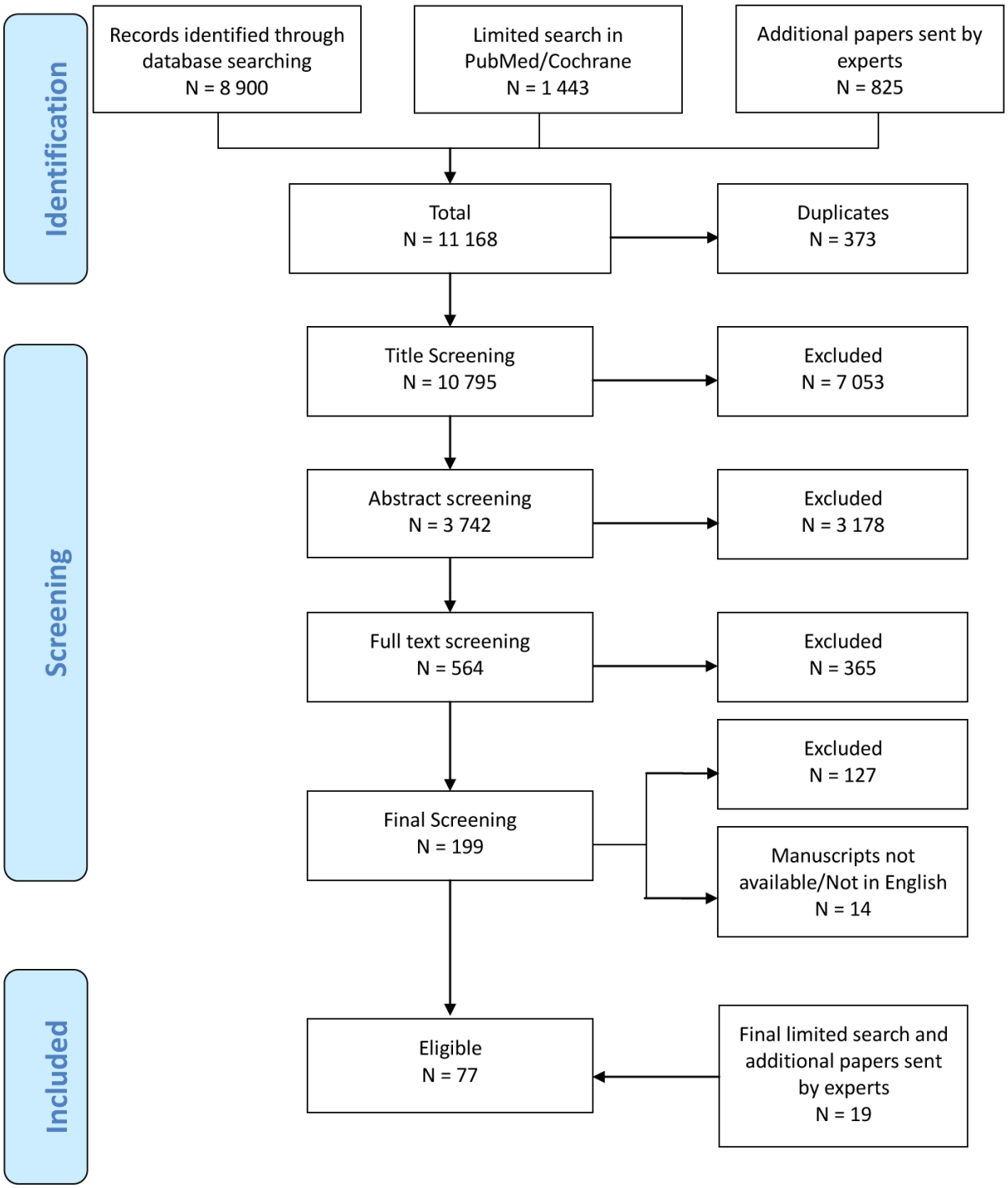


Figure 1. Overview of identification process for eligible studies.

Table 1. Summary description of included studies

	N
Study vaccine	
BCG	37
Measles	14
MMR	3
DTP	7
Pertussis	1
DT	4
TT	11
Other Vaccine/s used in study?	
Yes	24
No	31
Not described or not applicable	22
Age	
Neonate	15
Infant	18
Children	14
Adults	19
Elderly	0
Combination	11
Gender of study population	
Male and Female	39
Male	2
Female	1
Not reported	35
Geographic location	
Africa	19
Europe	22
Asia	8
Americas	20
Oceania	4
Combination	4
Co-administration with Vitamin A?	
Yes	3
No/Not reported	74
Presence of attribute that may affect response?	
Yes	22
No	55
Interval between vaccine administration and final outcome measure	
< 1 month	11
1 - < 6 months	29
6 - ≤12 months	25
>12months	10
Not reported	2
Number of participants	
Mean	206
Median	77
Range	3-2345

Study design	
RCT	25
Prospective Cohort	23
Prospective Case-control	23
Other	6

Methodological attributes of included studies

Included studies[5,11-87] had their methodological attributes analysed and tabulated according to the study vaccine used (Appendix C). No one study was rated as having low risk of bias for all criteria (Table 2). This is likely to be in part due to the heterogeneous spread of study designs. In addition the outcome of non-specific immunological effects does not feature as a primary outcome parameter in any of the RCTs. Only 55% of the included studies actually reported data in a usable format for this review (Table 3). A diverse array of immunological assays were utilised to report non-specific effects in the included studies, which taken in conjunction with the differences in measurement parameters and statistical analysis creates a high number of possible combinations in outcome reporting. For this reason no meta analysis of the data was possible. Data from the included papers were not presented in such a form (that is data sets were not sub-classified according to sex) that the affect of sex on non-specific immunological effects could be analysed. Overall review of the methodological attributes demonstrates a consistently low level of evidence and exemplifies the lack of any high quality (low risk of bias) randomised controlled trial with focussed primary endpoints designed around non-specific immunological outcomes.

Table 2. Risk of Bias Summary of Included Studies

Study Author	Vaccine	Random sequence generation	Allocation concealment	Blinding, All outcomes	Incomplete outcome data, All outcomes	Selective reporting	Other bias	Overall
Akkoc et al. 2010	BCG	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk		Unclear
Anderson et al. 2013	BCG	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High
Black et al. 2001	BCG	Low risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk	High
Black et al. 2002	BCG	Low risk	Low risk	Low risk	Low risk	Unclear risk		Unclear
Burl et al. 2010	BCG	Low risk	Low risk	Unclear risk	Low risk	Low risk		Unclear
Burl et al. (Aug.)	BCG	Low risk	Low risk	Unclear risk	Low risk	Unclear risk		Unclear
Djuardi et al. 2010	BCG	High risk	High risk	Unclear risk	Unclear risk	Unclear risk		High
Elliot et al. 2011	BCG	High risk	High risk	Unclear risk	High risk	Low risk	High risk	High
Faustman et al. 2012	BCG	Low risk	Low risk	Low risk	Low risk	Unclear risk		Unclear
Fjallbrant et al. 2007	BCG	Unclear risk	High risk	High risk	Low risk	Unclear risk		High
Gruber et al. 2000	BCG	Unclear risk	High risk	Unclear risk	High risk	Low risk		High
Hoft et al. 1998	BCG	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk		Unclear
Hoft et al. 1999	BCG	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk		Unclear
Hussey et al. 2002	BCG	High risk	High risk	Unclear risk	Unclear risk	Unclear risk		High
Kagina et al. 2009)	BCG	Low risk	Low risk	Unclear risk	Low risk	Unclear risk		Unclear
Kleinnijenhuis et al. 2012	BCG	High risk	High risk	Unclear risk	Low risk	Low risk		High
Lalor et al. 2009	BCG	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk	High
Lalor et al. 2010	BCG	High risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	High
Lalor et al. 2011	BCG	High risk	High risk	Unclear risk	Unclear risk	Low risk	High risk	High
Libraty et al. 2014	BCG	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk		Unclear
Lowry et al. 1998	BCG	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk	High
Marchant et al. 1999	BCG	Low risk	Low risk	Unclear risk	High risk	Unclear risk		High
Marks et al. 2003	BCG	High risk	High risk	High risk	Unclear risk	Low risk		High
Miles et al. 2008	BCG	High risk	Unclear risk	Unclear risk	High risk	High risk	High risk	High
Miles et al. 2009	BCG	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk	High
Ota et al. 2002	BCG	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk		Unclear
Smith et al. 2012	BCG	High risk	Unclear risk	Unclear risk	Low risk	Low risk		High
Soares et al. 2013	BCG	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk		Unclear
Steenhuis et al. 2007	BCG	High risk	Unclear risk	Low risk	Low risk	Unclear risk	High risk	High
Tastan et al. 2005	BCG	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear
van den Biggelaar et al. 2009	BCG	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk		Unclear
Vargas et al. 2004	BCG	Low risk	Unclear risk	Unclear risk	Low risk	Low risk		Unclear
Vekemans et al. 2004	BCG	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk		Unclear
Vijaya Lakshmi V. et al. 2005	BCG	High risk	High risk	High risk	Unclear risk	Unclear risk	High risk	High
Weir et al. 2004	BCG	Low risk	Low risk	Low risk	Low risk	Unclear risk		Unclear
Weir et al. 2008	BCG	Low risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk	High
Weir et al. 2008	BCG	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear
Armitage et al. 1993	TT	High risk	High risk	High risk	Unclear risk	Unclear risk		High
Boruti et al. 1980	TT	High risk	High risk	High risk	Unclear risk	Unclear risk		High
Chollet et al. 1979	TT	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk	High
Chui et al. 2004	TT	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk	High
Cooper et al. 1998	TT	High risk	High risk	Unclear risk	Unclear risk	Unclear risk		High
Di Genova et al. 2006	TT	High risk	High risk	Unclear risk	Unclear risk	High risk		High
Fernandez et al. 1994	TT	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk	High
Fevrier et al. 1977	TT	High risk	High risk	Unclear risk	Unclear risk	High risk	High risk	High
Gentile et al. 2006	TT	High risk	High risk	Unclear risk	Low risk	Unclear risk	Unclear risk	High
Livingston et al. 2013	TT	High risk	High risk	Unclear risk	Low risk	Unclear risk		High
Mahalingham et al. 2010	TT	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk		Unclear
Bertley et al. 2004	Measles	Unclear risk	Unclear risk	Unclear risk	High risk	High risk		High
Gans et al. 1999	Measles	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear
Gans et al. 2004	Measles	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk		High
Hennino et al. 2007	Measles	Low risk	Low risk	Low risk	High risk	Unclear risk	High risk	High
Hussey et al. 1996	Measles	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk	High
Jaye et al. 2014	Measles	High risk	Unclear risk	Unclear risk	High risk	Unclear risk		High
Liguori et al. 1998	Measles	Unclear risk	Unclear risk	Unclear risk	High risk	Low risk	High risk	High
Lisse et al. 1994	Measles	Unclear risk	Unclear risk	Unclear risk	High risk	Low risk		High
Nakayama et al. 1990	MMR	Unclear risk	Unclear risk	Unclear risk	Low risk	High risk	Unclear risk	High
Njie-Jobe et al. 2012	Measles	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear
Okada et al. 2001	Measles	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	High risk	High
Ovsyannikova et al. 2003	Measles	Low risk	Unclear risk	Unclear risk	High risk	High risk	High risk	High
Pabst et al. 1997	MMR	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk		Unclear
Pabst et al. 1999	Measles	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	High risk	Unclear
Rager-Zisman et al. 2003	MMR	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear
Samb et al. 1995	Measles	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk		Unclear
Schnorr et al. 2001	Measles	Unclear risk	High risk	Unclear risk	Unclear risk	High risk		High
Dirix et al. 2009	DTP/DT	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High
Fernandes et al. 2010	DTP/DT	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear
Fryauff et al. 1998	DTP/DT	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk	High
Halasa et al. 2008	DTP/DT	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear
He et al. 1998	DTP/DT	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	High risk	High
Heine et al. 2011	DTP/DT	High risk	Unclear risk	Low risk	Unclear risk	High risk	High risk	High
Jorgensen et al. 2013	DTP/DT	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear
Lin et al. 1997	DTP/DT	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk		High
Rowe et al. 2000	DTP/DT	Unclear risk	Unclear risk	Unclear risk	Low risk	High risk	Unclear risk	High
Yousfi et al. 2005	DTP/DT	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear
Zorzeto et al. 2009	DTP/DT	Low risk	Unclear risk	Low risk	Unclear risk	High risk		High
Di Tommaso et al. 1997	Pertussis	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear

Table 3. Immunological assays and the combination of reporting parameters used within the included studies

	Vaccine				
Counts	**BCG**	**TT**	**Measles**	**MMR**	**DTP**
N. Studies reporting data in usable format or supplying raw data	20	10	8	3	1
N. Immunological parameters (Cytokines/Chemokines)	88	21	23	10	1
N. Stimulants	20	14	6	5	7
Cytokine/Stimulant combinations	**167**	**36**	**35**	**13**	**7**
N. different units (pg/mL, SI, %, mm2, cpm)	16	11	9	3	1
N. different statistics report (Geometric mean, raw mean, median, % etc)	17	8	7	3	1
N. Total number of combinations of the above	**223**	**37**	**33**	**13**	**7**

Data from included studies

BCG

Overall 37 studies were found which measured non-specific immunological effects of BCG vaccination. In 11 of these papers the results of assays conducted were not reported as they were not the main focus of the paper. Of the included studies, 24 included children under the age of 5 years.

There were 20 papers reporting non-specific immunological effects with data reported in tables or a graphical format which could be extracted using a digitizer program, and one study which supplied raw data (Lalor *et al*). These papers reported 89 different immunological parameters the main ones being CD4, CD8, EGF, Eosinophils, Eotaxin, FGF-2, Flt-2L, Fractalkine, (FoxP3)+ regulatory CD4+ T cells, G-CSF, GM-CSF, GRO, γδ T cells, IFNα2, IFN-γ+/TNF-α+ CD4+ T cells, IFN-γ, IgE, IL-10, IL-12p40, IL-12p70, IL-13 IL-15, IL-17, IL-1α, IL1-β, IL-1Rα IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IP-10, Leukocytes, MCP-1, MCP-3, MDC, MFI TLR4, MIP-1α, MIP-1β, PDGF-AA, PDGF-AB/BB, Proliferation (delta cpm), Proliferation (Stimulation Index) , RANTES, sCD40L, sIL-2Ra, TGF-α, TNF-α, TNF-β, Total lymphocytes , VEGF, MFI CD11b, CD11b in CD14, CXCR1 in CD14, TLR4 in CD14, MFI CD14, MFI CXCR1, MFI dectin-1, TLR2 in CD14, MFI TLR2, MR in CD14 and MFI MR.

There were 20 types of stimulants used in the above assays (*C. albicans*, ConA, Diphtheria toxin, *E. coli*, House dust mite, HBsAg, IPP plus IL-2, LPS, *M. avium* PPD (CVL), *M. avium* PPD (SSI), *M. intracellulare* PPD (SSI), *M. intracellulare* PPD-B, *M. leprae*, *M. scrofulaceum* PPD (SSI), PHA, *S. aureus*, SK/SD, Tetanus toxoid and unstimulated assays) resulting in 167 unique combinations of the above. Immunological responses to PHA stimulated and unstimulated cultures were most frequently reported.

There were 6 papers from which data could not be extracted;

- Black *et al* 2001 report IFN-γ responses to control antigens (*M. avium* (SSI), *M. avium* (CVL), *M. intracellulare* (PPD–B), *M. intracellulare* (SSI), *M. scrofulaceum* (SSI), M. *marinum*, *M. kansasii* (SSI)), *M. kansasii* (UCL), *M. fortuitum*, and *M. vaccae*.) in lymphocyte cultures from 616 young adults in Malawi however the analyses are correlation coefficients between IFN-γ responses for all possible pairs of antigens used in this study.
- Faustman *et al* 2012 report on 6 diabetic and 6 healthy non-diabetic subjects randomised to BCG vaccination or control. T-cells, auto-antibodies and C-peptide are reported on 3 placebo and 3 BCG vaccinated subjects from each group. No group summary statistics are presented.
- Burl *et al* 2010 present a scatter plot of activated T cells (CD4+CD25+) in 48 children (aged 4 ½ months) who were vaccinated at birth and 39 unvaccinated control children. There were no

statistically significant differences between vaccinated and unvaccinated children (p=0.9388). Other NSIE were not reported.

- Ota *et al* 2002 reported PBMC proliferation, cytokine responses and antibody responses to TT and HBsAg in newborns according to timing of BCG vaccination (birth, 2.5 months and 4 months). Significant differences were identified for at least one comparison between study groups at 2 and 4.5 months for all NSIE assays.
- Miles *et al* 2009 reported on newborns of HIV positive (n=16) and negative (n=21) Malawian women. Maternal HIV status resulted in differential expression of T cells in children vaccinated at birth. No unvaccinated control group was included in the study.
- Kagina *et al* 2009 reported SEB-induced cytokine expressing CD4+ T cell responses (IFN-γ, TNF-α, IL-2) in 25 children vaccinated at birth and 21control children (Vaccinated at 10 weeks of age). Comparisons at 10 weeks were non-significant.

Data for the overall immunological outcomes of the included studies were summarized for all available parameters to provide a perspective on the effect of vaccination on these parameters in the following way. The direction of effect was calculated for each parameter by creating a ratio of the response in those vaccinated compared to the response in the unvaccinated participants. The response could be, the median, geometric mean or fold-rise depending on the statistics reported in the paper. No formal combination of these ratios (such as in a meta-analysis) has been conducted since the ratios are statistically non-comparable. Plots as designed to give a 'feel' for the overall diversity of responses and point to any general trends that may be occurring in the data. The size of each study cohort is represented by the size of the data point 'bubble'. For papers which reported comparisons at multiple time points for the same children the first comparison only is plotted so that each cohort of children is only reported once per study per parameter.

These ratios for all unstimulated assays and PHA stimulation are displayed below (Figures 2 and 3). No general patterns according to pro-inflammatory or anti-inflammatory classifications were observable for either plot. Results for both unstimulated (unstimulated cultures and total cell counts) and PHA stimulated assays show a range of both increases and decreases in response for most parameters.

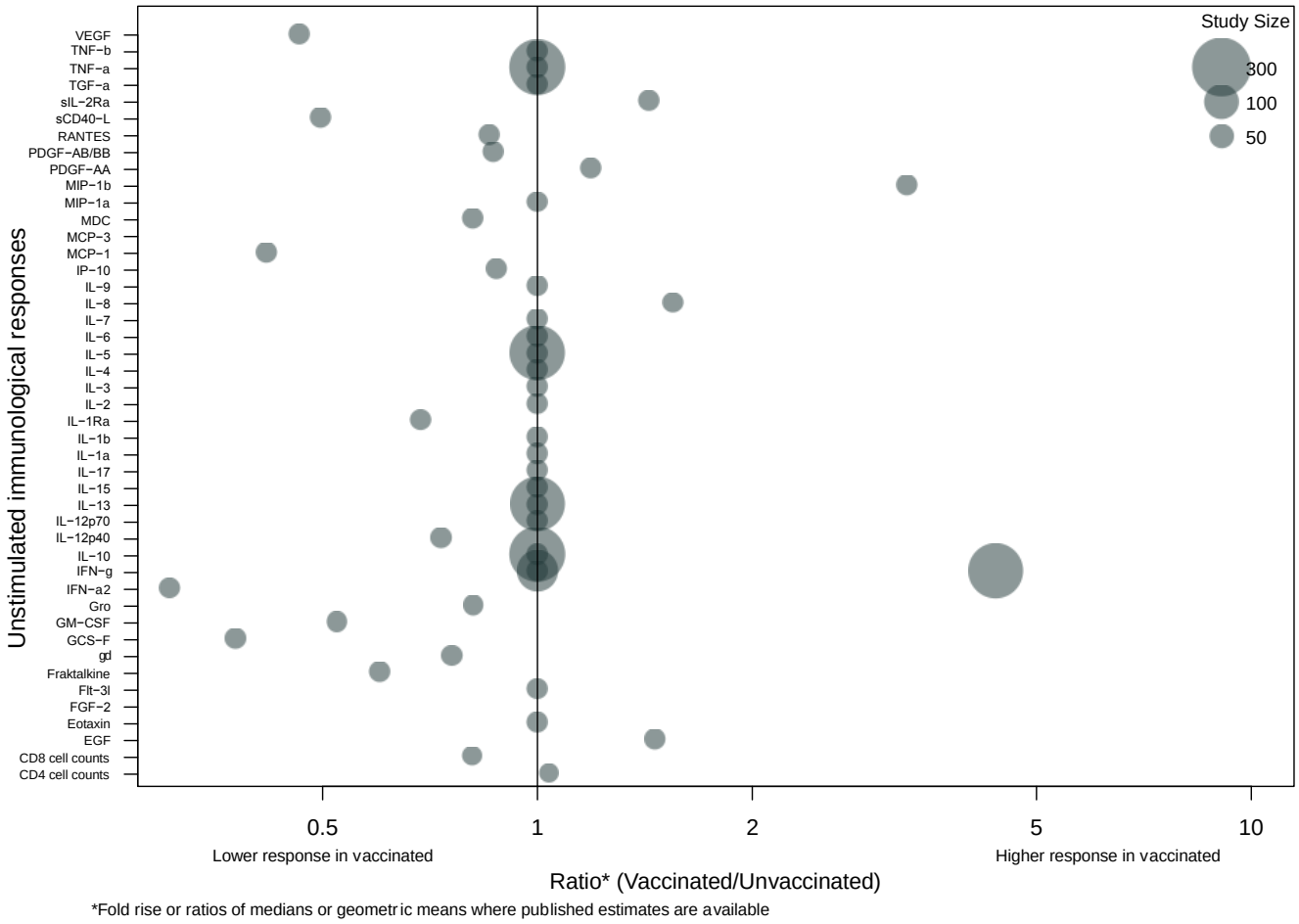


Figure 2. Leukocyte count and unstimulated culture response ratios, comparing vaccinated to unvaccinated, from included BCG studies reporting non-specific immunological effects.

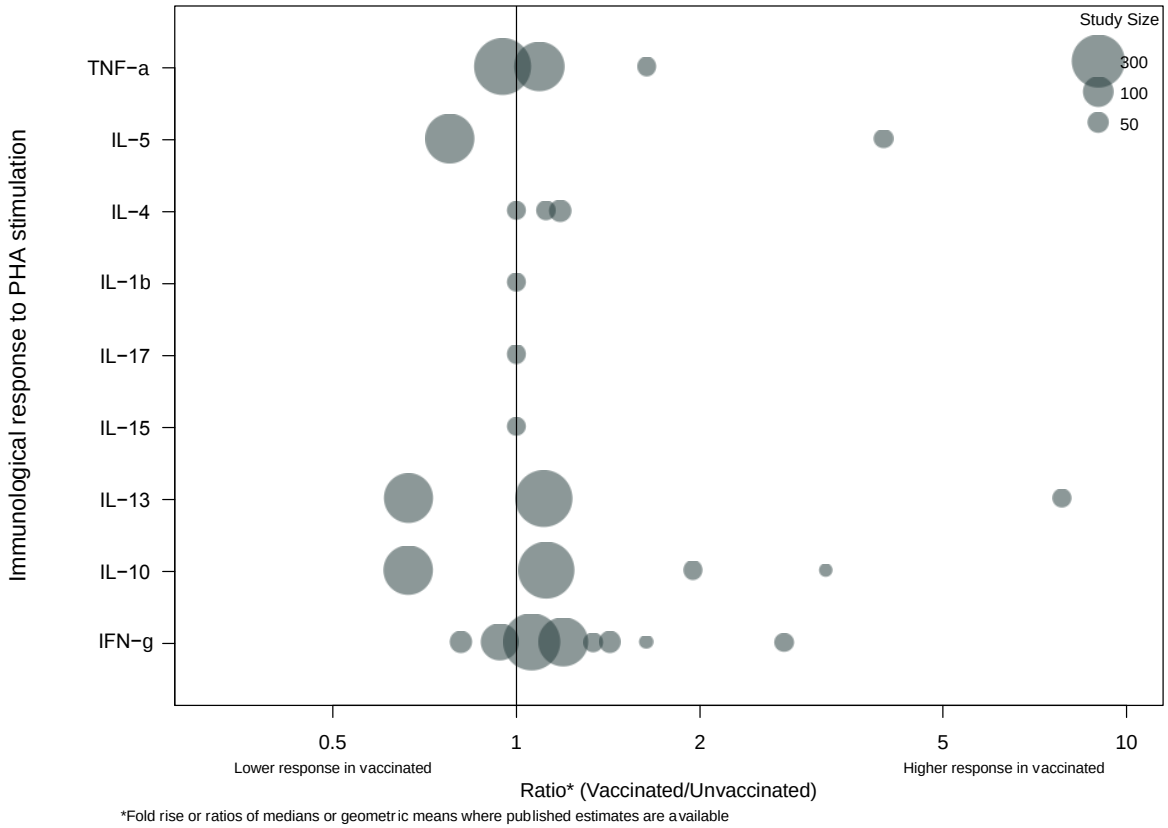


Figure 3. PHA stimulated culture response ratios, comparing vaccinated to unvaccinated, from included BCG studies reporting non-specific immunological effects.

IFN-γ

IFN-γ was the most commonly reported parameter. Data could be extracted from 11 papers and one paper supplied unpublished raw data from unstimulated assays upon request. Stimulants included *C. albicans*, HBsAg, LPS, *M. leprae*, PHA, *S. aureus*, SK/SD, PMA, Tetanus toxoid and unstimulated assays. Results from 6 papers reported results in using PHA stimulation were available (Figure 4). One cohort study (Djuardi *et al* 2010) reported a significant increase 24 months after vaccination in 98 children at birth, but no significant differences at 5 or 12 months after vaccination. The remaining 5 studies reported no significant differences between vaccinated and unvaccinated children.

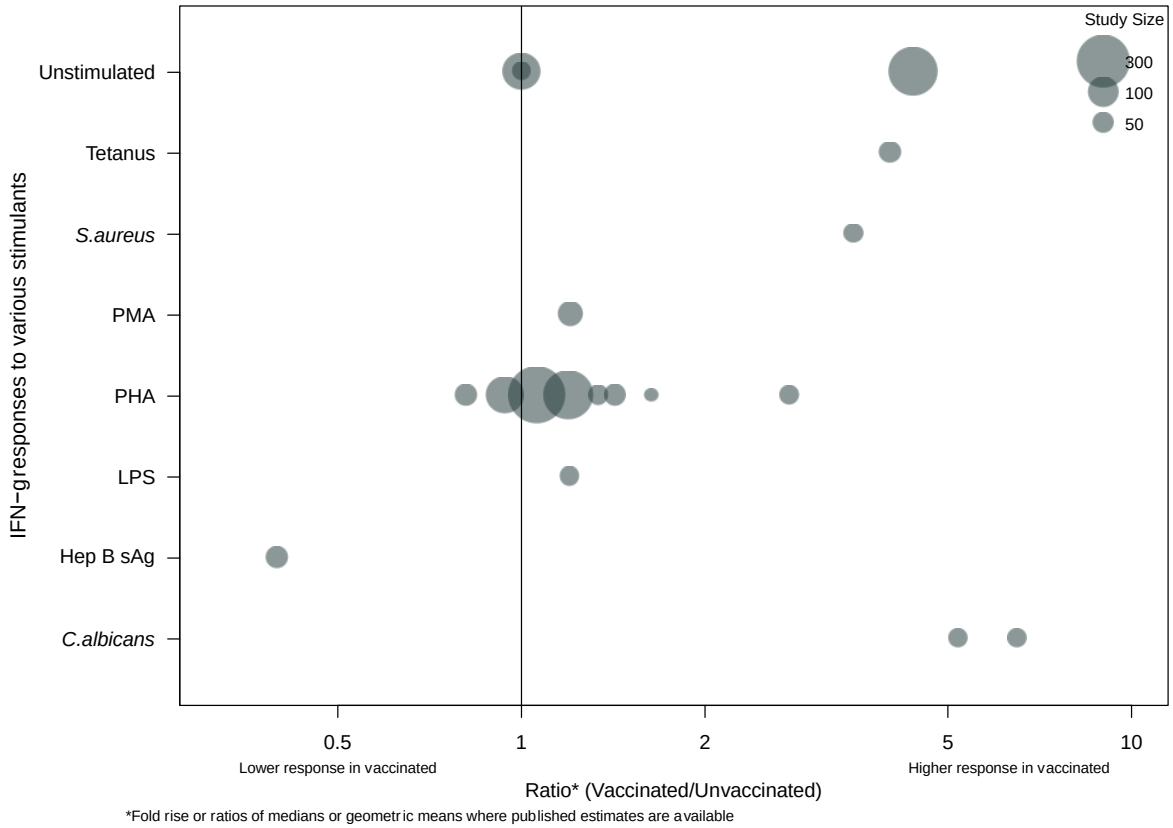


Figure 4. IFN-γ response ratios, comparing vaccinated to unvaccinated, following non-specific antigen stimulation of cultures from included BCG studies.

Two studies reported data, which could be extracted for unstimulated IFN-γ responses, and one study provided raw data for this same assay. All studies reported similarly large numbers of results below the level of detection of the assay. One study (Black *et al* 2002) reported low percentages (6% and 2%) of responses above 62 pg/mL in both Malawian and UK vaccinated teens respectively. Djuardi *et al* 2010 reported no differences between vaccination at birth and results at 5, 12, or 24 months and a further study supplied raw data for which the large majority of responses were below the level of detection (<3.2 pg/mL) for vaccinated and unvaccinated children in Malawi and UK. No statistically significant differences were reported.

The remaining studies with extracted data reported IFN-γ responses to LPS (one study: no significant difference), *C. albicans* (one study – significant differences between pre- and post-vaccination in adults), HBsAg (one study: no significant difference) and PMA (one study: no statistical comparison between vaccinated and unvaccinated).

IL-2

IL-2 responses to the mitogen ConA and unstimulated assays, demonstrated a statistically significantly higher response in the vaccinated group for Con A. There was no effect for the unstimulated assay (Figure 5).

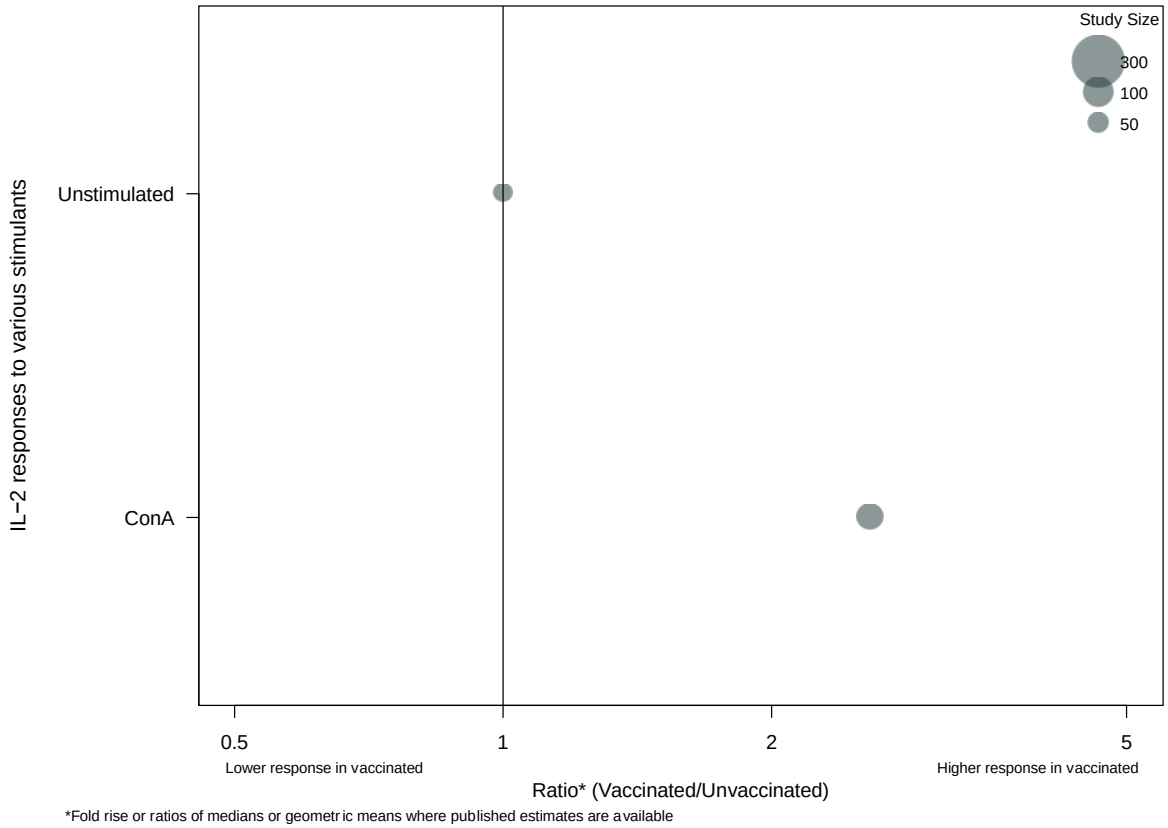


Figure 5. IL-2 response ratios, comparing vaccinated to unvaccinated, following non-specific antigen stimulation of cultures from included BCG studies.

IL-4

Hoft *et al* 1999, Marchant *et al* 1999 and Vargas *et al* 2004 reported data for IL-4 responses. IL-4 responses to the mitogens PMA was not statistically compared between vaccinated and control groups in Vargas *et al* 2004. PHA and unstimulated responses did not show any statistically significant difference between vaccinated and unvaccinated responses (Figure 6).

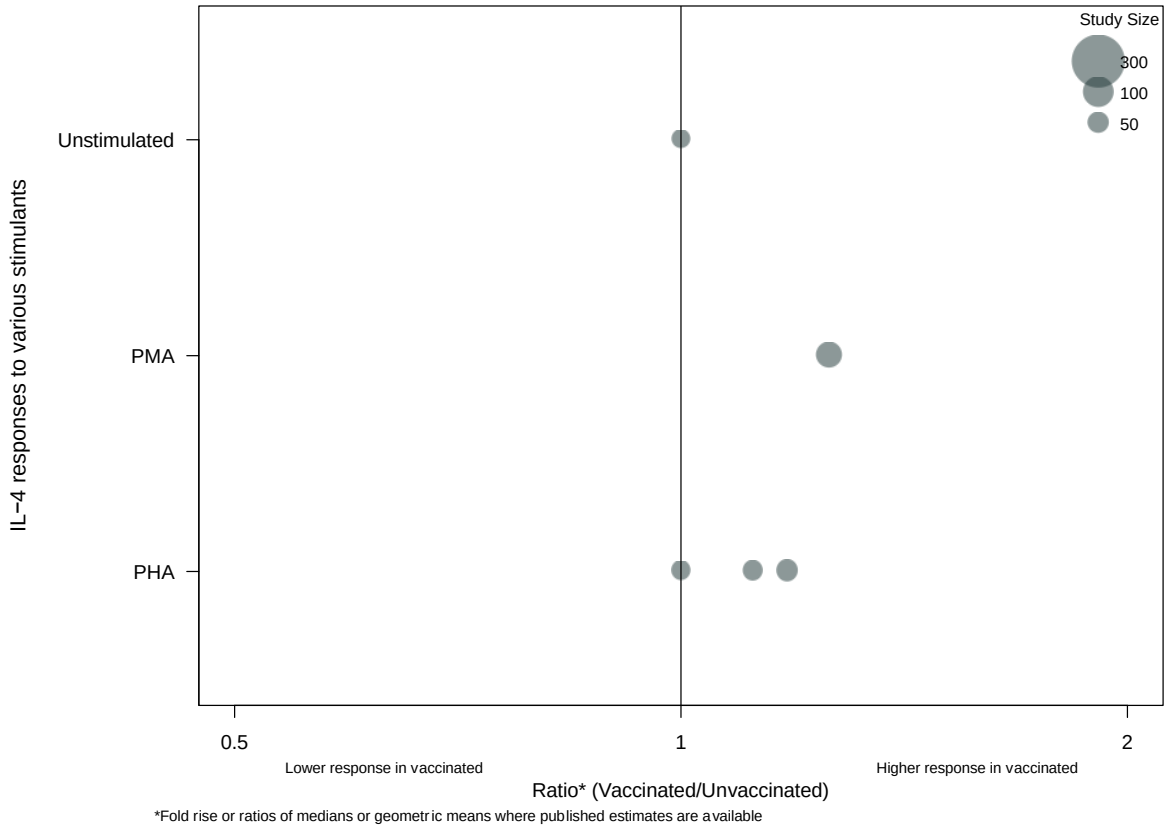


Figure 6. IL-4 response ratios, comparing vaccinated to unvaccinated, following non-specific antigen stimulation of cultures from included BCG studies.

IL-10

IL-10 results were extracted from 6 papers. Stimulants used in these assays included HDM, LPS, *M. avium* PPD (CVL), *M. avium* PPD (SSI), *M. intracellulare* PPD (SSI), *M. intracellulare* PPD-B, *M. scrofulaceum* PPD (SSI), PHA and unstimulated (medium alone). Four papers reported results using PHA stimulation (Figure 7). Three of these studies reported no significant differences between vaccinated and unvaccinated children. One study (Akkoc *et al* 2010) reported significant differences but no consistent effect with a significant increase compared to pre-vaccination levels 2 months following vaccination and a significant decrease 8 months after vaccination in 10 infants vaccinated at birth. No significant differences were observed between pre- and post-vaccination in the 9 infants vaccinated at two months of age in this same study and no statistically significant difference was observed between 9 unvaccinated children at 2 months of age compared to 10 children vaccinated at birth and measured at two months. Figure 7 includes this last comparison of vaccinated versus unvaccinated children only.

Two of the papers reporting responses to PHA also reported responses to LPS. No statistically significant differences were reported.

Other stimulants reported include HDM, *M. avium* PPD (CVL), *M. avium* PPD (SSI), *M. intracellulare* PPD (SSI), and *M. intracellulare* PPD-B which were all reported in one paper and were all $p > 0.05$. IL-10 responses to *M. scrofulaceum* PPD (SSI) were reported once with $p=0.015$ in Malawian infants and $p=0.838$ in UK infants. Response to HDM was significantly lower in those vaccinated ($p<0.0001$).

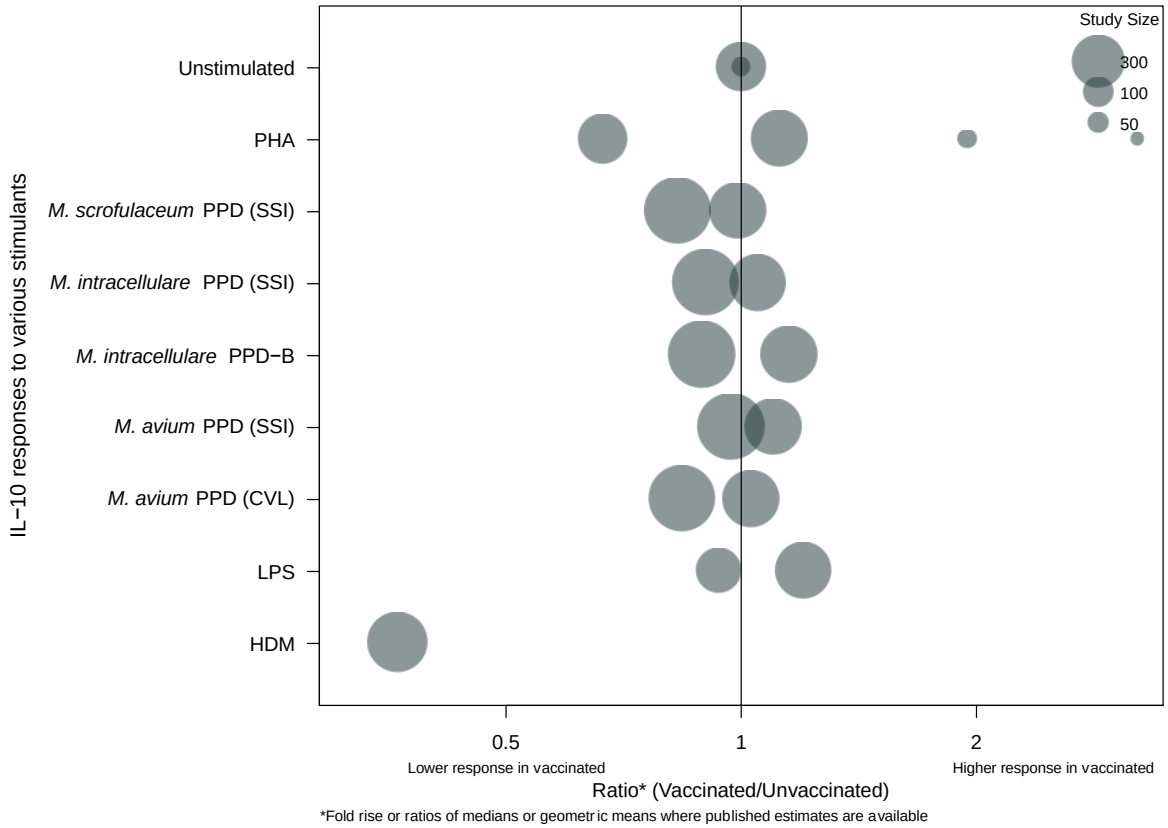


Figure 7. IL-10 response ratios, comparing vaccinated to unvaccinated, following non-specific antigen stimulation of cultures from included BCG studies.

TNF-α

TNF-α results were extracted from five papers and one paper supplied raw data. Stimulants used in these assays included *C. albicans*, *E. coli* LPS, *M. avium* PPD (CVL), *M. avium* PPD (SSI), *M. intracellulare* PPD (SSI), *M. intracellulare* PPD-B, *M. scrofulaceum* PPD (SSI), PHA, *S. aureus* and unstimulated.

Three studies reported results using PHA stimulation (Figure 8). Two of these studies also reported results for LPS stimulation. There were no significant differences reported in these three studies.

One study reported unstimulated TNF-α responses and one supplied raw data for this same assay. The large majority of responses were below the limit of detection and no significant differences were reported.

Other reported responses were to the following stimulants (All of which were non-significant): *C. albicans*, *E. coli*, *M. avium* PPD (CVL), *M. avium* PPD (SSI), *M. intracellulare* PPD (SSI), *M. intracellulare* PPD-B, *M. scrofulaceum* PPD (SSI) and *S. aureus.*

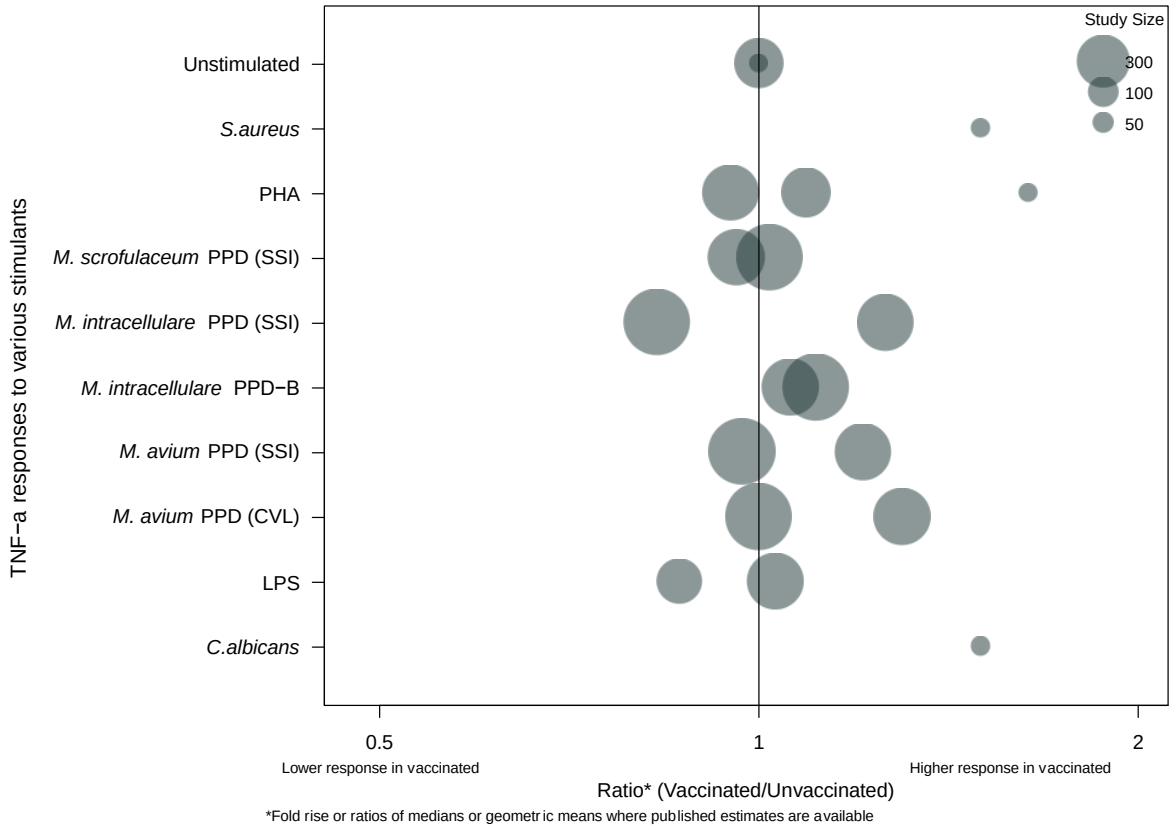


Figure 8. TNF-α response ratios, comparing vaccinated to unvaccinated, following non-specific antigen stimulation of cultures from included BCG studies.

IL-13

IL-13 results were extracted from four papers and one paper supplied raw data. Stimulants used in these assays included PHA and unstimulated (medium alone). Results from 3 papers, reported data using PHA stimulation (Figure 9). One of these papers (Djuardi *et al* 2010) reported a significant decrease in IL-13 at 5 months (but not at 12 or 24 months) in infants vaccinated at birth whilst the remaining two studies reported no differences.

Unstimulated responses were reported in one paper and one study supplied the raw data. The large majority of these responses were below the limit of detection and no significant differences were reported.

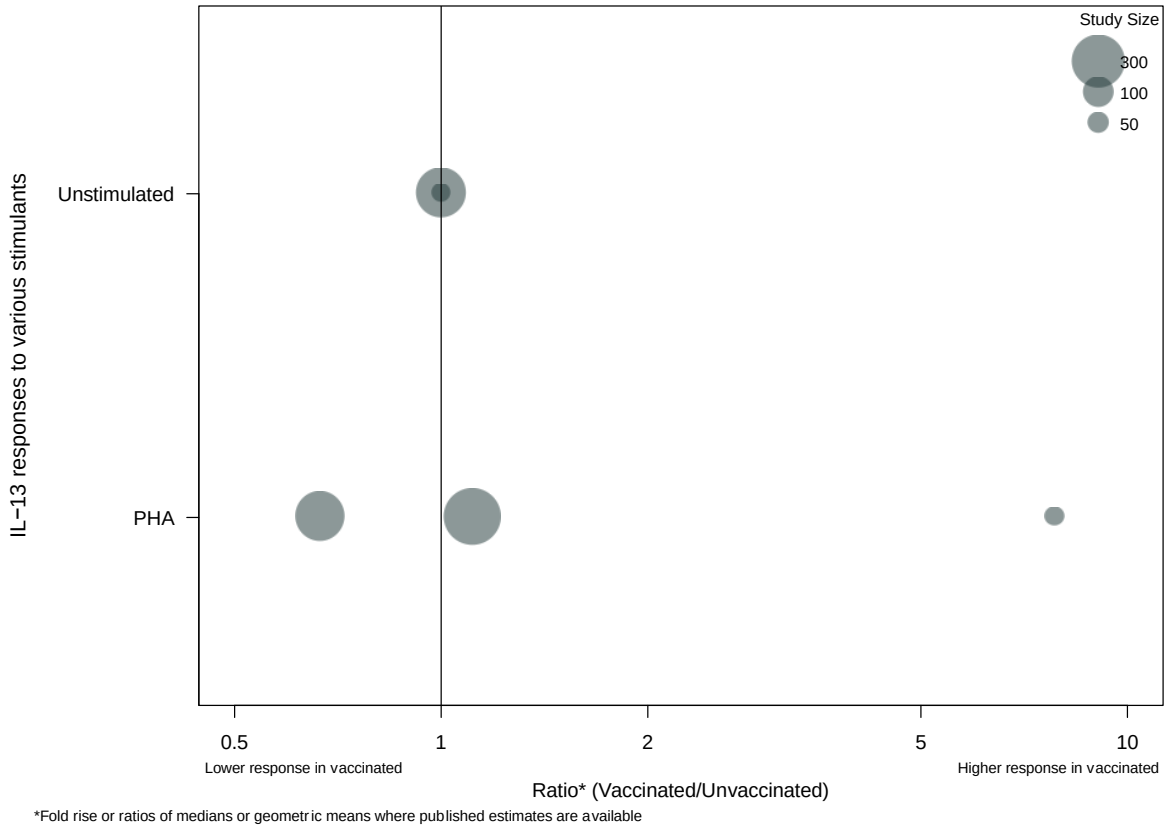


Figure 9. IL-13 response ratios, comparing vaccinated to unvaccinated, following non-specific antigen stimulation of cultures from included BCG studies.

IL-5

Data from two studies containing IL-5 responses to PHA stimulation were extracted and graphically represented (Figure 10). There were no significant differences reported in these studies. Responses to HDM, reported by Marks *et al* 2003 also showed no difference between vaccinated and unvaccinated.

Unstimulated responses from one published paper, and from data supplied in raw format demonstrated the majority of readings to be below the limit of detection with no reported differences seen.

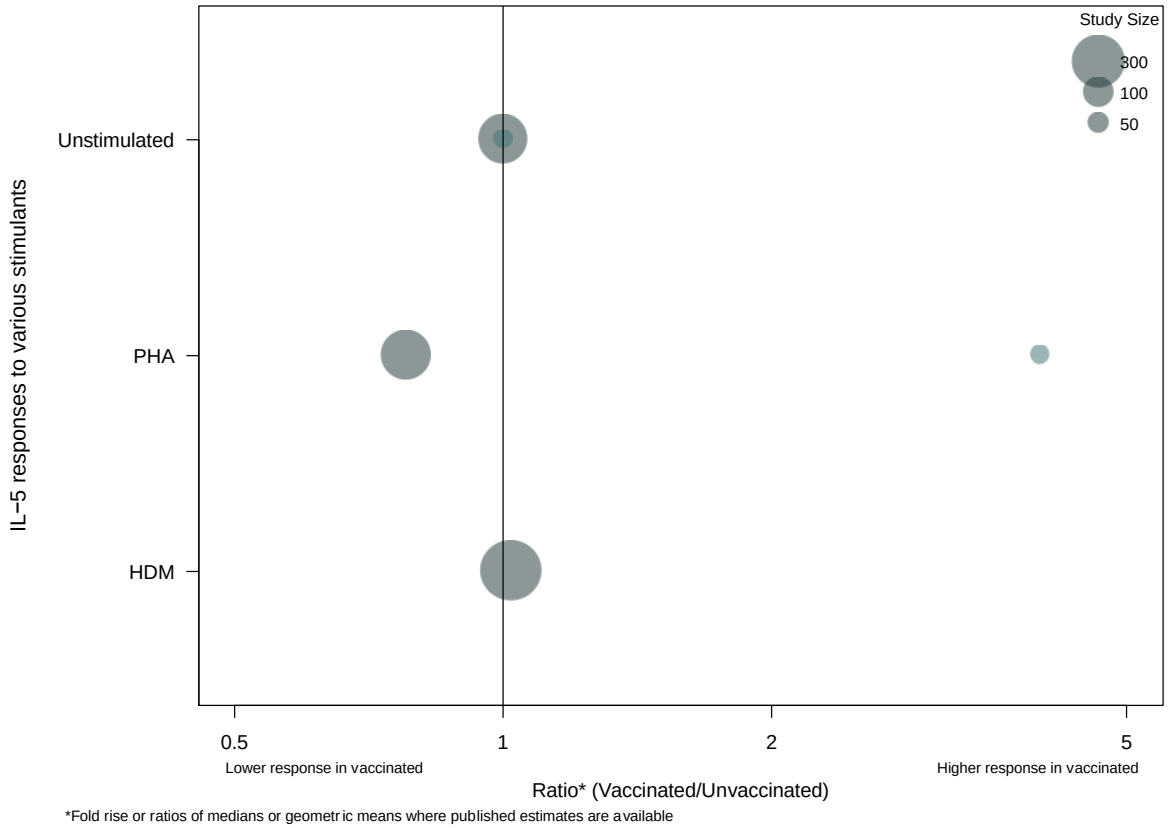


Figure 10. IL-5 response ratios, comparing vaccinated to unvaccinated, following non-specific antigen stimulation of cultures from included BCG studies.

Leukocytes

Two studies reported total leukocyte and eosinophil counts (Figure 11). No significant differences were reported in Steenhuis *et al* 2007 whilst no statistical comparison between vaccinated and unvaccinated children was reported in Vargas *et al* 2004.

Tarstan *et al* 2005 presents results for total lymphocyte responses that were significantly increased post-vaccination at both 2 and 4 months of age in children vaccinated at 48 hours and 2 months respectively. Results for aβ+ T lymphocytes were significantly reduced post-vaccination in both groups whereas gδ+ T lymphocytes were significantly decreased in the group vaccinated at 48 hours but were no different in the group vaccinated at 2 months.

In contrast gδ+ T lymphocytes were significantly increased in Hoft *et al* 1998 in response to IPP plus IL-2 stimulation but not in response to tetanus stimulation nor for unstimulated media responses.

CD4 and CD8 T cell responses were all measured in relatively small sample sizes (Hoft *et al* 1998). Both CD4 and CD8 T cell responses to stimulation with IPP together with IL-2 were significantly higher in the vaccinated group. CD4 and CD8 T cell responses to Tetanus and in unstimulated cultures were similar in the vaccinated and unvaccinated group and no statistical differences were reported.

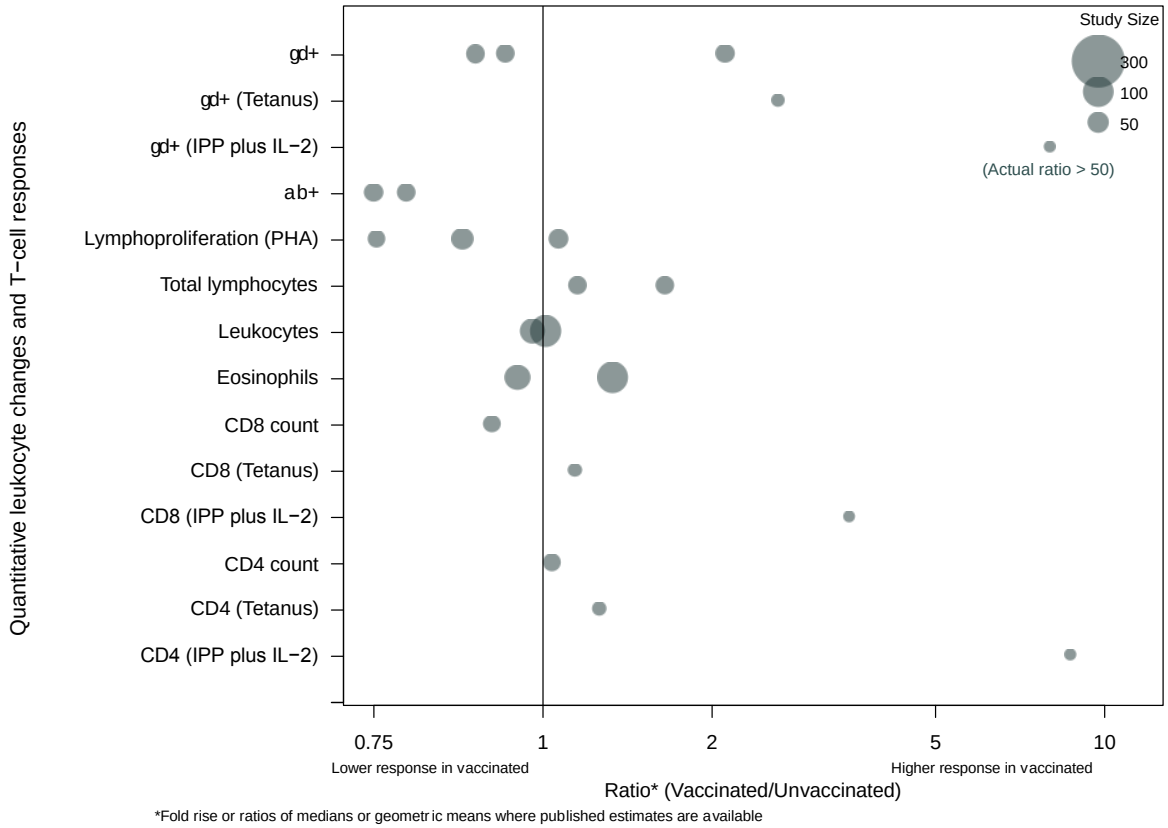


Figure 11. Responses rations of lymphoproliferation following non-specific antigen stimulation and Leukocyte counts, in vaccinated compared to unvaccinated groups, from included BCG studies.

Tetanus

There were 10 papers found reporting responses to non-specific stimuli with data either reported in table format or that could be extracted from graphs. These papers reported 21 different immunological parameters the main ones being proliferation (^{3}H-thymidine incorporation), CD25 and CD69, antigen reactive cells, Area of Skin Reactivity, B population, blastic transformation , IFN-γ , IL-10, IL-13, IL-17, IL-2, IL-4, IL-5, Stimulation Index, T1 population, T2 population, TNF-α, total proliferation and 25-hydroxyvitamin D, T and B lymphocytes and T-derived lymphocytes.

There were 14 types of stimulants used in the above assays (Candida-E, Candida-I, Cell electrophoresis, ConA, ERFC, HSV, Mumps-E, Mumps-I, PBS, PHA, PPD, PWM, unstimulated) resulting in 36 unique combinations of the above.

Only one study, Borut *et al* 1980, involved children under the age of 5 years, who only made up a fraction of the total study cohort.

No two papers reported the same parameters. No meta-analysis was possible nor plots created.

The following results were reported:

- Armitage *et al* 1993 report mitogen-induced blastogenesis in lymphocytes cultured with the mitogens PHA and ConA from 17 elderly and 17 young subjects. Differences were observed between the age groups with younger participants having higher responses. No comparison to baseline was made.
- Chollet *et al* 1979 report results for cell electrophoresis (B population, T1 population and T2 population) and non-specific blastic transformation with mitogens PHA, ConA and PWM in 6 individuals over 8 days after TT booster. B, T1 and T2 populations all increased from baseline to Day 2 and Day 3. T2 population was also significantly increased at Day 8. No differences were reported in non-specific blastic transformation.

- Cooper *et al* 1998 report peripheral blood mononuclear cell proliferation and cytokine production (IFN-γ, IL-4, IL-5, IL-10) to purified protein derivative of tuberculin before and 6 months after vaccination in 19 *O. volvulus*–infected subjects and 20 comparable non-infected controls. IL-4, IL-5 and IL-10 responses were negligible. No significant differences were reported.
- Gentile *et al* 2006 report PHA stimulated IFN-γ and IL-13 responses in 15 subjects with allergic rhinitis (AR) and 15 similar healthy subjects. Significant increases from baseline were reported in those without AR but not in those with AR.
- Donnenberg *et al* 1984 report a 'modest but significant' rise in HSV-specific antigen reactive cells at 28 days post immunization in 15 individuals. No p values or confidence intervals for the fold rise from baseline are reported and it is unclear whether the fold rise at 7 days is significant.
- Fevrier *et al* 1977 reported ^{3}H-thymidine incorporation by either total blood lymphocytes, purified B cells, purified T cells or a mixture of purified B and T cells stimulated with mitomycin-treated allogeneic lymphocytes. No statistical tests were performed
- Heine *et al* 2007 report staphylococcus enterotoxin B (SEB) stimulated cytokine responses (IFN-γ, TNF-α, IL-2, IL-4, IL-5, IL-10) and 25-hydroxyvitamin D in 32 individuals randomised to receive 2000 IU of vitamin D or placebo and followed for 10 weeks are TT booster immunization. The paper reports that Vitamin D supplementation did not affect SEB stimulated responses however 25-hydroxyvitamin D levels differed as would be expected. After booster TT immunization 25-hydroxyvitamin D levels decreased ($p \leq 0.0007$) within the placebo (no Vitamin D supplementation) group alone when compared to pre-booster levels.
- Livingston *et al* 2013 reported PBS antigen-specific cytokine secretion (IFN-γ, TNF-α, IL-2, IL-4, IL-5, IL-10, IL-13, IL17) by PBMC cultures before and after booster immunization with tetanus toxoid in previously vaccinated individuals who had not been boosted in at least 5 years as well as intracellular cytokine expression by CD4+ T-cells. Results are compared to responses to TT stimulation (which were higher). Changes in PBS results are plotted but not specifically tested for changes in those results alone.
- Mahalingam *et al* 2010 reported a significant rise in ConA stimulated IFN-γ in 108 healthy female adults, 56 days after vaccination when compared to baseline levels, but not at 28 days after vaccination. This rise in ConA stimulated IFN-γ was more substantial in those receiving 400mg of vitamin E supplementation (tocotrienol-rich fraction (TRF).

Data could not be extracted from the following papers;

- Di Genova *et al* 2006 reported proliferative responses to unrelated antigens PPD and *C. albicans* in 12 individuals at variable time points (between 1 and 12 weeks) after vaccination. Individuals' results are plotted but group summary statistics are not presented.
- Fernandez *et al* 1994 reported lymphoproliferation activity for 3 individuals to different levels of PPD stimulation. No comparisons are reported.
- Fryauff *et al* 1999 conducted lymphoproliferation assays stimulated with PHA however the data were not shown.
- Chui *et al* 2004 described the conduction of lymphoproliferation assays to unstimulated and HBsAg stimulation, but did not report the results. IFN-ϒ ELIspots were also performed using PHA, HBsAg and unstimulated controls, however these results were also not reported.

Measles

There were 8 papers reporting non-specific effects with data in a format that could be extracted. These papers report 23 different immunological parameters the main ones being B cells, β2-microglobin, CD4, CD4:CD8 ratio, CD8, IFN-γ, IL-10, IL-2, sIL-2Ra, IL-4, IL-6, lymphocytes, lymphoproliferation, malaria parasites, MIP-1β, Neopterin, sCD4, sCD8, T-cell proliferation, TNF-α, and WBC (Figures 12, 13 and 14).

There were 6 types of stimulants used in the above assays (Candida, PHA, tetanus toxoid, and unstimulated) resulting in 31 unique combinations of the above.

All of the papers contained participants who were under five years of age however there were no consistent findings for the main parameters (IFN-γ, IL-10, sIL-2Ra, IL-2, CD4, CD8) reported in papers where data could be extracted.

In addition to the studies described below the following studies conducted assays for non-specific immunological outcomes to measles vaccine, but did not report the results:

- Gans *et al* 2004 conducted T cell proliferation assays to PHA following vaccination with monovalent measles vaccine, however the results were not reported.
- Jaye *et al* 2014 conducted assays examining cytotoxic T cell responses following vaccination, however the non-specific outcome data were not reported.
- Okada *et al* 2001 report that on day 7 after measles vaccination, average numbers of total lymphocytes were relatively decreased to the lower limit of normal ranges before rising again by day 30. No p-values are reported and it is unclear what statistical testing was conducted.

In addition to the studies described above the following studies described non-specific immunological outcomes to measles vaccine with non-significant changes:

- Bertley *et al* 2004 reported unstimulated (vero) lympoproliferative responses in children following measles vaccination with either one or two doses, with no significant changes between groups noted.
- Gans *et al* 1999 conducted assays measuring IFN-γ in unstimulated culture supernatants, but did not report the results. T cell proliferative responses to PHA were also conducted with no significant differences reported between or within the study groups comparing before to after vaccination. Measles vaccine was given initially with MMR subsequently given at 12 months.
- Pabst *et al* 1999 measured non-specific proliferative responses to unstimulated (vero), tetanus toxoid, Candida and reported that there were no decreases in any of these responses after vaccination with AIK-C or CLL in 6 month olds. Additionally, there were no differences between groups or vaccines.

In addition to the studies described above the following studies described non-specific immunological outcomes to measles vaccines with significant changes noted for at least one parameter:

- Hennino *et al* 2007 reported eczema severity, utilising a scoring system in infants vaccinated with measles against placebo, with no significant change noted. Serum levels of CCL18 were significantly decreased in 2 measles vaccinated individuals compared to baseline. There were no significant differences in any individuals for serum E-selectin levels.
- Hussey *et al* 1996 reported PBMC proliferation to PHA at time-points following measles vaccination with either E-Z or Schwarz strains. There was a significant decrease from baseline to 3 months, within the group that received Schwarz at 6 months. There was also a significant decrease from baseline to 2 weeks and 3 months within the group that received Schwarz at 9 months. No significant changes were noted within the E-Z group. In the group that received Schwarz at 6 months there was a significant decrease in lymphoproliferation to PHA at 3 months compared to baseline. In the groups that received Schwarz at 9 months there was a significant decrease in lymphoproliferation at 2 weeks and 3 months compared to baseline. There was increased soluble CD8 and β2 microglobulin at 2 weeks and 3 months compared to baseline and also increased Neopoterin at 2 weeks compared to baseline in this study group. All other parameters in the three study groups were not significant.
- Samb *et al* 1995 report a significantly lower response to Rabies antibodies in 32 girls who received high-titre E-Z compared to 31 girls receiving Schwarz measles vaccine after all children had received 2 doses of rabies vaccine 4 weeks apart at age 36-44 months. No difference was seen in boys or overall. No differences were reported for Yellow fever antibodies.
- Ovsyannikova *et al* 2003 report on PHA stimulated TNF-α, IL-2, IL-4 and IL-6 (all non-significant when comparisons between younger children and older children). Unstimulated TNF-α responses

following vaccination were significantly higher in infants compared to older children but IL-4 and IL-6 were not.

- Njie-Jobe *et al* 2012 report a drop in unstimulated MIP-1β levels in response to a booster dose of E-Z vaccine at 36 months of age in both those who received a single priming dose of E-Z or 2 priming doses.

IFN-γ

IFN-γ data were extracted from five papers. PHA was the only stimulant reported and unstimulated assays were also conducted. Results from three papers, which reported results using PHA stimulation were plotted. One study (Ovsyannikova *et al* 2003) reported a significant difference between younger children (12-15 months) after one dose of Attenuvax and older children (4-12 years) who had received a second dose. Pabst *et al* 1999 and Schnorr *et al* 2001 did not report any significant differences between vaccinated and unvaccinated children. All three studies reported on different measles vaccines to each other (E-Z, Schwarz, AIK-C, CLL and Attenuvax).

Three studies reported data relating to unstimulated IFN- γ production. Ovsyannikova *et al* 2003 reported a significant difference when comparing production of IFN- γ following two doses of Attenuvax in older children compared to one dose in younger children. Njie-Jobe *et al* 2013 reported no difference in response to E-Z vaccine and Liguori *et al* 1998 also reported no difference (vaccine strain not reported).

IL-10

IL-10 data were extracted from three papers. PHA was the only stimulant reported and unstimulated assays were also conducted. Results from 2 studies that reported results using PHA stimulation were plotted. One study (Schnorr *et al* 2001) reported a significantly higher difference between measles vaccinated children (E-Z or Schwarz strains) at 6 or 9 months of age compared to unvaccinated children who were on average 10 months of age. Pabst *et al* 1999 reported no differences in response to AIK-C and CLL strains 8 weeks after vaccination at 6 months of age. The vaccinated children had received either E-Z or Schwarz vaccine according to local standard procedures.

Njie-Jobe *et al* 2012 report a drop in unstimulated IL-10 in response to a booster dose of E-Z vaccine at 36 months of age in both those who received a single priming dose of E-Z or 2 priming doses.

IL-2

IL-2 data were extracted from two study reports using PHA stimulation. Results from these two studies, which reported results in pg/mL and calculated geometric means or medians with IQR were plotted. One study (Schnorr *et al* 2001) reported a significant higher difference between vaccinated children at 6 or 9 months of age compared to unvaccinated children who were on average 10 months of age. The vaccinated children had received either E-Z or Schwarz vaccine according to local standard procedures. Ovsyannikova *et al* 2003 reported no differences. Both studies reported different measles vaccine strains to each other including E-Z, Schwarz, Attenuvax.

Soluble interleukin-2 receptor alpha subunit (sIL-2Ra)

sIL-2Ra data were extracted from three papers reporting unstimulated or PHA stimulated responses. No meta-analysis of these data was possible. Results from two papers, which reported unstimulated results in pg/mL and calculated medians with IQR were charted. One study (Ovsyannikova 2003) reported a significantly higher difference between younger children (12-15 months) after one dose of Attenuvax and older children (4-12 years) who had received a second dose. Njie-Jobe *et al* 2012 report no significant differences. Both studies reported different measles vaccine strains to each other (E-Z, Attenuvax).

Hussey *et al* 1996 report PHA stimulated sIL-2Ra responses to HT E-Z and Schwarz vaccines (at 6 and 9 months of age). sIL-2Ra values after vaccination were no different to baseline. Comparisons between the vaccine groups (HT E-Z, Schwarz at 6 months and Schwarz at 9 months) were statistically significant at 2 weeks and 3 months after immunization however they were also significantly different at baseline (pre-vaccination) thus these results don't appear to represent the effect of the vaccine.

CD4 and CD8 T lymphocytes

Three manuscripts reported total CD4 and CD8 counts with medians and IQR or means and 95% CIs. Lisse *et al* 1994 reports a follow-up of two separate studies. No significant differences were noted within any of the studies.

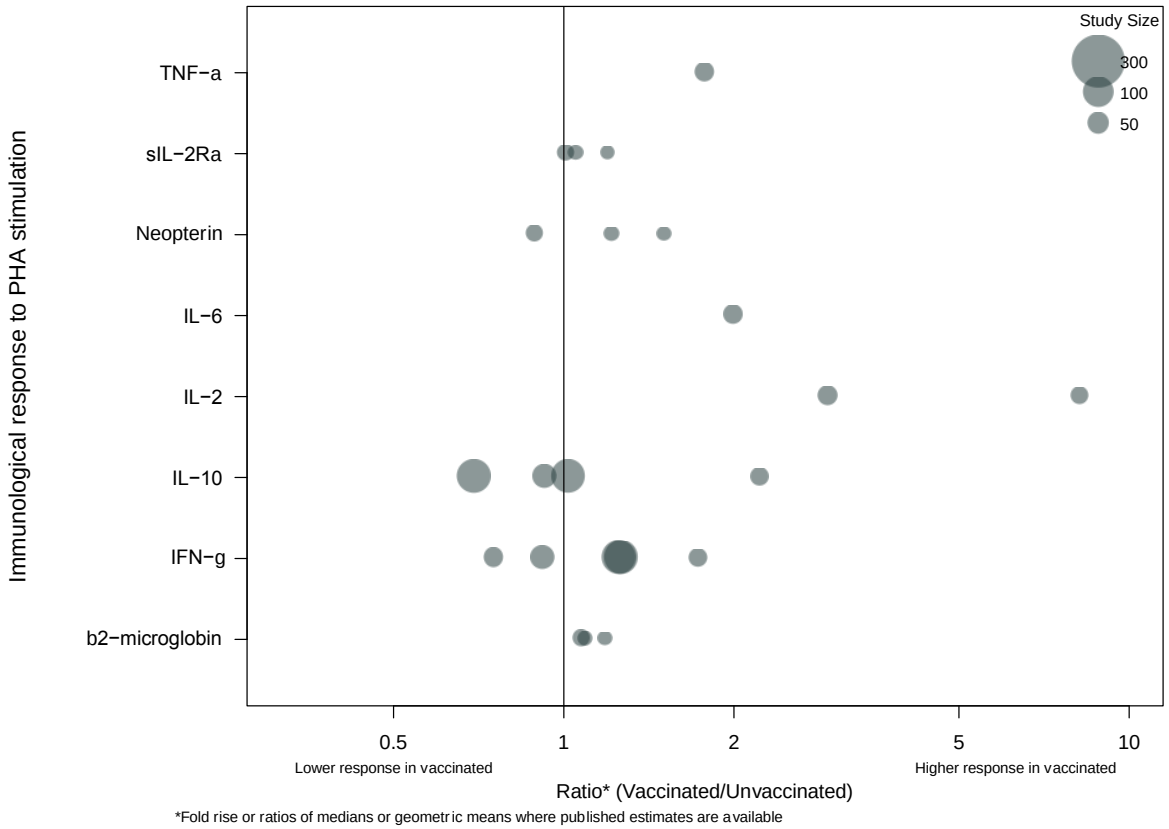


Figure 12. Immunological response ratios, comparing vaccinated to unvaccinated, in PHA stimulated cultures, from included measles vaccine studies.

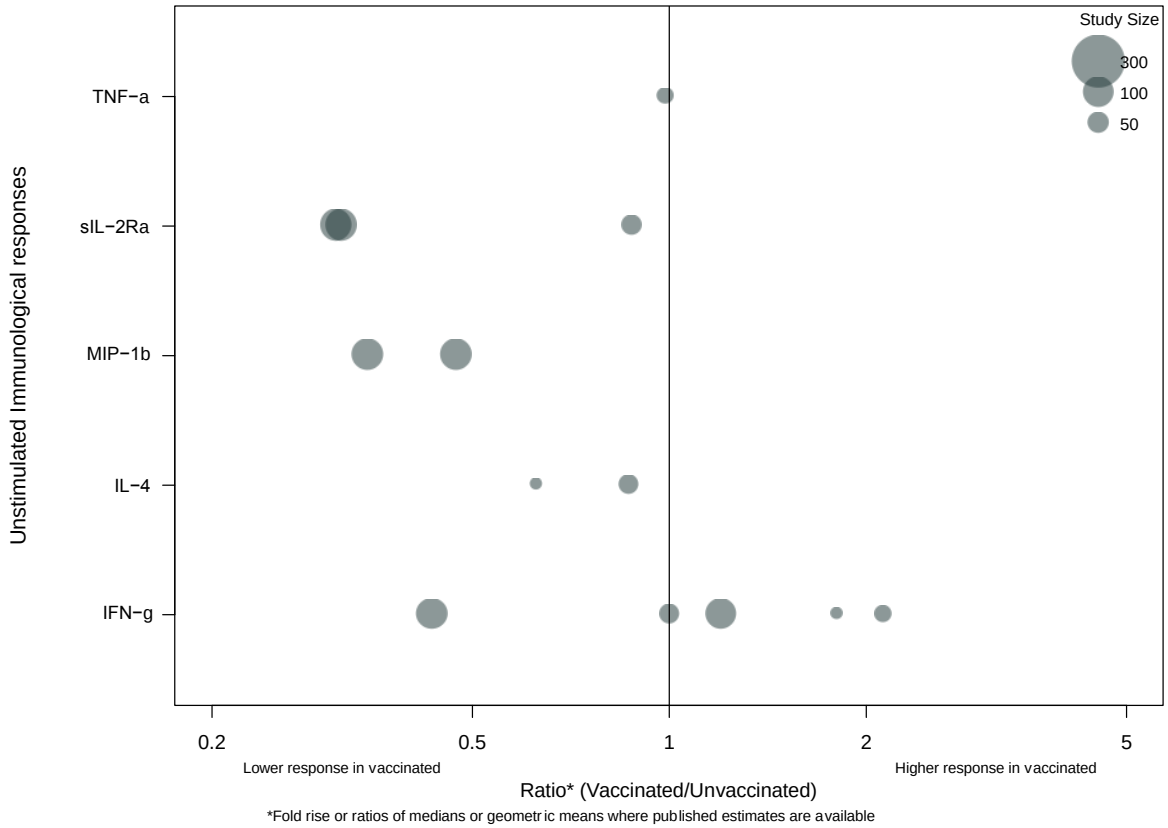


Figure 13. Immunological response ratios, comparing vaccinated to unvaccinated, in unstimulated cultures, from included measles vaccine studies.

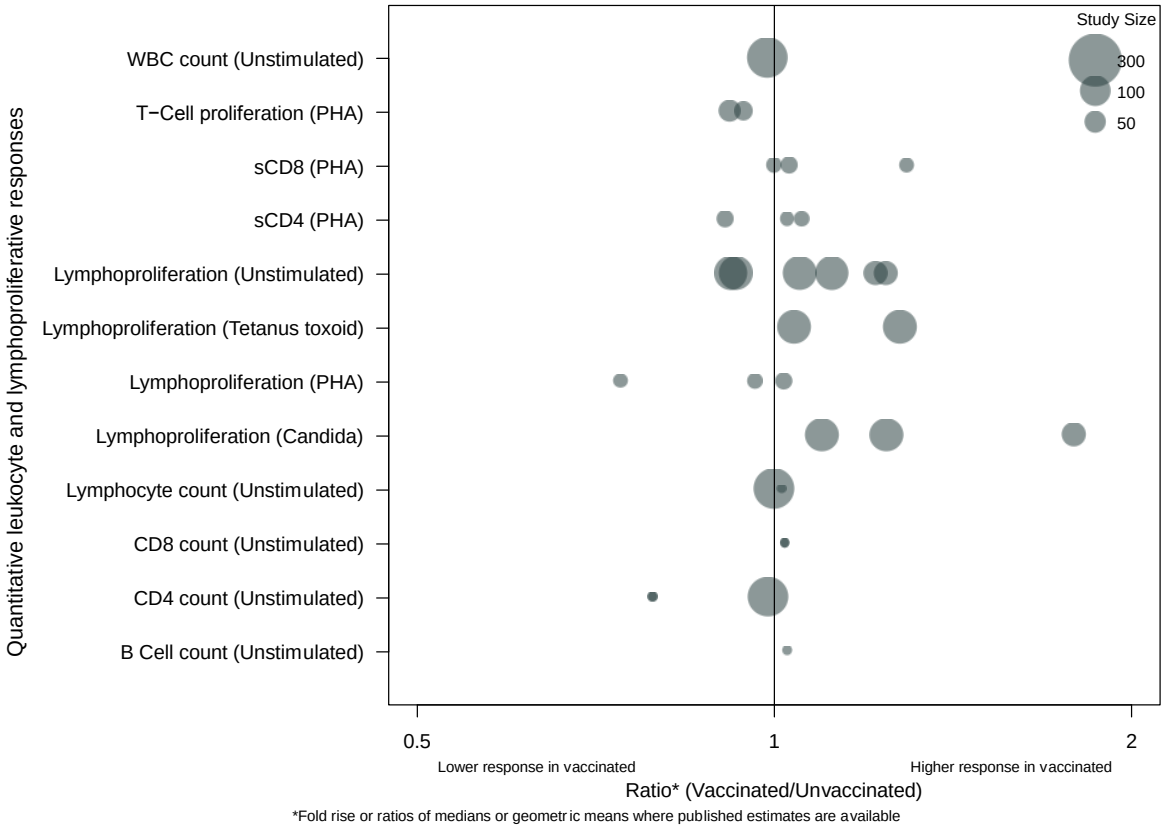


Figure 14. Non-specific antigen stimulated lymphoproliferation and leukocyte count response ratios, comparing vaccinated to unvaccinated, from included measles vaccine studies.

MMR

There were three papers reporting responses to non-specific stimuli with data reported in a format which could be used or extracted. Two papers conducted studies in children less than 5 years, whilst the third followed up vaccinated infants at mean age of 6.14 years. These papers reported 10 different immunological parameters the main ones being, CD4, CD4:CD8, CD56, CD8, IFN-γ, lymphoproliferation, NK, T-Cell proliferation and WBCs.

There were five types of stimulants used in the above assays (Candida, PHA, TT, and unstimulated) resulting in 13 unique combinations of the above.

Described below are the main parameters reported in papers from where data were extracted. Results that were not plotted (due to only being reported in one paper) include;

- Pabst *et al* 1997 report no difference in blast transformation in PBMC in response to tetanus toxoid or no antigens in the month post vaccination. One significant decrease in blast transformation to candida antigen was reported at 22 days after vaccination but was not significant at 14, 30 or 38 days.
- Gans *et al* 1999 report T cell proliferative responses to PHA of infants before and 12 weeks after measles/MMR immunization were no different.
- Rager-Zisman *et al* 2003 report there was a significant increase in mean percent CD56+ cells before and after secondary MMR immunization and proliferative responses to PHA were unchanged (P = 0.158) and to TT (P = 0.006) were improved after immunization in n=28, 6 year olds.
- Assays for IFN-α responses from unstimulated lymphocytes, from children vaccinated with MMR were conducted by Nakayama *et al* 1990, however the results were not reported.

CD4 T Lymphocytes

CD4 counts (%) were extracted from two studies (Figure 15). Both studies reported statistically significant decreases in CD4: Rager-Zisman *et al* 2003 report a significant difference between pre and one-month post booster vaccination in 28 children approximately 6 years of age and Pabst *et al* 1997 report a significant decline in CD4 T lymphocytes from pre to 38 days post-priming vaccination in 33 infants. No significant difference was seen in a separate cohort tested at 30 days post vaccine dose.

CD8 T lymphocytes

CD8 counts (%) were extracted from two papers. Both studies reported statistically significant results but in different directions: Rager-Zisman *et al* 2003 report a significant decline between pre and 1 month post booster vaccination in 28 children approximately 6 years old whereas Pabst *et al* 1997 report a significant increase in CD8 T lymphocytes from pre to 38 days post-priming vaccination in 33 infants. No significant difference was seen in a separate cohort tested at 30 days post dose.

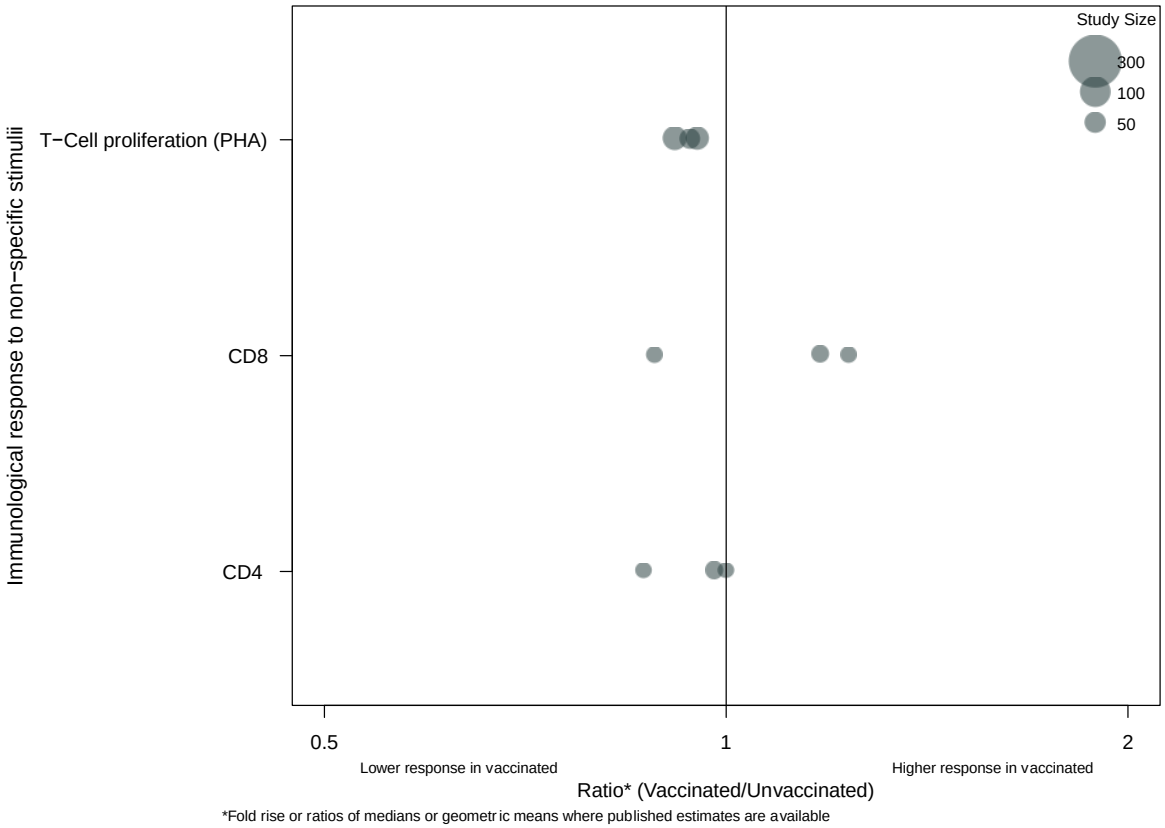


Figure 15. Immunological response ratios, comparing vaccinated to unvaccinated, for T cell proliferation to PHA stimulation and total counts of CD4 and CD8 T cells in included MMR vaccine studies.

DTP and DT

There were ten studies identified that contained assays of non-specific immunological responses following immunization with DTP or DT. There were four studies, which co-administered a polio vaccine, whilst Zorzeto *et al* 2009 did not describe co-administration with polio, however it is likely given the study demographic. No two studies had data that were extractable and could be compared descriptively in a graphical form.

Four of the studies were in children aged below five years of age. Only one study showed a significant increase in IL-5 and IL-13 after DTP in infants, however this was not replicated in any other study.

Dirix *et al* 2009 reported IFN-γ, IL-12p70 and IL-10 responses to PHA stimulation of PBMCs in infants who had received Tetravac. No significant changes over time following vaccination were noted.

Fernandes *et al* 2010 measured B lymphocyte subsets in adults following DT vaccination, with no significant changes noted. Pre-plasma cell IgA and IgG responses to Polio and HSV were also measured with significant increases in HSV IgA, IgG, and Polio IgA at day 7 compared to day -7 and day 28.

Fryauff *et al* 1999 measured lymphocyte proliferation to PHA following DT immunisation in adults, however the results were not reported.

Halasa *et al* 2008 reported polio neutralisation assays, and pneumococcal antibody levels following immunisation of infants with either 4 or 5 doses of DTP. In the 4 dose compared to 5 dose group there was a significantly higher Pneumococcal serotype 14 GMC at 7 months. In the 5 dose compared to 4 dose group there was a significantly higher Polio 1 and 3 GMC at 18 months.

He *et al* 1998 conducted cytokine mRNA expression studies following PHA and medium alone stimulation of PBMCs following DTP vaccination, however the results were not reported. Proliferative responses were also measured with no significant differences noted following immunisation in the medium alone cultures. The data for the PHA stimulated proliferative responses were not reported.

Heine *et al* 2011 conducted T cell activation studies using Staphylococcus enterotoxin and without any stimulation following DT vaccination of adults, with no statistical differences reported. Supplementary data reported a range of immunological parameters, with only the monocyte count being significantly reduced in the placebo group following vaccination.

Lin *et al* 1997 conducted studies examining lymphocyte proliferation to ConA, PHA and PWM following DTP vaccination of adults with no significant changes noted. Cytokine responses from these cultures were also examined with no significant differences noted either.

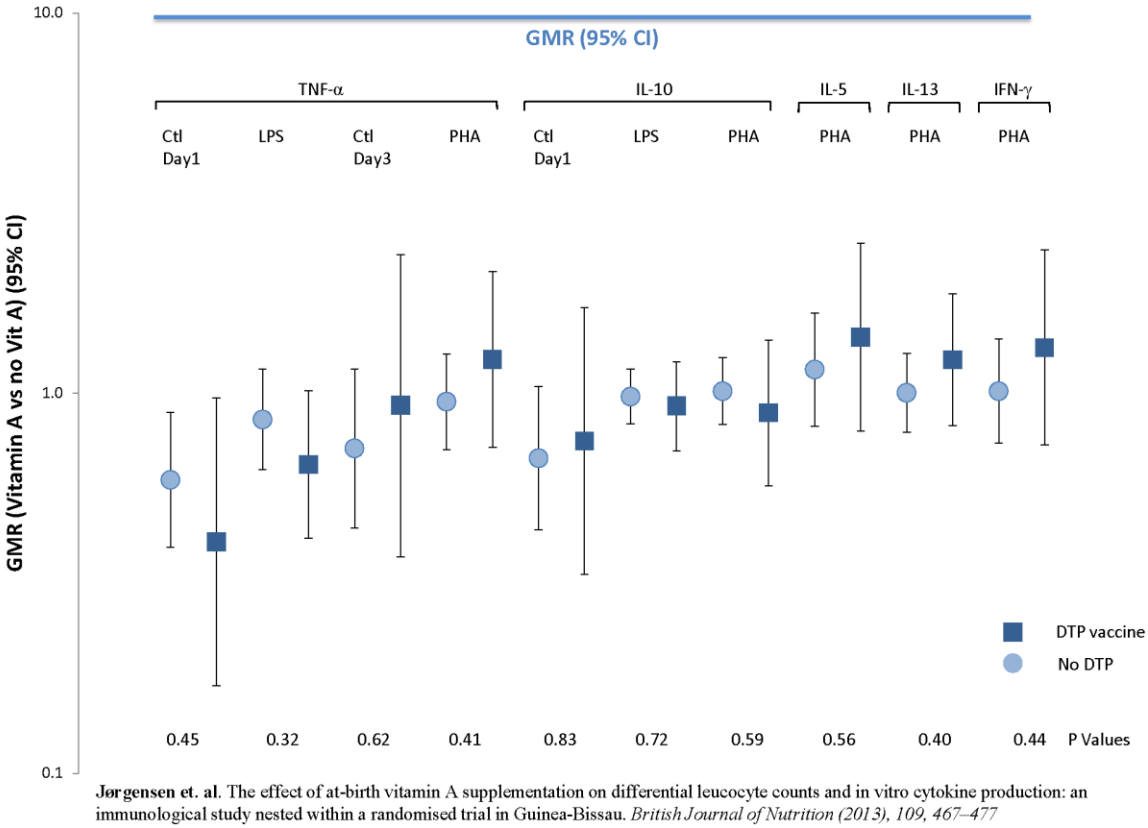
Rowe *et al* 2000 examined cytokine responses by PBMCs to PHA stimulation following DTP vaccination of infants and demonstrated significant increases in IL-5 and IL-13 at 12 months.

Yousfi *et al* 2005 examined serum biochemical markers and leukocyte following vaccination with a DT-Polio-Typhim vaccine in elderly and young adults. There were significant increases in CRP, AGP, Fibrinogen, Haptoglobin and a decrease in Transthyretin following vaccination. There were also significant changes in monocyte (increase), lymphocyte (decrease) and neutrophil (increase) counts following vaccination.

Zorzeto eta la 2009 reported lymphocyte sub-population proliferation and cytokine production to PHA by infants immunised with either a conventional DTP vaccine or a low LPS content DTP vaccine. There were no significant changes noted.

DTP and Vitamin A

One study explored the effect of Vitamin A on cytokine (IFN-γ, TNF-α, IL-10, IL-5, and IL-13) responses in relation to receipt of DTP vaccination (Figure 16). The data were reported as geometric mean ratios of Vitamin A supplementation to no Vitamin A supplementation within each group of DTP vaccinated or unvaccinated subjects. No significant differences were noted.



Jørgensen et. al. The effect of at-birth vitamin A supplementation on differential leucocyte counts and in vitro cytokine production: an immunological study nested within a randomised trial in Guinea-Bissau. *British Journal of Nutrition (2013), 109, 467–477*

Figure 16. Effect of Vitamin A supplementation on cytokine responses to non-specific antigen stimulation of whole blood from DTP vaccinated and DTP unvaccinated infants.

Pertussis

Di Tommaso *et al* 1997 conducted lymphoproliferative assays to TT stimulation and media alone, after vaccinating four healthy adults who failed to previously seroconvert, with a monovalent pertussis toxin vaccine. The TT results were reported but not statistically analysed. The unstimulated controls were not reported. There were no included studies, which reported non-specific immunological effects in children less than 5 years of age.

Interpretation

The improvement in technology for testing immunological parameters (e.g. multiplex assays) allows multiple tests to be assessed at one time using one blood sample and greatly increases the chances of false positive results occurring due to chance alone. The standard arbitrary cut-point used for significance testing in these situations is $p<0.05$ means that there is a 5% chance of a false positive result with every p value computed. If a study reports the results of a multiplex assay testing 42 separate parameters and each one is tested at the $p<0.05$ level then the chances that one of those parameters will show a significant difference where none exists is high.

Our review has shown that there are a multitude of parameters, which have been used to assess potential non-specific immunological effects of vaccines during the past 6 decades. Many of these are only reported once and it is in these situations that single significant p values need to be interpreted with caution. Stronger evidence for any effect can be observed where more than one study has assessed the same parameter and where confirmatory results can be found from different studies.

Overall there is a very heterogeneous spread of study designs that could not be meta- analysed, with a low level of evidence provided by these studies. Thus we could not conclude from the current available data that there are any consistent findings to confirm non-specific immunological effects following vaccination with BCG, diphtheria, pertussis, tetanus or measles containing vaccines. In addition, the data from the included papers were not presented in a form such that the effect of sex on non-specific immunological effects could be analysed. More meaningful conclusions might be drawn if raw data analyses could be conducted using unpublished and published data. If the same summary statistics could be computed for each study then meta-analysis would be possible.

These findings do not exclude the possibility of important non-specific immunological effects of vaccines, which are well described in animal studies and accepted as occurring in humans by most immunologists. However, the human data do not provide the necessary evidence to provide any confidence in the nature, quality, quantity, kinetics or impact of non-specific immunological effects in young children after vaccination. At this stage it is not possible to provide any guidance of an expected effect or when/how to measure it.
To further investigate the subject, future detailed studies might be undertaken using a systems biology approach to capture the functional genomic, genetic, epigenetic and immunological effects of vaccines in a kinetic study, which provides data on the timing, duration, quality and magnitude of such effects. This would entail a rigorous statistical approach within a test cohort with confirmation by replication in an additional cohort of subjects from the same study. It would be of particular importance to gain an understanding of whether any such measurable effects are able to influence future inflammatory or innate/acquired immunological responses to exposure with vaccines or infectious agents. If reproducible signals are identified, these could then be used in large scale studies with relevant epidemiological endpoints to characterize the clinical significance of such vaccine effects.

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Systematic review of the non-specific effects of BCG, DTP and measles containing vaccines

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Contents

1 Executive Summary

This report describes the results of a systematic review of epidemiological evidence concerning the non-specific effects of BCG vaccine, DTP vaccine and measles vaccine as routinely administered to infants and children. It focuses on all-cause mortality and, where data permit, examines the effects of various potential effect measure modifiers (gender of the child, age at vaccination, vitamin co-administration, order of vaccination). A detailed assessment of the risk of bias inherent in each study was also performed, and the available evidence subjected to a formal assessment of the quality of the evidence using the GRADE approach. In this executive summary we omit mention of studies assessed at being at such high risk of bias that they do not contribute useful information.

Five clinical trials and 9 observational studies provided comparisons of mortality rates among BCG-vaccinated and BCG non-vaccinated children in the neonatal period. The results indicated a beneficial effect of BCG on overall mortality in the first 6-12 months of life. Relevant follow-up in some of the trials was short, and all of the observational studies were regarded as being at risk of bias, so the confidence in the findings was rated as very low according to the GRADE criteria. No strong evidence of differential effects by gender or vitamin A was available, and there was a suggestion that BCG vaccination may be more beneficial the earlier it is given.

Ten observational studies (but no clinical trials) provided comparisons of DTP with no DTP. Oral polio vaccine was administered concomitantly with DTP in most included studies. The findings were inconsistent, with a majority of the studies indicating a detrimental effect of DTP, and two studies indicating a beneficial effect. All of the studies were regarded as being at risk of bias, so the confidence in the findings was rated as very low according to the GRADE criteria. One study reported a larger detrimental effect in girls, but overall there was not convincing evidence of a differential between girls and boys, or of differential effects by age at vaccination or vitamin A administration.

For measles vaccine, four randomized trials and 18 results from observational studies were included. There was consistent evidence of a beneficial effect of measles vaccine, although all observational studies were assessed as being at risk of bias and the GRADE rating was of low confidence. There was an apparent difference between the effect in girls and boys, with girls benefitting more from measles vaccination. We did not identify sufficient evidence to draw conclusions about effect modification by vitamin A, or about the age at which measles vaccination is most effective.

There was limited evidence on alternatives to the WHO-recommended ordering of vaccinations. Three observational studies provided a suggestion that simultaneous administration of BCG and DTP may be preferable to the recommended schedule of BCG before DTP; and there was suggestion that mortality risk may be higher when DTP is given with, or after, measles vaccine compared with when it is given before measles vaccine (from five, and three, observational studies, respectively). These results are consistent with hypotheses that DTP vaccine may have detrimental effects on mortality, although a majority of the evidence was generated by a group centred in Guinea-Bissau who have often written in defence of such a hypothesis.

2 Background

Over the past 30 or more years, an increasing number of vaccines have reached a greater proportion of the world's children, targeting some of the leading causes of morbidity and mortality, especially in children living in poor countries with high infant and child mortality rates. These vaccines, such as those against measles, diphtheria-pertussis-tetanus (DTP) and polio, have produced extraordinary declines in morbidity and mortality from the diseases targeted by the vaccines. In this context, a number of studies and related publications have suggested that some of the vaccines routinely administered to infants and children have non-specific effects on the immune system, and that these effects alter the risk of illness and death from conditions other than the specific infectious disease the vaccine is designed to prevent. These have come to be called non-specific effects of vaccines. Among hypotheses concerning these non-specific effects have been assertions that some vaccines (e.g. measles and Bacillus Calmette–Guérin (BCG) vaccines) are associated with lower subsequent risk of illness and death from other causes, while other vaccines (such as some DTP vaccines) are associated with higher subsequent risk of illness and death from other causes. It is further postulated that these effects may vary depending on factors including a child's gender and whether or not vitamin A supplements have been administered. Because hypotheses concerning possible non-specific effects of various infant immunizations arose after these vaccines had become part of the routine immunization schedule, randomized trials testing these hypotheses have been difficult or impossible to conduct on ethical grounds; as a result, with few exceptions, studies testing these hypotheses have been observational in nature.

This report describes the results of a systematic review of epidemiological evidence concerning the non-specific effects of vaccines routinely administered to infants and children. A separate review addresses immunological evidence. The present review was limited from the outset to studies of the effects of three vaccines: BCG vaccine, DTP vaccine and measles vaccine. Furthermore, it was decided to limit the review to studies, both published and unpublished, that permit an assessment of the effect, if any, of receipt of one of these vaccines on the subsequent risk of dying by five years of age. Children who had received medium or high titre measles vaccine were excluded. The protocol for the review specified a primary outcome of mortality from causes other than those associated with the disease the vaccine is intended to prevent (i.e. the non-specific effect of the vaccine on mortality) and a secondary outcome of mortality from all causes. This report focuses on the latter outcome of all-cause mortality, for which there is more evidence. Whenever the available data permitted, the effects of various potential effect measure modifiers (e.g. gender of the child, vitamin co-administration, order of vaccination) on the relationship between receipt of a given vaccine and the subsequent risk of dying were examined.

Because re-analyses and multiple analyses of data from some of the relevant studies have been published or are available, particular attention was given to avoiding the use of information for the same child for the same period of time more than once in the review. As described further below, a detailed assessment of the risk of bias inherent in each study was also performed, and the available evidence was subjected to a formal assessment of the quality of the evidence using the GRADE approach required for all WHO reviews.

The methods of the review are summarized in Section 1, and the numbers of articles identified and included are summarized diagrammatically in Section 2. Details of the included papers are provided in Annex A; data selected for presentation in the present report are explained in Annex B; and assessments of risk of bias are provided in Annex C. Findings for mortality from causes other than the disease the vaccine is intended to prevent are presented in Annex D, and a list of abbreviations is provided in Annex E. A series of appendices provides additional supplementary information.

3 Is administration of BCG vaccine in infancy associated with an effect on all-cause mortality?

Five clinical trials (two clearly randomized (1, 2) and three less clear in their allocation methods (3-5)), 12 cohort studies (6-19) and one case-control study (20) were identified that provided comparisons of mortality rates among BCG-vaccinated and BCG non-vaccinated children in the neonatal period and are presented in Figure 1. Four results from the cohort studies were considered to be at very high risk of bias in relation to the effect of BCG, and are presented separately at the bottom of the forest plot. We consider results that are assessed as being at very high risk to be uninformative, and such results do not contribute to our conclusions or GRADE assessments.

The clinical trials all pointed towards a beneficial effect of BCG on mortality. The randomized trials are essentially two periods of a single trial, involving new-borns recruited before and after it was restarted. We present 1-month mortality data from these, since the control group went on to receive BCG at a delayed time point (recommended age 6 weeks). The main phase of the trial found a halving of mortality risk among the BCG-vaccinated children, with a 95% confidence interval excluding 'no effect' (ES = 1). For the quasi-randomized trials (which allocated children to groups by alternation, or unclear methods), we could obtain only longer follow up (to 2 or 5 years of age). The quasi-randomized

trials were all performed in North America in the mid-20th century. They are the only studies in the review that were undertaken in high-income countries.

Excluding the results considered to be at very high risk of bias, the results of the nine non-randomized studies (all considered nevertheless to be at high risk of bias) also indicated a beneficial effect of BCG on overall mortality in the first 6-12 months of life. Four results had confidence intervals that excluded 'no effect', each demonstrating a beneficial effect of BCG. Estimated effects are in the region of a halving of mortality risk. Many of the analyses were undertaken by the Guinea-Bissau investigators, comprising four in which they conducted the original study [Guinea-Bissau 1984-1985, #851 (9); Guinea-Bissau 1989-1999, #839 (10); Guinea-Bissau 1990-1996, #9466 (8); Senegal 1996-1999, #9433 (18)] and two in which results of other investigators' data were re-analysed [India 1987-1989, #8996 (14); Malawi 1995-1997, #664 (16)].

The four studies with particularly high risks of bias produced highly variable results. Their results however point in the same direction as the other studies: of a beneficial effect of BCG on overall mortality.

As noted in the Background, the available studies typically provided data on all-cause mortality, and did not allow examination of the 'non-specific effects' of BCG vaccine on deaths from causes other than tuberculosis. However, deaths from tuberculosis are infrequent in infants and children in the first five years of life, so any effect of BCG vaccine on all-cause mortality is not likely to be attributable to any great extent to fewer deaths from tuberculosis (i.e. to a specific effect of BCG vaccine against tuberculosis).

3.1 Is there a difference in the effect between boys and girls?

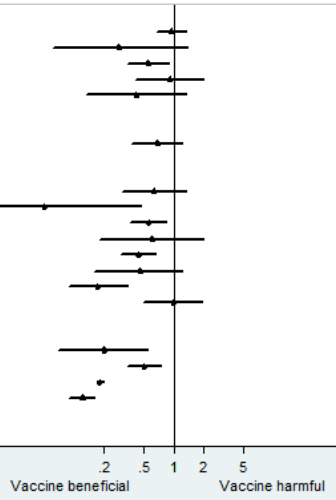
Nine of the cohort studies provided comparisons of BCG with no BCG separately for boys and girls, including one randomized trial, six cohort studies without very high risk of bias and two cohort studies with very high risk of bias for the main effects in Figure 1. The findings are shown in Figure 2. They reflect the main observation above of a beneficial effect of BCG. To examine the potential for differential effects between boys and girls, we need to look at the (statistical) interaction between them. Figure 3 illustrates the difference in vaccine effect between boys and girls, which is equivalent to the comparison in boy-girl mortality ratios between BCG-vaccinated and BCG-unvaccinated children[1]. The studies do not provide any suggestion of a differential effect on mortality of BCG between boys and girls.

[1] For one study [Senegal 1996-1999, #9433], boy-girl mortality ratios are used to compute interactions in Figure 3 rather than the data in Figure 2, since they allow for adjustment for age.

Figure 1. BCG and all-cause mortality.

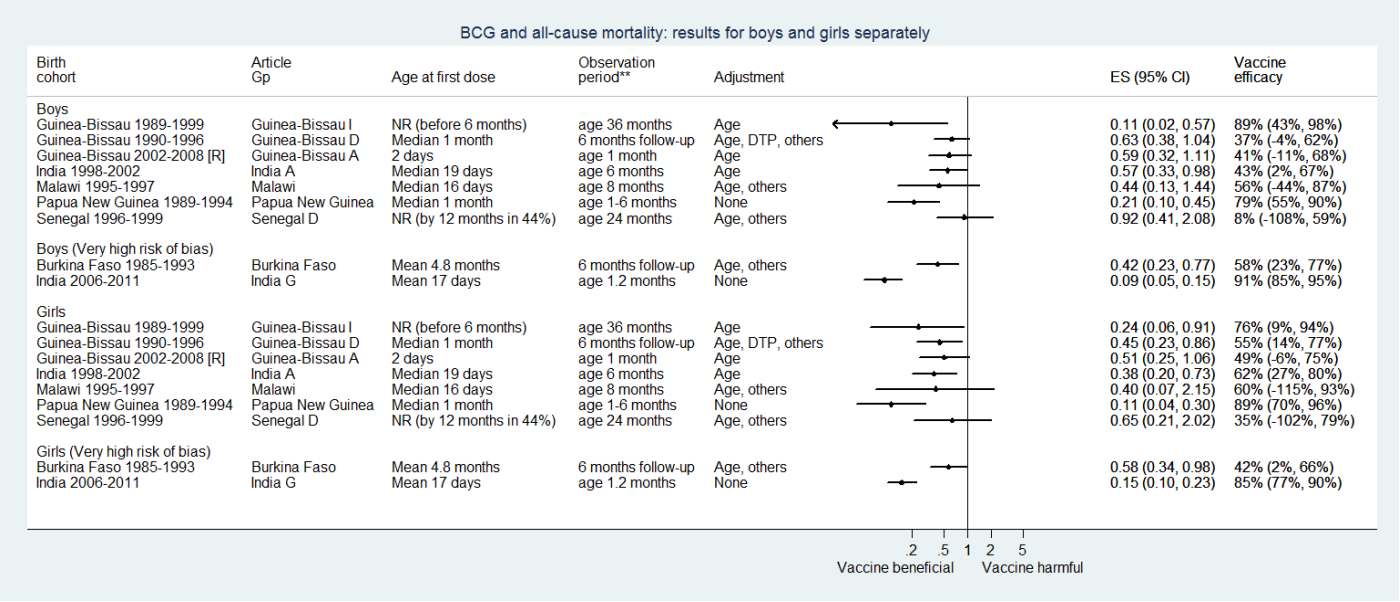
BCG and all-cause mortality

Birth cohort	Article Gp	Pub'n year	Deaths/ Children	Subseq. DTP*	Subseq. MV*	Age at first dose	Observation period**	Adjustment	ES (95% CI)	Vaccine efficacy
1. Randomized and quasi-randomized trials										
Canada 1933-1945	Canada	1949	(53+63)/609	None	None	10 days	age 60 months	None	0.94 (0.67, 1.32)	6% (-32%, 33%)
Guinea-Bissau 2002-2008 (early)	Guinea-Bissau A	2012	(2+6)/105	None	None	2 days	age 1 month	Age	0.28 (0.06, 1.37)	72% (-37%, 94%)
Guinea-Bissau 2002-2008 (main)	Guinea-Bissau A	2011	(27+48)/2343	None	None	2 days	age 1 month	Age	0.55 (0.34, 0.89)	45% (11%, 66%)
USA c.1935	USA A	1948	(12+13)/3008	None	None	0-4 years	age 48 months	None	0.91 (0.41, 1.99)	9% (-99%, 59%)
USA c.1941	USA B	1961	(4+9)/451	None	None	7-10 days	age 60 months	None	0.42 (0.13, 1.35)	58% (-35%, 87%)
2. Case-control studies										
Benin 1983-1987	Benin	1991	(34+39)/294	Many	Many	NR	age 4-36 months	Age, gender, others	0.68 (0.38, 1.23)	32% (-23%, 62%)
3. Cohort studies										
Guinea-Bissau 1984-1985	Guinea-Bissau E	2004	NR/1657	Many	Some	NR (0-8 months)	age 8 months	Age, gender, DTP, others	0.63 (0.30, 1.33)	37% (-33%, 70%)
Guinea-Bissau 1989-1999	Guinea-Bissau I	2004	(2+14)/695	Many	Few	1-7 days	age 6 months	Age, gender, others	0.05 (0.01, 0.46)	95% (54%, 99%)
Guinea-Bissau 1990-1996	Guinea-Bissau D	2002	(92+97)/4418	Many	Some	Median 1 month	6 months follow-up	Age, DTP, others	0.56 (0.37, 0.84)	44% (16%, 63%)
India 1987-1989	India E	2012	(3+29)/3072	None	Some	Median 1.6 months	age 12 months	None	0.60 (0.18, 1.97)	40% (-97%, 82%)
India 1998-2002	India A	2005	208/10274	Many [cens]	Few	Median 19 days	age 6 months	Age	0.44 (0.29, 0.66)	56% (34%, 71%)
Malawi 1995-1997	Malawi	2006	NR/751	Many [cens]	Few	Median 16 days	age 8 months	Age, others	0.45 (0.16, 1.23)	55% (-23%, 84%)
Papua New Guinea 1989-1994	Papua New Guinea	2005	NR/3937	Many	Few	Median 1 month	age 1-6 months	Age, DTP, others	0.17 (0.09, 0.34)	83% (66%, 91%)
Senegal 1996-1999	Senegal D	Unpub.	(9+372)/4421	Many [cens]	Many [cens]	NR (by 12 months in 44%)	age 24 months	Age, others	0.98 (0.50, 1.90)	2% (-90%, 50%)
Excluded (Very high risk of bias)										
Bangladesh 1986-2001	Bangladesh A	2004	184/9704	Many (OS)	Many	0-2 months	age 0-60 months	Age	0.20 (0.07, 0.54)	80% (46%, 93%)
Burkina Faso 1985-1993	Burkina Faso	2004	(28+280)/9085	Many (SS)	Many [cens]	Mean 4.8 months	6 months follow-up	Age, others	0.50 (0.34, 0.75)	50% (25%, 66%)
Ghana 1998-2004	Ghana C	2010	NR/17967	Many	Many	NR (by 12 months in 57%)	age 60 months	Age, others	0.18 (0.17, 0.20)	82% (80%, 83%)
India 2006-2011	India G	2013	(45+285)/11390	Few	None	Mean 17 days	age 1.2 months	None	0.12 (0.09, 0.16)	88% (84%, 91%)



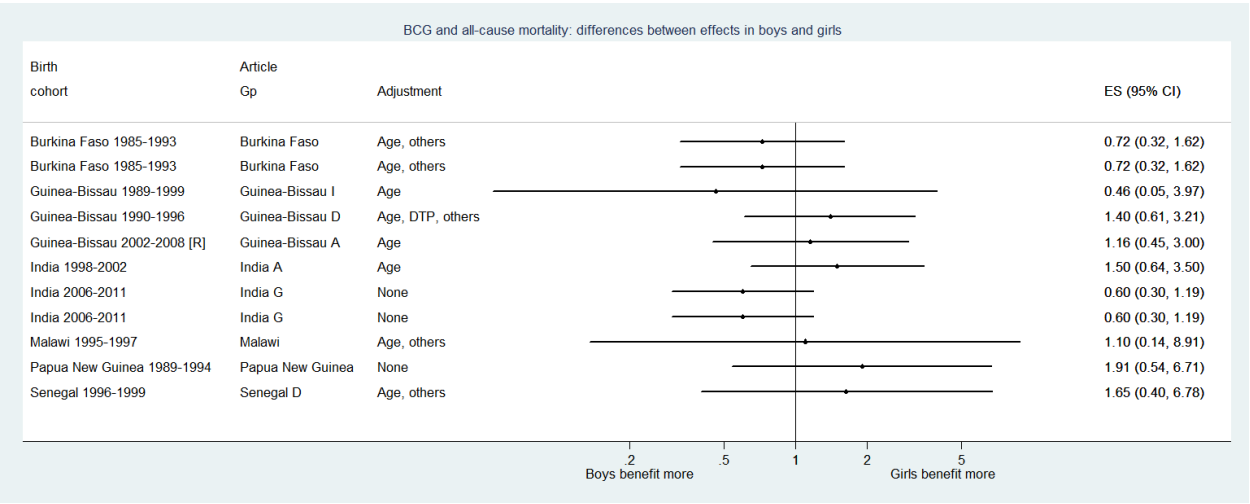
ES = effect size (hazard ratio, rate ratio or risk ratio; odds ratio for the case-control study). NR = not reported.
Deaths/Children = (BCG deaths + Non-BCG deaths)/Total children or Total deaths/Total children
In the two cohort studies with 'None' as adjustment for confounding, we computed unadjusted rate ratios from rates presented in the paper.
Vaccine efficacy is computed as (1 – ES) × 100%. A non-negative number describes the proportion of deaths prevented by the vaccine. A negative number reflects a higher death rate among the vaccinated. For example, if vaccine efficacy = -100%, then an *additional* 100% of the deaths that would have occurred without vaccine would occur with the vaccine.
Guinea-Bissau 2002-2008 (early): early phase of the trial stopped prematurely because of faulty randomization procedure in one of the centres; Guinea-Bissau 2002-2008 (main): main trial report with larger sample size.
*Subseq. DTP: what proportion of children were likely to receive DTP during the period of observation. Subseq. MCV: what proportion of children were likely to receive measles vaccine during the period of observation. [cens] means this event was censored in the analysis].
SS = sometimes given simultaneously with DTP; OS = often given simultaneously with DTP
**This is the period of observation applicable to the result presented in the forest plot, aiming to capture the effect of BCG with minimal impact of subsequent vaccinations. The full study may have had a longer period of follow up.

Figure 2. BCG and all-cause mortality: results for boys and girls separately.



ES = effect size (hazard ratio, rate ratio or risk ratio)
R = Randomized trial (the main phase of the trial) (all other studies are cohort studies)
**This is the period of observation applicable to the result presented in the forest plot, aiming to capture the effect of BCG with minimal impact of subsequent vaccinations. The full study may have had a longer period of follow up.

Figure 3. BCG and all-cause mortality: differences between effects in boys and girls.



ES = effect size (ratio of hazard ratios, rate ratios or risk ratios)
R = Randomized trial (the main phase of the trial) (all other studies are cohort studies)

3.2 Is there a difference in the effect by age?

Age at vaccination

The average age at which BCG vaccination was administered varied across studies (see Figure 1), from very soon after birth to 4.8 months of age or later. However, there is not strong evidence of a pattern of association between observed effects on mortality and age of vaccination in Figure 1.

In two studies, effects were reported for children vaccinated at different ages. In both Bangladesh 1986-2001 (6) and Guinea-Bissau 1989-1999, #839 (10), the effect lessened as the age of vaccination increased. These results are illustrated at the top of Figure 4.

The two randomized comparisons examined BCG at birth versus delayed BCG (recommended at 6 weeks) among low birth weight infants. After 1 year, the early phase of the trial observed 5 deaths among 51 allocated to the at-birth arm and 11 deaths among 54 allocated to the delayed arm (risk ratio 0.48, 95% CI 0.18 to 1.29). After the same period of follow-up, the larger second phase observed 105 deaths among 1182 allocated to the at-birth arm and 124 deaths among 1161 allocated to the delayed arm (risk ratio 0.83, 95% CI 0.65 to 1.06). These results suggest a possible benefit of early BCG over delayed BCG.

Further research may help determine whether these effects are real or artefactual.

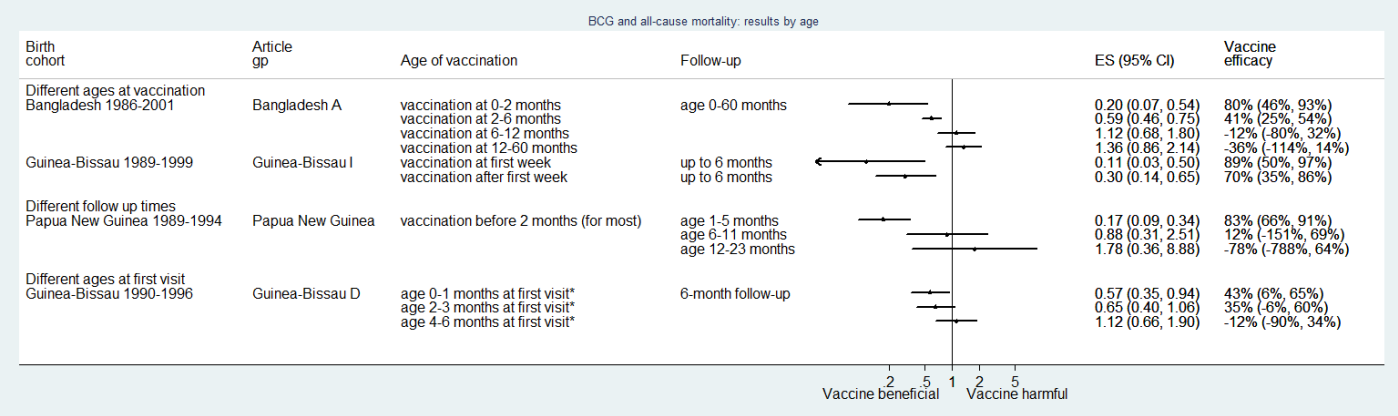
Age at follow-up

For Papua New Guinea 1989-1994 (17), results were available for multiple follow-up times. These results are illustrated in the middle portion of Figure 4. Interpretation of these is made challenging by the effects of subsequent vaccines and by the potential for selection biases to push results for later follow-up periods towards (and even beyond) the no effect line. Smaller effects are seen at later ages.

Other results by age

One study reports results by age of the child the first time they were seen ('first visit') so the findings likely reflect both age at vaccination and age at follow-up [Guinea-Bissau 1990-1996, #2726 (21)]. Again, a potential pattern of smaller effects at later ages is seen.

Figure 4. BCG and all-cause mortality: results by age.

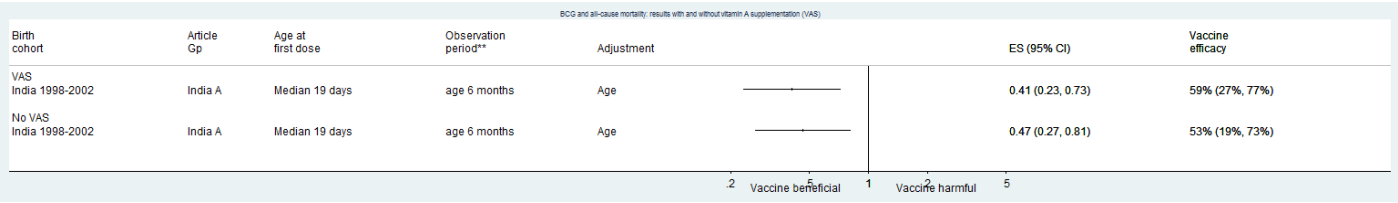


ES = effect size (hazard ratio, rate ratio or risk ratio)
All studies are cohort studies.
*Differences by age at first visit may reflect a combination of ages at vaccination and ages at follow up.

3.3 Is there a difference in the effect by vitamin A administration?

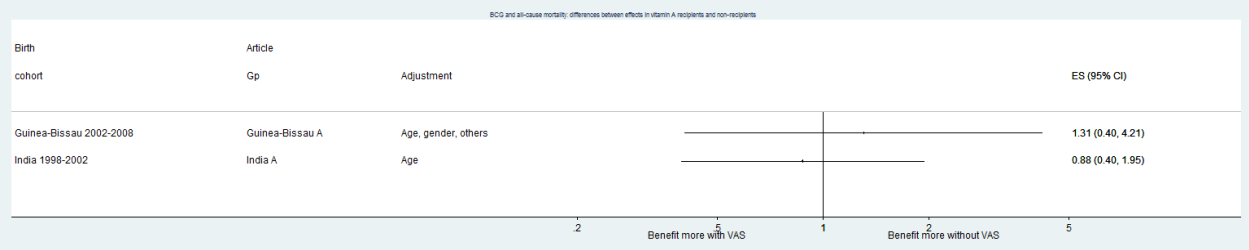
We sought results for interaction between BCG effect and (prior or concurrent) administration of vitamin A. To understand interaction we needed either (i) the effect of BCG separately among vitamin A recipients and vitamin A non-recipients or (ii) the effect of vitamin A separately among BCG recipients and BCG non-recipients. One cohort [India 1998-2002, #741 (13)] provided the former (presented in Figure 5) and one presented the latter [Guinea-Bissau 2002-2008, #339 (22)]. The resulting estimates of interaction are illustrated in Figure 6. There is insufficient evidence to determine any difference in effect of BCG according to vitamin A status.

Figure 5. BCG and all-cause mortality: results for vitamin A recipients and vitamin A non-recipients separately.



ES = effect size (hazard ratio, rate ratio or risk ratio; odds ratio for the case-control study)

Figure 6. BCG and all-cause mortality: differences between effects between vitamin A recipients and vitamin A non-recipients.



ES = effect size (ratio of hazard ratios, rate ratios or risk ratios)
Both studies are cohort studies.

3.4 Comments on study methodology and bias

All of the results from observational studies were judged to be at high risk of bias or very high risk of bias, so the findings above should be interpreted with caution. The main potential sources of bias in the observational studies were confounding (inherent differences in children vaccinated and children not vaccinated: no studies were considered to have overcome this); misclassification bias relating to determination of non-vaccination status; bias arising from selection of participants after vaccines were given (and hence after they could have impacted on mortality); co-interventions including administration of DTP vaccine; and misclassification bias relating to lack of information about vaccinations that were administered (including 'survival bias' arising from taking a retrospective approach to the analysis (23).

The very high risk of bias studies were seriously affected by co-administration of DTP [Bangladesh 1986-2001, #797 (6)], starting follow up long after BCG vaccination [Burkina Faso 1985-1993, #799 (7)], highly correlated co-interventions [Ghana 1998-2004, #9464 (19)], and strong confounding by age; [India 2006-2011, #9463 (15)]. Some of these studies had additional reasons for serious concern, but for which we were unable to make a judgement from the written reports.

We regard the estimates of interaction (for differences by gender and vitamin A) to be less affected by bias, since many of the biases affecting direct estimates of vaccine effects are likely to cancel out when these are contrasted between boys and girls or between vitamin A recipients and vitamin A non-recipients.

For full details of methodological features and assessments of risk of bias, see Annex C.

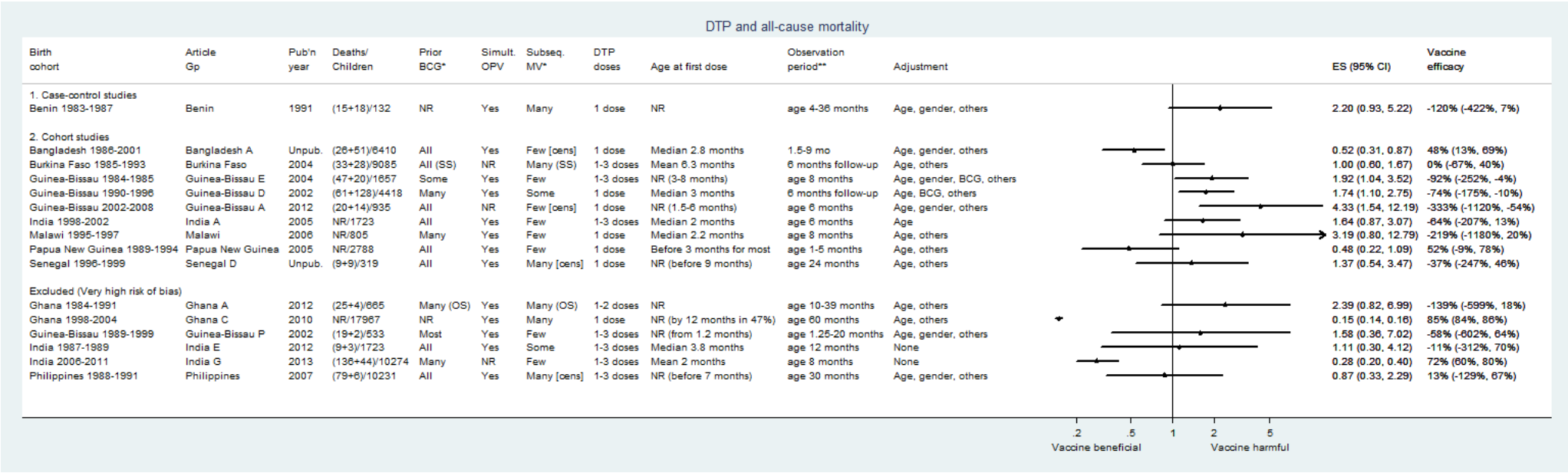
4 Is administration of DTP vaccine in infancy associated with an effect on all-cause mortality?

Fifteen cohort studies (7-9, 13-19, 24-28) and one case-control study (20) were identified that provided comparisons of DTP with no DTP. These results are presented in Figure 7. No randomized trials of DTP versus no DTP were identified. Oral polio vaccine (OPV) was administered concomitantly with DTP in most included studies; two studies did not report OPV co-administration [Burkina Faso 1985-1993, #799 (7); India 2006-2011, #9463 (15)]. Six results from the cohort studies were considered to be at very high risk of bias in relation to the effect of DTP, and are presented separately at the bottom of the forest plot.

Excluding the results considered to be at very high risk of bias, the results of the 10 studies (all considered nevertheless to be at high risk of bias) produced diverse results, ranging from a halving of mortality risk after DTP administration to a four-fold increase in mortality risk after DTP administration. The majority of studies indicated a deleterious effect of DTP on mortality. Three of these had 95% confidence intervals that excluded no effect. These were all undertaken in Guinea-Bissau [#25 (26); #9466 (8); #851 (9)]. Three of the other results were from the Guinea-Bissau investigators [Bangladesh 1986-2001 #9477 (24); Malawi 1995-1997, #664 (16); Senegal 1996-1999, #9433 (18)], two of which were re-analyses of studies undertaken by other teams [Bangladesh 1986-2001 #9477 (24); Malawi 1995-1997, #664 (16)]. Two of these suggested possible deleterious effects and one (a re-analysis of a Bangladesh study[2]) had a 95% confidence interval favouring a beneficial effect of DTP. The three studies from different investigator teams produced more equivocal

[2] The result reported by the original investigators, which was considered to be at very high risk of bias for this research question due to high rates of co-administration of DTP with BCG, was an ES (mortality rate ratio) of 0.76 (95% CI 0.67 to 0.88).

Figure 7. DTP and all-cause mortality.



Birth cohort	Article Gp	Pub'n year	Deaths/ Children	Prior BCG*	Simult. OPV	Subseq. MV*	DTP doses	Age at first dose	Observation period**	Adjustment	ES (95% CI)	Vaccine efficacy
1. Case-control studies												
Benin 1983-1987	Benin	1991	(15+18)/132	NR	Yes	Many	1 dose	NR	age 4-36 months	Age, gender, others	2.20 (0.93, 5.22)	-120% (-422%, 7%)
2. Cohort studies												
Bangladesh 1986-2001	Bangladesh A	Unpub.	(26+51)/6410	All	Yes	Few [cens]	1 dose	Median 2.8 months	1.5-9 mo	Age, gender, others	0.52 (0.31, 0.87)	48% (13%, 69%)
Burkina Faso 1985-1993	Burkina Faso	2004	(33+28)/9085	All (SS)	NR	Many (SS)	1-3 doses	Mean 6.3 months	6 months follow-up	Age, others	1.00 (0.60, 1.67)	0% (-67%, 40%)
Guinea-Bissau 1984-1985	Guinea-Bissau E	2004	(47+20)/1657	Some	Yes	Few	1-3 doses	NR (3-8 months)	age 8 months	Age, gender, BCG, others	1.92 (1.04, 3.52)	-92% (-252%, -4%)
Guinea-Bissau 1990-1996	Guinea-Bissau D	2002	(61+128)/4418	Many	Yes	Some	1 dose	Median 3 months	6 months follow-up	Age, BCG, others	1.74 (1.10, 2.75)	-74% (-175%, -10%)
Guinea-Bissau 2002-2008	Guinea-Bissau A	2012	(20+14)/935	All	NR	Few [cens]	1 dose	NR (1.5-6 months)	age 6 months	Age, gender, others	4.33 (1.54, 12.19)	-333% (-1120%, -54%)
India 1998-2002	India A	2005	NR/1723	All	Yes	Few	1-3 doses	Median 2 months	age 6 months	Age	1.64 (0.87, 3.07)	-64% (-207%, 13%)
Malawi 1995-1997	Malawi	2006	NR/805	Many	Yes	Few	1 dose	Median 2.2 months	age 8 months	Age, others	3.19 (0.80, 12.79)	-219% (-1180%, 20%)
Papua New Guinea 1989-1994	Papua New Guinea	2005	NR/2788	All	Yes	Few	1 dose	Before 3 months for most	age 1-5 months	Age, others	0.48 (0.22, 1.09)	52% (-9%, 78%)
Senegal 1996-1999	Senegal D	Unpub.	(9+9)/319	All	Yes	Many [cens]	1 dose	NR (before 9 months)	age 24 months	Age, others	1.37 (0.54, 3.47)	-37% (-247%, 46%)
Excluded (Very high risk of bias)												
Ghana 1984-1991	Ghana A	2012	(25+4)/665	Many (OS)	Yes	Many (OS)	1-2 doses	NR	age 10-39 months	Age, others	2.39 (0.82, 6.99)	-139% (-599%, 18%)
Ghana 1998-2004	Ghana C	2010	NR/17967	NR	Yes	Many	1 dose	NR (by 12 months in 47%)	age 60 months	Age, others	0.15 (0.14, 0.16)	85% (84%, 86%)
Guinea-Bissau 1989-1999	Guinea-Bissau P	2002	(19+2)/533	Most	Yes	Few	1-3 doses	NR (from 1.2 months)	age 1.25-20 months	Age, gender, others	1.58 (0.36, 7.02)	-58% (-602%, 64%)
India 1987-1989	India E	2012	(9+3)/1723	All	Yes	Some	1-3 doses	Median 3.8 months	age 12 months	None	1.11 (0.30, 4.12)	-11% (-312%, 70%)
India 2006-2011	India G	2013	(136+44)/10274	Many	NR	Few	1-3 doses	Mean 2 months	age 8 months	None	0.28 (0.20, 0.40)	72% (60%, 80%)
Philippines 1988-1991	Philippines	2007	(79+6)/10231	All	Yes	Many [cens]	1-3 doses	NR (before 7 months)	age 30 months	Age, gender, others	0.87 (0.33, 2.29)	13% (-129%, 67%)

ES = effect size (hazard ratio, rate ratio or risk ratio; odds ratio for the case-control study)
Deaths/Children = (DTP deaths + Non-DTP deaths)/Total children or Total deaths/Total children
All studies are cohort studies.
In the two studies with 'None' as adjustment for confounding, we computed unadjusted rate ratios from rates presented in the paper.
Vaccine efficacy is computed as (1 – ES) × 100%. A non-negative number describes the proportion of deaths prevented by the vaccine. A negative number reflects a higher death rate among the vaccinated. For example, if vaccine efficacy = -100%, then an *additional* 100% of the deaths that would have occurred without vaccine would occur with the vaccine.
*Prior BCG: whether children studied had received BCG. Subseq. MCV: what proportion of children were likely to receive measles vaccine during the period of observation [*cens* means this event was censored in the analysis].
SS = sometimes given simultaneously with DTP; OS = often given simultaneously with DTP.
**This is the period of observation applicable to the result presented in the forest plot, aiming to capture the effect of DTP with minimal impact of subsequent measles vaccination. The full study may have had a longer period of follow up.

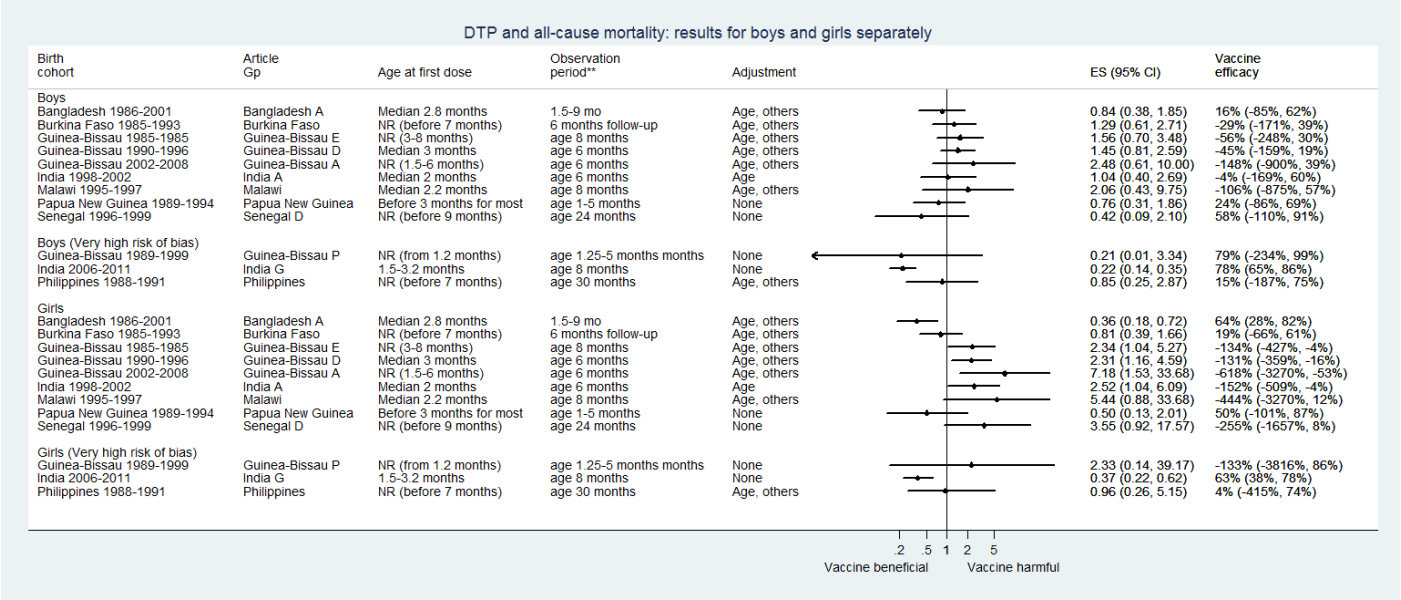
results, with one suggesting a beneficial effect of DTP [Papua New Guinea 1989-1994, #784 (17)], one providing rate ratios in the region of 1 [Burkina Faso 1985-1993, #799 (7)] and two suggesting deleterious effects [Benin 1983-1987, #9372 (20), India 1998-2002, #741 (13)].

The six studies with very high risks of bias produced highly variable results, and do not contribute to our conclusions or GRADE assessments.

4.1 Is there a difference in the effect between boys and girls?

Twelve of the 15 cohort studies provided comparisons of DTP with no DTP separately for boys and girls, including three that were regarded as being at very high risk of bias. The findings are shown in Figure 8. They broadly reflect the main findings above, but suggest that effects may be more deleterious or variable in girls. To examine the potential for differential effects between boys and girls, we need to look at the (statistical) interaction between them. Figure 9 illustrates the difference in vaccine effect between boys and girls, which is equivalent to the comparison in boy-girl mortality ratios between DTP-vaccinated and DTP-unvaccinated children[3]. One of the studies found evidence of a difference [Senegal 1996-1999, #9433 (18)], with 95% confidence intervals indicating that boys benefit more (or equivalently, boys suffer less; this analysis does not tell us about whether DTP vaccine is beneficial or deleterious). For none of the other studies was there similarly strong evidence of a difference in either direction. Four studies in Guinea-Bissau, and three others by these investigators (including the Senegal study), found a tendency for DTP to have a more beneficial effect in boys than in girls. Two of the remaining four studies observed more beneficial effects in girls, with one pointing in neither direction and one observing more beneficial effects in boys; all four were inconclusive.

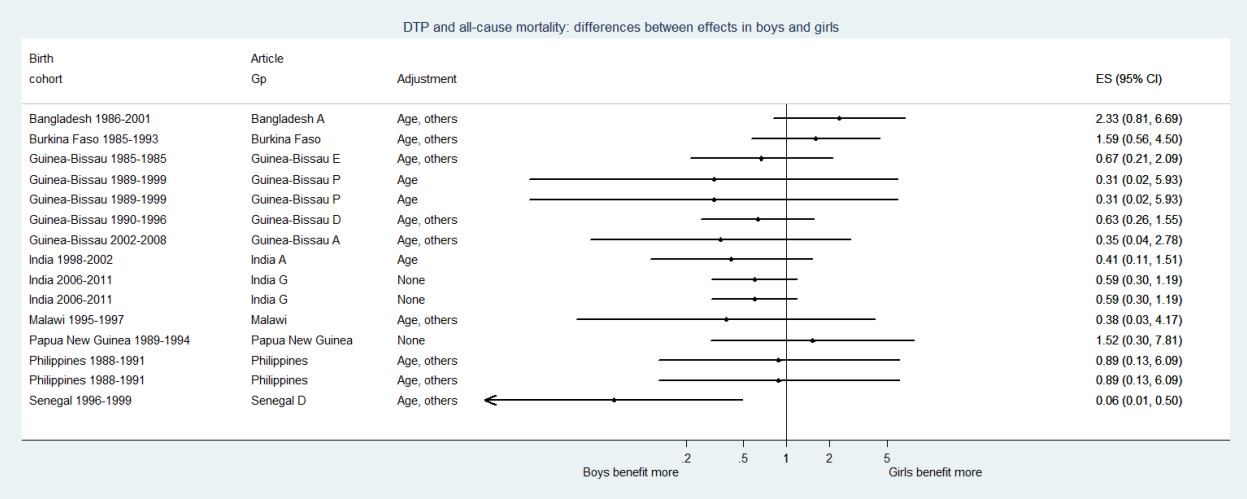
Figure 8. DTP and all-cause mortality: results for boys and girls separately.



ES = effect size (hazard ratio, rate ratio or risk ratio; odds ratio for the case-control study)
All studies are cohort studies.
**The is the period of observation applicable to the result presented in the forest plot, aiming to capture the effect of DTP with minimal impact of subsequent measles vaccination. The full study may have had a longer period of follow up.

[3] For two studies [Guinea-Bissau 1989-1999, #2622; Senegal 1996-1999; #9433], boy-girl mortality ratios are used to compute interactions rather than the data in Figure 8, since they allow adjustment for age.

Figure 9. DTP and all-cause mortality: differences between effects in boys and girls.



ES = effect size (ratio of hazard ratios, rate ratios or risk ratios)
All studies are cohort studies.
For Guinea-Bissau 1989-1999 and Senegal 1996-1999, interaction estimates are computed from male-female mortality ratios for among DTP recipients and DTP non-recipients; for all other studies they are computed from results in Figure 8.
**The is the period of observation applicable to the result presented in the forest plot, aiming to capture the effect of DTP with minimal impact of subsequent measles vaccination. The full study may have had a longer period of follow up.

4.2 Is there a difference in the effect by age?

Age at vaccination

As can be seen in Figure 7, age at vaccination was variable both within and across studies, and detailed information was not available in many studies. No studies directly reported results for different ages at DTP vaccination. Meaningful examination of differences in effect of DTP according to age at administration was therefore not possible. Further research may be warranted on this question.

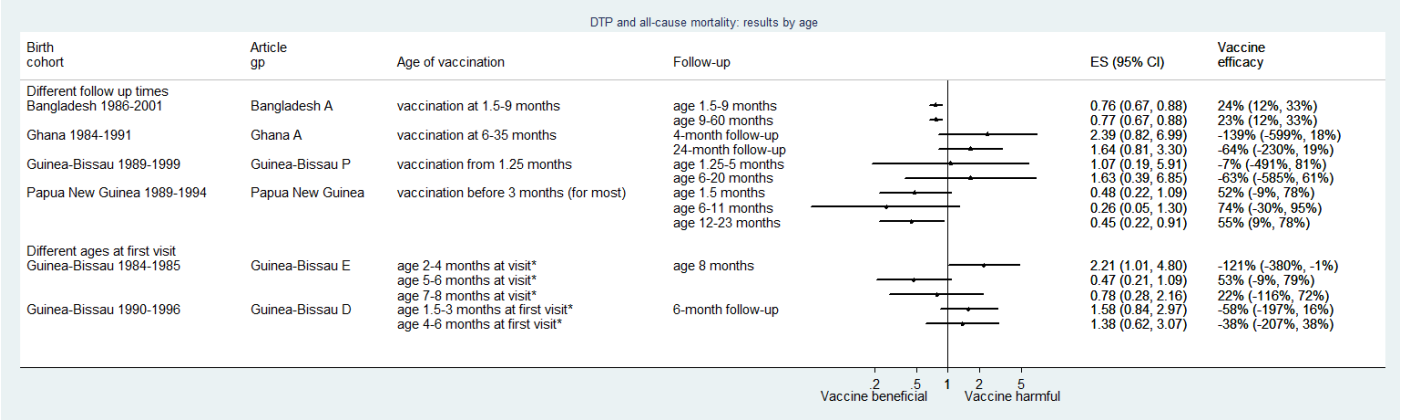
Age at follow-up

Four studies report different ages of follow-up [Bangladesh 1986-2001, #797 (6); Ghana 1984-1991, #3294 (25); Guinea-Bissau 1989-1999, #2622 (27); Papua New Guinea 1989-1994, #784 (17)]. These results are illustrated at the top of Figure 10. No consistent pattern is apparent.

Other results by age

Two studies report results by age of the child the time they were seen ('first visit' or 'visit') so the findings either reflect both age at vaccination and age at follow-up [Guinea-Bissau 1990-1996, #2726 (21)] or may be only loosely correlated with age at vaccination [Guinea-Bissau 1984-1985, #851 (9)]. Again no pattern is apparent.

Figure 10. DTP and all-cause mortality: results by age.

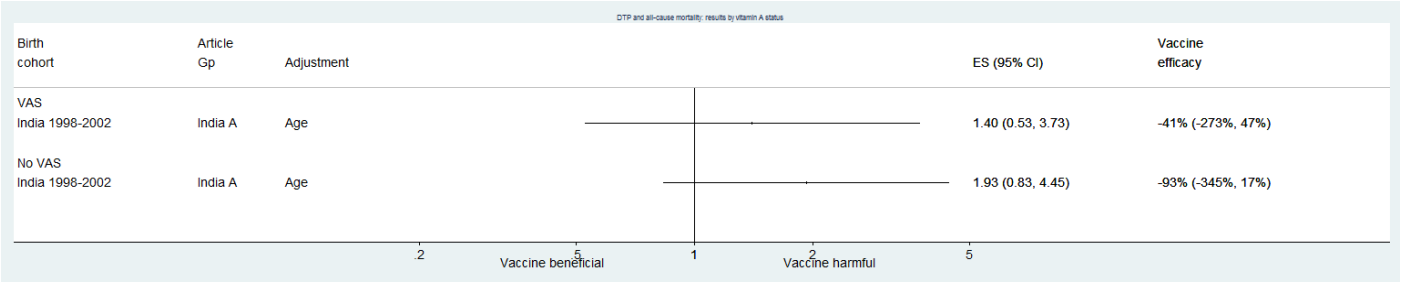


ES = effect size (hazard ratio, rate ratio or risk ratio)
All studies are cohort studies.
*When we know only the age of the children at their visit, the differences likely reflect a combination of age at vaccination and age at follow-up. For Guinea-Bissau 1984-1985, 178 children were seen more than once.

4.3 Is there a difference in the effect by vitamin A administration?

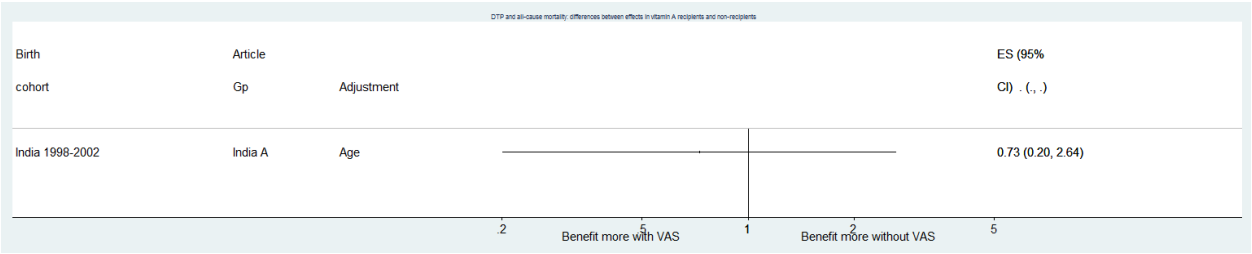
We sought results for interaction between DTP effect and (prior or concurrent) administration of vitamin A. Although results relating to the impact of vitamin A on mortality are prevalent in the literature, to understand interaction we needed either (i) the effect of DTP separately among vitamin A recipients and vitamin A non-recipients or (ii) the effect of vitamin A separately among DTP recipients and DTP non-recipients. Only one cohort study [India 1998-2002, #741 (13)] provided this information. This was based on a randomized trial of vitamin A supplementation at birth. The results are illustrated in Figure 11 and Figure 12. There is insufficient evidence concerning any difference in effect of DTP according to vitamin A status.

Figure 11. DTP and all-cause mortality: results for vitamin A recipients and vitamin A non-recipients separately.



ES = effect size (hazard ratio, rate ratio or risk ratio)
All studies are cohort studies.

Figure 12. DTP and all-cause mortality: differences between effects between vitamin A recipients and vitamin A non-recipients.



ES = effect size (ratio of hazard ratios, rate ratios or risk ratios)
All studies are cohort studies.

4.4 Comments on study methodology and bias

All of the results from observational studies were judged to be at high risk of bias or very high risk of bias, so all the findings above should be interpreted with caution. Full methodological details and assessments of risk of bias are included in Annex C. We re-emphasize here that DTP was almost always given with OPV, and the findings should be interpreted in that context.

There were 10 observational studies with slightly lesser methodological concerns. All of these were regarded as at risk of bias due to confounding (inherent differences in vaccinated and unvaccinated children). Although most results were adjusted for some confounding factors, only one study addressed a measure from each of our four pre-specified domains of confounding (health of the child, socio-economic status, age and gender), and this was achieved in part by matching children in a case-control design [Benin 1983-1987, #9372 (20)]. Only one further study adjusted for the first three domains [Burkina-Faso 1985-1993, #799 (7)]. Three studies adjusted for a measure of health status of the child [Benin 1983-1987, #9372 (20); Burkina-Faso 1985-1993, #799 (7); Guinea-Bissau 2002-2008, #25 (26)]. Six studies included a measure of socio-economic status [Bangladesh 1986-2001, #9477 (24); Benin 1983-1987, #9372 (20); Burkina-Faso 1985-1993, #799 (7); Guinea-Bissau 1990-1996, #9466 (8); Guinea-Bissau 1984-1985, #851 (9); Senegal 1996-1999, #9433 (18)], mostly using a measure of geographic location.

Four studies were considered to be at risk of bias because children were recruited after vaccines had been given (and hence after the vaccine could have impacted on mortality). In the Burkina-Faso study, children had to survive until the first visit (up to 7 months of age) to be included in the 'landmark approach' analysis, which we selected in preference to the 'retrospective approach' analysis [Burkina-Faso 1985-1993, #799 (7)]. However, we considered this to be at risk of bias

because any child who died before the first visit was unable to contribute to the analysis, as well as misclassification bias (since some children who were vaccinated between visits did not have their status updated). The latter would lead to bias towards the null, which is the reason it is selected in preference to the 'retrospective approach', but the former was considered to lead to a more serious risk of bias, having the potential to switch the direction of effect. In three Guinea-Bissau studies, children were included only if they were seen at a date subsequent to most DTP vaccinations, again raising the risk of bias [Guinea-Bissau 2002-2008, #25 (26); Guinea-Bissau 1990-1996, #9466 (8); Guinea-Bissau 1984-1985, #851 (9)].

Potential for misclassification bias was identified in six further results which made assumptions about non-vaccination of children in the absence of concrete information [Burkina-Faso 1985-1993, #799 (7); Guinea-Bissau 1990-1996, #9466 (8); Guinea-Bissau 1984-1985, #851 (9); India 1998-2002, #741 (13); Malawi 1995-1997, #664 (16); Senegal 1996-1999, #9433 (18)]. One of these also used vaccination information that was updated retrospectively, although the interval between visits to children was short (at two weeks) so this would be unlikely to be very problematic [India 1998-2002, #741 (13)]. In most of the studies, we also had concerns about the possibility of co-interventions (post-vaccination differences between vaccinated and non-vaccinated children), particularly in relation to subsequent measles vaccination. This would be more serious for studies with longer follow-up. Although some studies censored subsequent measles vaccination, we considered this to introduce a different risk of bias because measles vaccination is potentially related to both DTP vaccination and to mortality risk (often known as 'informative censoring').

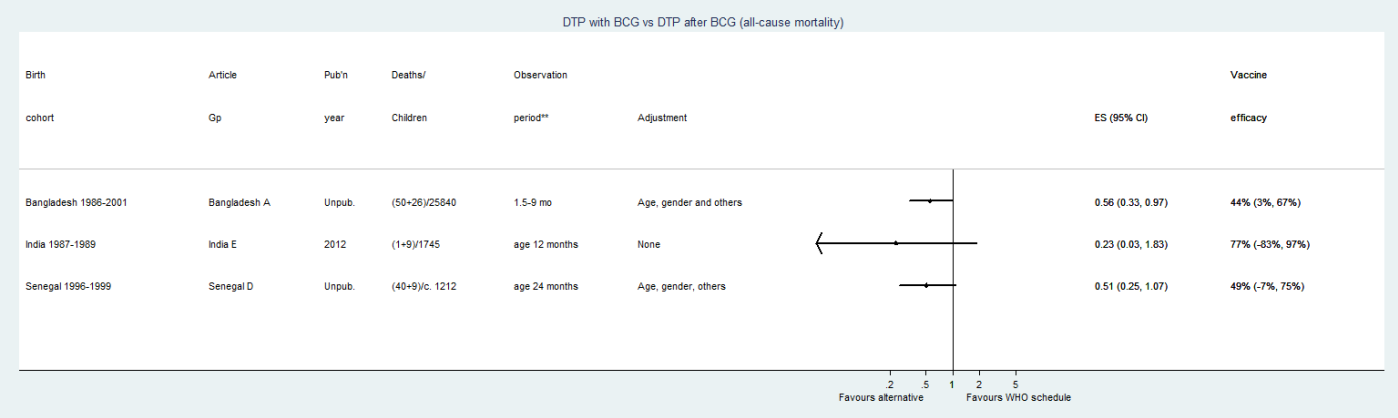
The six 'very high' risk of bias studies were seriously affected by co-administration of BCG [Ghana 1984-1991, #3294 (25)], high correlation between BCG, DTP and measles vaccines [Ghana 1998-2004, #9464 (19)], starting follow-up after DTP vaccination [Ghana 1984-1991, #3294 (25); Guinea-Bissau 1989-1999, #2622 (27); Philippines 1988-1991, #555 (28)], restricting the sample according to measles vaccination [Guinea-Bissau 1989-1999, #2622 (27)], and strong confounding by age [India 1987-1989, #8996 (14); India 2006-2011, #9463 (15)]. Some of these studies had additional reasons for concern (including a possibility that vaccination could be seriously misclassified for children who had died), but for which we were unable to make a firm judgement from the written reports.

We regard the estimates of interaction (for differences by gender and vitamin A) to be less affected by bias, since many of the biases affecting direct estimates of vaccine effects are likely to cancel out when these are contrasted between boys and girls or between vitamin A recipients and vitamin A non-recipients.

5 Does co-administration of BCG and DTP affect all-cause mortality?

Three studies provided results for the comparison of DTP given *simultaneously* with BCG against the current WHO recommendation of DTP after BCG [Bangladesh 1986-2001, #9477 (24); India 1987-1989, #8996 (14); Senegal 1996-1999, #9433 (18)] and these are presented in Figure 13. All results were reported by the Guinea-Bissau investigators; two of them were adjusted for age differences as well as other potential differences between children receiving the different schedules. The three results would suggest that simultaneous administration may be associated with lower mortality; one of them had a 95% confidence interval that excluded 'no difference'.

Figure 13. Sequence of DTP and BCG and all-cause mortality: simultaneous administration of DTP and BCG compared with BCG before DTP.

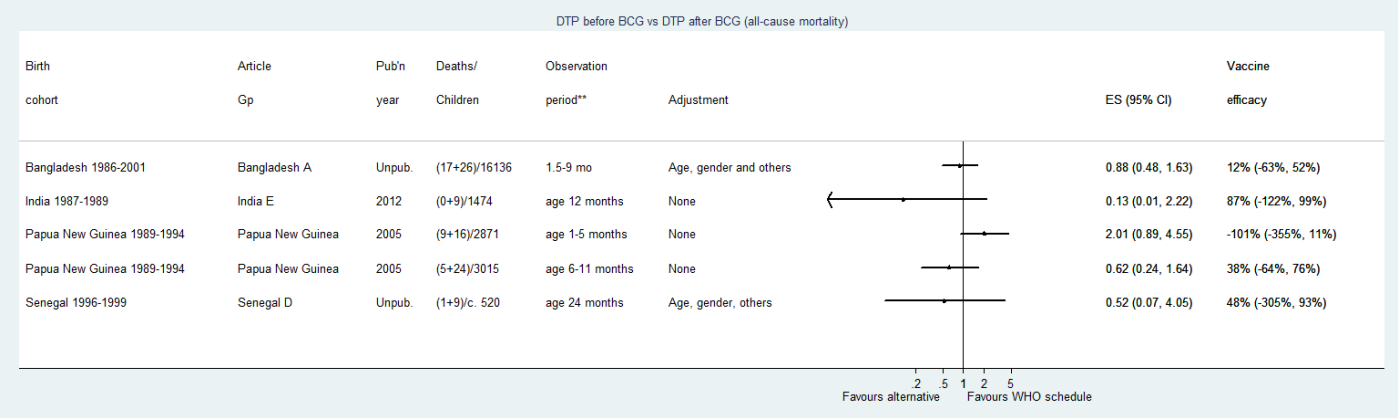


ES = effect size (hazard ratio, rate ratio or risk ratio)
Deaths/Children = (Deaths simultaneous + Deaths WHO recommended)/Total children or Total deaths/Total children
All studies are cohort studies.

6 Does order of BCG and DTP affect all-cause mortality?

Three studies reported results for the comparison of DTP given *before* BCG against the current WHO recommendation of DTP after BCG [Bangladesh 1986-2001, #9477 (24); India 1987-1989, #8996 (14); Senegal 1996-1999, #9433 (18)]. A fourth study reported on DTP vaccine given *before or with* BCG versus the current WHO recommendation [Papua New Guinea 1989-1994, #784 (17)]. We present these results, including two different periods of observation for Papua New Guinea, in Figure 14. No clear differences are apparent.

Figure 14. Sequence of DTP and BCG and all-cause mortality: administration of DTP before BCG compared with BCG before DTP.



ES = effect size (hazard ratio, rate ratio or risk ratio)
Deaths/Children = (Deaths reverse order + Deaths WHO recommended)/Total children or Total deaths/Total children
All studies are cohort studies.

7 Is administration of measles containing vaccine in infancy associated with an effect on all-cause mortality?

Four randomized trials (29-32), 22 cohort studies (6, 14-19, 21, 25, 33-44) and two case-control studies (20, 45) were identified that provided comparisons of mortality among children who had or had not received measles vaccine. These results are presented in Figure 15. Six results from the cohort studies were considered to be at very high risk of bias in relation to the effect of measles vaccine, and are presented separately at the bottom of the forest plot.

From the randomized trials in Guinea-Bissau, we present results for mortality up to 9 months, at which point all three administered measles vaccine in the control group. Due to the short follow-up, the numbers of deaths were low and the findings inconclusive. Directions of effect in these trials, as well as the fourth trial in Nigeria, pointed towards a beneficial effect of measles vaccine.

Excluding the results considered to be at very high risk of bias, the results of the 18 non-randomized studies (all considered nevertheless to be at high risk of bias) consistently observed effects indicating a beneficial effect of measles vaccine on mortality. For 11 of these, the 95% confidence interval excluded no effect. Estimated effects are in the region of a halving of mortality risk. Again, most of the analyses were undertaken by the Guinea-Bissau investigators.

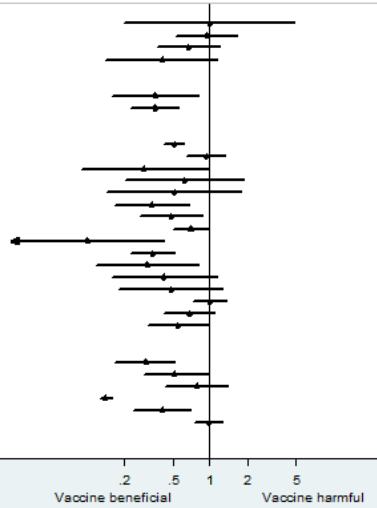
The six studies with very high risks of bias produced variable results. Their results however point in the same direction as all the other studies: of a beneficial effect of measles vaccine on overall mortality.

As noted in the Background, we present here the data on all-cause mortality, rather than an examination of the 'non-specific effects' of measles vaccine on deaths from causes other than measles. In populations with very high coverage of measles vaccine, deaths from measles should be infrequent. In Annex D we present the results we extracted where measles deaths had been removed or censored. They suggest that if these effects are real then they are not fully explained by deaths that were established as due to measles.

Figure 15. Measles vaccine and all-cause mortality.

Measles vaccine and all-cause mortality

Birth cohort	Article Gp	Pub'n year	Deaths/ Children	Prior BCG*	Prior DTP*	Age at first dose	Observation period**	Adjustment	ES (95% CI)	Vaccine efficacy
1. Randomized trials										
Guinea-Bissau 1989-1999	Guinea-Bissau H	2003	(3+3)/300	NR	Many	6 months	age 6-9 months	None	1.00 (0.20, 4.91)	0% (-392%, 80%)
Guinea-Bissau 1989-1999	Guinea-Bissau S	2007	(42+40)/8511	NR	Many	6 months	age 6-9 months	None	0.94 (0.53, 1.67)	6% (-67%, 47%)
Guinea-Bissau 2002-2008	Guinea-Bissau C	2010	(16+48)/6417	NR	All	4.5 months	age 4.5-9 months	Age	0.67 (0.38, 1.19)	33% (-19%, 62%)
Nigeria c.1961	Nigeria	1963	(5+12)/1962	NR	NR	6-24 months	6-20 months follow-up	None	0.41 (0.14, 1.15)	59% (-15%, 86%)
2. Case-control studies										
Benin 1983-1987	Benin	1991	(12+49)/252	Many	Many	NR	age 4-36 months	Age, gender, others	0.36 (0.16, 0.81)	64% (19%, 84%)
India 1991-1998	India F	2003	(252+66)/636	Most	Most	NR (before 12 months)	age 12-60 months	None	0.36 (0.23, 0.56)	64% (44%, 77%)
3. Cohort studies										
Bangladesh 1977-1985	Bangladesh B	2003	(170+321)/16268	Some	Some	NR (from 9 months)	age 9-60 months	Age, gender, others	0.51 (0.42, 0.62)	49% (38%, 58%)
Bangladesh 1986-2001	Bangladesh A	2004	NR/36660	Many	Many	NR (from 9 months)	age 9-60 months	Age, gender, BCG, DTP, others	0.93 (0.65, 1.34)	7% (-34%, 35%)
DR Congo 1973-1975	DR Congo	1981	(3+21)/c.600	NR	NR	Mean 8.8 months	age 7-21 months	None	0.29 (0.09, 0.98)	71% (2%, 91%)
Guinea-Bissau 1978-1983	Guinea-Bissau T	1984	(7+5)/c.210	NR	NR	NR (6-35 months)	13 months follow-up	None	0.62 (0.20, 1.88)	38% (-88%, 80%)
Guinea-Bissau 1978-1983	Guinea-Bissau L	1984	(3+8)/99	NR	NR	NR (6-35 months)	12 months follow-up	Age	0.51 (0.15, 1.81)	49% (-81%, 86%)
Guinea-Bissau 1984-1985	Guinea-Bissau M	1990	NR/722	NR	NR	Median 11.1; 15 months	age 17.5 months or more	Age, gender, others	0.34 (0.17, 0.68)	66% (32%, 83%)
Guinea-Bissau 1990-1996	Guinea-Bissau D	2000	(19+94)/4230	Many	Many	Median 10.6 months	age 7-19 months	Age, BCG	0.48 (0.27, 0.87)	52% (13%, 73%)
Guinea-Bissau 1999-2002	Guinea-Bissau G	Unpub.	(65+137)/10112	Many	Many	NR (by 12 mo in 55%)	age 9-24 months	Age	0.70 (0.50, 0.98)	30% (2%, 50%)
Haiti 1981-1982	Haiti	1990	NR/1381	NR	NR	Median 9 months	age 9-39 months	None	0.10 (0.02, 0.42)	90% (58%, 98%)
India 1986-1991	India C	1998	(94+37)/12034	Most	Most	NR (at 6-8 [8-11] mo in 85% [15%])	age 12-60 months	Age, gender	0.34 (0.23, 0.51)	66% (49%, 77%)
India 1987-1989	India E	2012	NR/3883	Many	Many	Median 9.4 months	age 12-60 months	None	0.31 (0.12, 0.80)	69% (20%, 88%)
Malawi 1995-1997	Malawi	2006	NR/669	Most	Most	Median 10.8 months	age 9-18 months	Age, others	0.42 (0.16, 1.14)	58% (-14%, 84%)
Papua New Guinea 1989-1994	Papua New Guinea	2005	NR/4048	All	Many	NR (by 12 months in 74%)	age 6-11 months	Age, DTP, others	0.48 (0.18, 1.26)	52% (-26%, 82%)
Senegal 1985-1987	Senegal A	1993	(53+124)/2030	NR	NR	Mean 15.8 months	age 9-24 months	None	0.99 (0.72, 1.37)	1% (-37%, 28%)
Senegal 1987-1989	Senegal B	1993	(31+34)/1159	NR	NR	Mean 11.6 months	age 9-24 months	None	0.68 (0.42, 1.10)	32% (-10%, 58%)
Senegal 1996-1999	Senegal D	Unpub.	(13+372)/4133	Some	Some	NR (by 12 [24] mo in 9% [20%])	age 24 months	Age, gender, others	0.55 (0.31, 0.98)	45% (2%, 69%)
Excluded (Very high risk of bias)										
Burundi 1984-1988	Burundi	1994	(16+66)/1899	NR	NR	NR (at 9-11 months in 59%)	6 months follow-up	None	0.30 (0.17, 0.52)	70% (48%, 83%)
Ghana 1984-1991	Ghana A	2012	(17+27)/1793	Many	All (OS)	NR (6-35 months)	4 months follow-up	Age, others	0.51 (0.29, 0.97)	49% (3%, 71%)
Ghana 1994-1999	Ghana B	2001	NR/17701	All	All	Median 9.1 months	age 9-11 months	None	0.78 (0.43, 1.41)	22% (-41%, 57%)
Ghana 1998-2004	Ghana C	2010	NR/17987	Many	Many	NR (by 12 [24] mo in 5% [64%])	age 60 months	Age, others	0.14 (0.13, 0.16)	86% (84%, 87%)
India 2006-2011	India G	2013	(58+17)/11390	Many	Many	Mean 9.4 months	age 9-15 months	None	0.41 (0.24, 0.70)	59% (30%, 76%)
Senegal 1989-1996	Senegal C	2005	(20+35)/7796	Many	Many	Median 9.7 months	age up to 24 months	None	0.98 (0.75, 1.27)	2% (-27%, 25%)

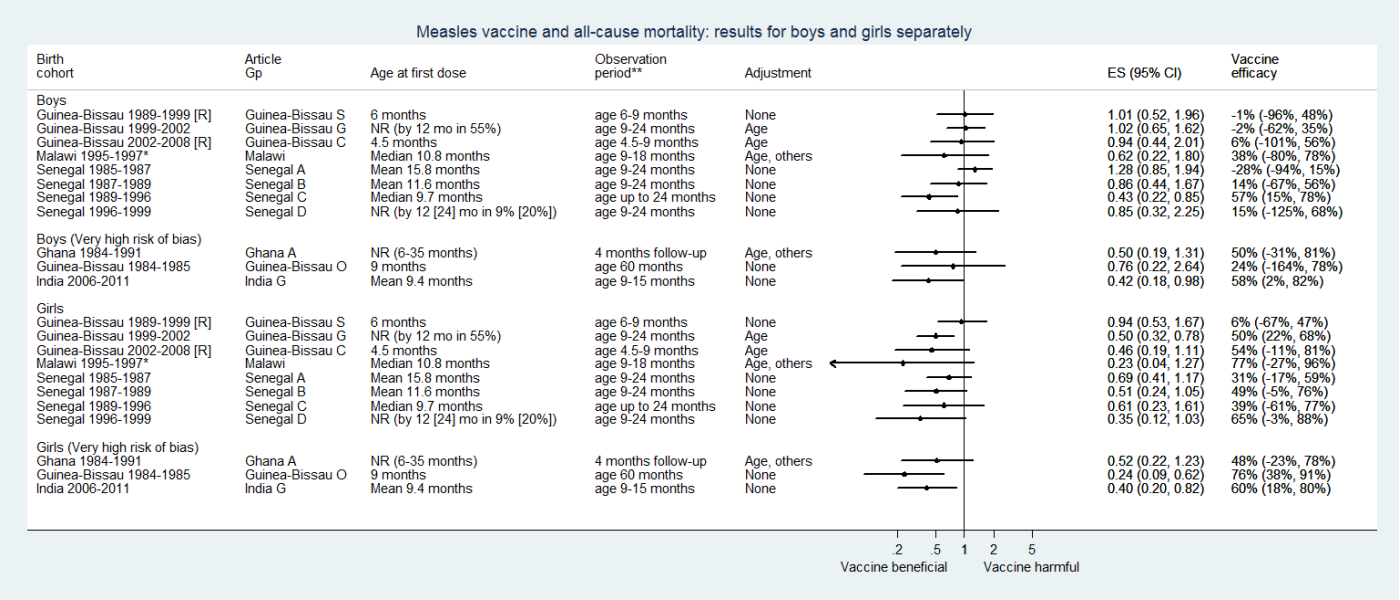


ES = effect size (hazard ratio, rate ratio or risk ratio; odds ratio for the case-control studies)
Deaths/Children = (Measles vaccine deaths + Non-measles vaccine deaths)/Total children or Total deaths/Total children
In most observational studies with 'None' as adjustment for confounding, we computed unadjusted rate ratios from rates presented in the paper.
Vaccine efficacy is computed as (1 – ES) × 100%. A non-negative number describes the proportion of deaths prevented by the vaccine. A negative number reflects a higher death rate among the vaccinated. For example, if vaccine efficacy = -100%, then an *additional* 100% of the deaths that would have occurred without vaccine would occur with the vaccine.
*Prior BCG: whether children studied had received BCG. Prior DTP: whether children studied had received DTP.
OS = often given simultaneously with DTP.
**This is the period of observation applicable to the result presented in the forest plot. The full study may have had a longer period of follow up.

7.1 Is there a difference in the effect between boys and girls?

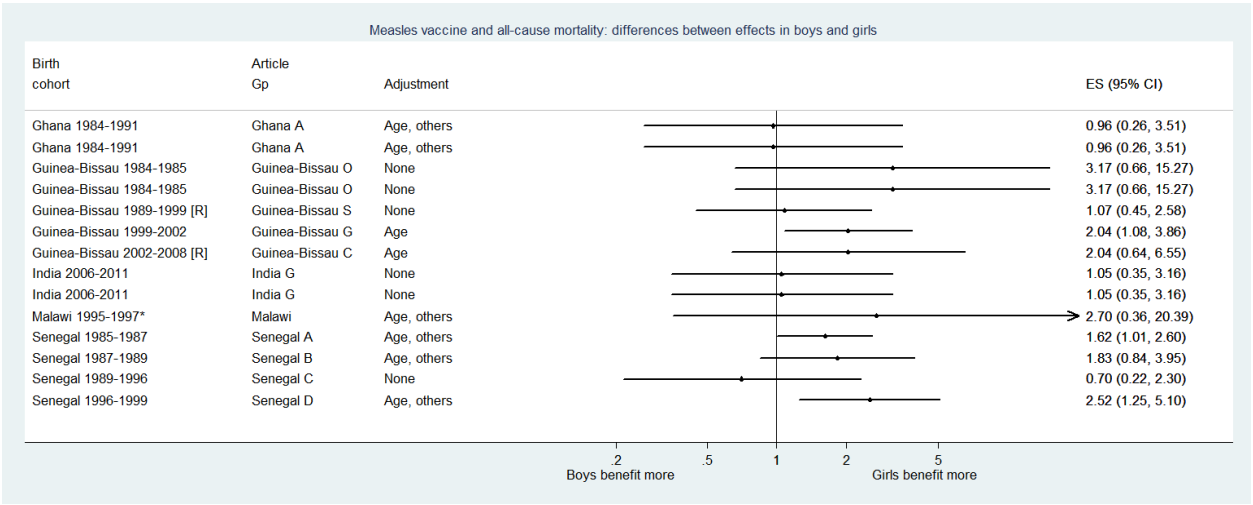
Nine of the cohort studies and two randomized trials provided comparisons of measles vaccine with no measles vaccine separately for boys and girls; three of the cohort studies were considered to be at very high risk of bias. The findings are shown in Figure 16. Effects of the vaccine in girls appear to be more beneficial than in boys. Figure 17 illustrates the difference in vaccine effect between boys and girls, which is equivalent to the comparison in boy-girl mortality ratios between measles-vaccinated and measles-unvaccinated children[4]. Three of the studies found statistical evidence of a difference, indicating that girls benefit more. The other studies did not find convincing evidence in either direction.

Figure 16. Measles vaccine and all-cause mortality: results for boys and girls separately.



ES = effect size (hazard ratio, rate ratio or risk ratio)
R = Randomized trial (all other studies are cohort studies)
*Results from an analysis with vaccination status updated retrospectively. In an analysis with vaccination status updated prospectively (the preferred landmark approach) there were no deaths among the girls, so interaction cannot be computed along with a confidence interval. Among the boys, the MRR was 0.66 (95% CI 0.22, 2.03)
**The is the period of observation applicable to the result presented in the forest plot. The full study may have had a longer period of follow up.

Figure 17. Measles vaccine and all-cause mortality: differences between effects in boys and girls.



ES = effect size (hazard ratio, rate ratio or risk ratio)
R = Randomized trial (all other studies are cohort studies)
*Results from analysis with vaccination status updated retrospectively.

[4] For three studies [Senegal 1985-1987 and 1987-1989, #6904; Senegal 1996-1999, #9433], boy-girl mortality ratios are used to compute interactions rather than the data in Figure 16, since they allow for adjustment for age.

7.2 Is there a difference in the effect by age?

Age at vaccination

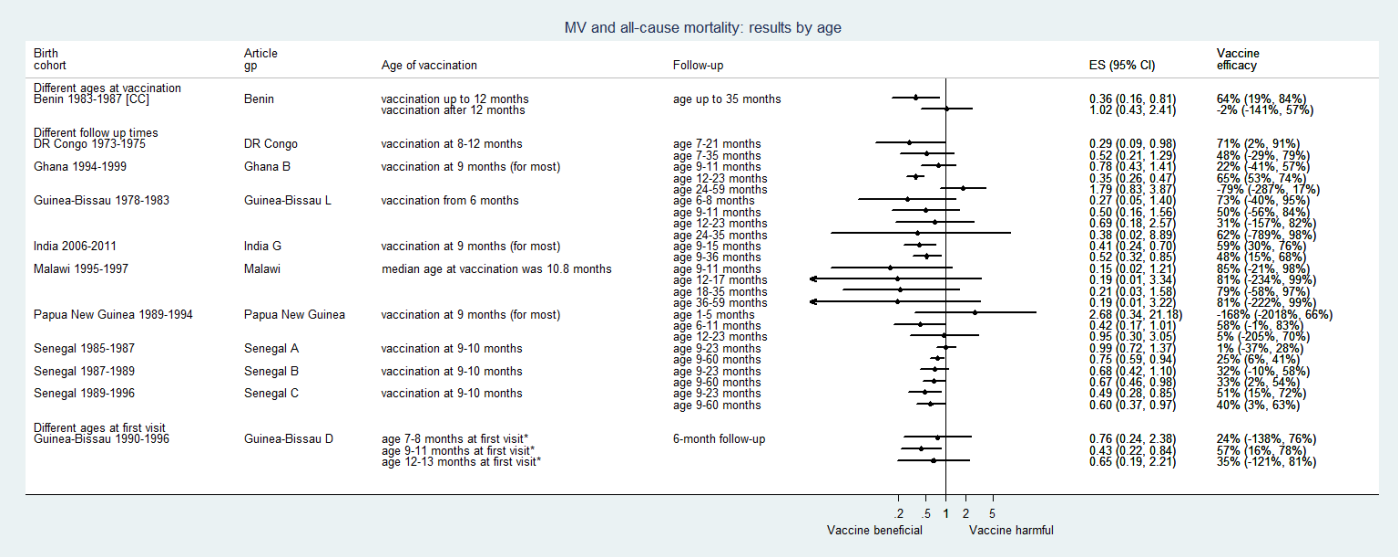
As can be seen in Figure 15, age at vaccination was not always reported. Where vaccination ages were available, they ranged from 4.5 months in one of the randomized trials to a median of 15.8 months in one of the cohort studies. Vaccination typically took place shortly after children were 9 months old. Meaningful examination of differences in effect of measles vaccination according to age at administration was not possible from these results. One case-control study reported effects separately for children vaccinated before 12 months and after 12 months, shown at the top of Figure 18.

The three randomized trials involving early measles vaccination (at 4.5 or 6 months) included vaccination for all children at 9 months, so a comparison of early versus later vaccination is not offered by these trials. Another included article provided some relevant information, although the results were not included formally in the review because our eligibility criteria did not include direct comparisons of ages at vaccination: in the Guinea-Bissau 1978-1983 cohort (46), a comparison of mortality after vaccination at age 4-8 months with vaccination at age 9-11 months suggested a more beneficial effect in the earlier period. Further research may be warranted on the question of age at measles vaccination.

Age at follow-up

Figure 18 presents results for different follow-up periods in nine studies. The Figure also includes results for a study that provided effect estimates for children entering the study at different ages. No consistent patterns are discernible across these findings.

Figure 18. Measles vaccine and all-cause mortality: results by age.

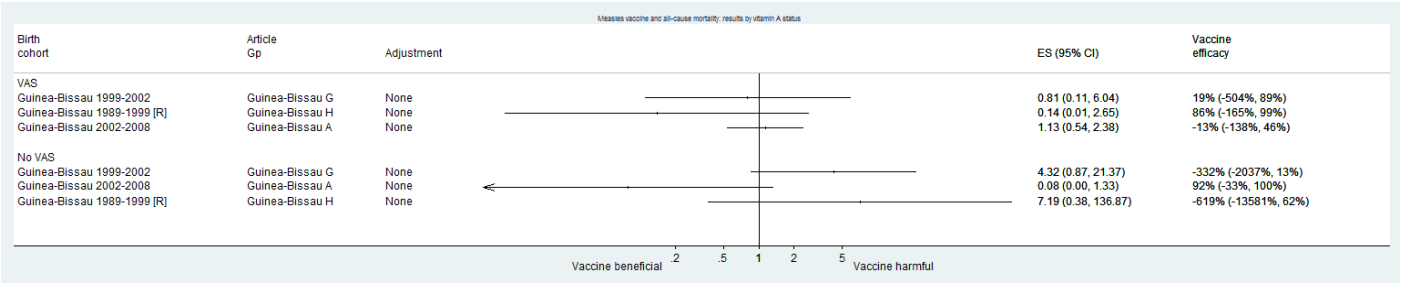


ES = effect size (hazard ratio, rate ratio or risk ratio)
CC = Case-control study (all others studies are cohort studies).
*When we know only the age of the children at their first visit, the differences likely reflect a combination of age at vaccination and age at follow-up.

7.3 Is there a difference in the effect by vitamin A administration?

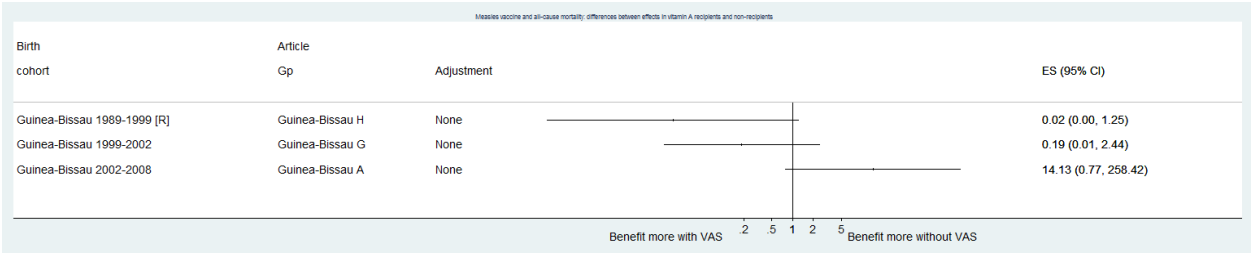
We identified three studies providing results for interaction between measles vaccination and (prior or concurrent) administration of vitamin A. The vaccine effects are presented separately for vitamin A recipients and non-recipients in Figure 19, and the differences between them are given in Figure 20. There is no consistent message across these studies concerning a difference in effect of measles vaccine according to vitamin A status.

Figure 19. Measles vaccine and all-cause mortality: results for vitamin A recipients and vitamin A non-recipients separately.



ES = effect size (hazard ratio, rate ratio or risk ratio)
R = Randomized trial (all other studies are cohort studies)

Figure 20. Measles vaccine and all-cause mortality: differences between effects between vitamin A recipients and vitamin A non-recipients.



ES = effect size (hazard ratio, rate ratio or risk ratio)
R = Randomized trial (all other studies are cohort studies)

7.4 Comments on study methodology and bias

All of the results from observational studies were judged to be at high risk of bias or very high risk of bias, so all the findings above should be interpreted with caution. As for the other vaccines, the main potential sources of bias were confounding (again an important issue for all studies); bias arising from selection of participants some time after vaccines had been administered; misclassification bias relating to ascertainment of vaccination status; and differences between groups with regard to DTP administration. For instance, among the 18 observational studies that were at slightly lesser risk of bias, four were restricted to children observed at a time point after measles vaccinations had taken place, raising the possibility of selection bias [Guinea-Bissau 1990-1996, #2726 (21); Guinea-Bissau 1999-2002, #9441 (37); Haiti 1981-1982, #7013 (41); India 1986-1991, #6720 (42)]. Three results made assumptions about non-vaccinated children [Guinea-Bissau 1990-1996, #2726 (21); India 1987-1989, #8996 (14); Malawi 1995-1997, #664 (16)]. Information about potential co-interventions between administration of measles vaccine and the end of the follow-up period was seldom available.

The very high risk of bias studies were seriously affected by recruiting children long after their vaccinations [Burundi 1984-1988, #6889 (34)]; strong confounding by DTP and/or BCG administration [Ghana 1984-1991, #3294 (25); Ghana 1998-2004, #9464 (19); Senegal 1989-1996, #740 (44)] or by age [India 2006-2011, #9463] and various problems caused by visits to children being annual [Ghana 1994-1999, #7190]. Some of these studies had additional reasons for serious concern, but for which we were unable to make a judgement from the written reports.

We regard the estimates of interaction (for differences by gender and vitamin A) to be less affected by bias, since many of the biases affecting direct estimates of vaccine effects are likely to cancel out when these are contrasted between boys and girls or between vitamin A recipients and vitamin A non-recipients.

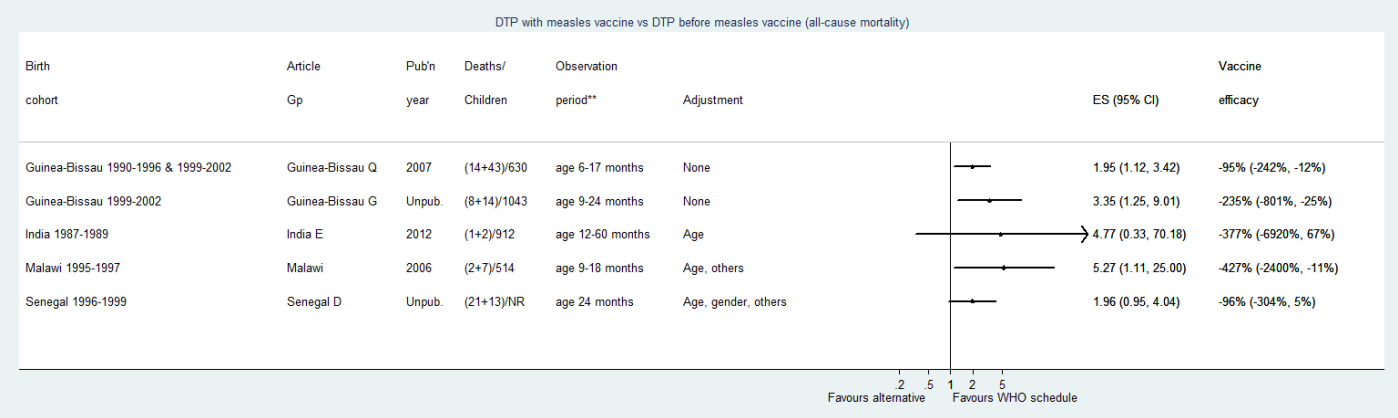
For full details of methodological features and assessments of risk of bias, see Annex C.

8 Does co-administration of DTP and measles vaccine affect all-cause mortality?

Five studies provided results for the comparison of DTP given *simultaneously* with measles vaccine against the current WHO recommendation of measles vaccine after DTP and these are presented in Figure 21 [combined analysis of Guinea-Bissau 1990-1996 and 1999-2002, #2218 (47); Guinea-Bissau 1999-2002, #9442 (48); India 1987-1989, #8996 (14); Malawi, #664 (16); Senegal 1996-1999, #9433 (18)]. All results were reported by the Guinea-Bissau investigators; three of them

were adjusted for age differences and two of these also for other potential differences between children receiving the different schedules. The five results would suggest that simultaneous administration may be associated with higher mortality.

Figure 21. Sequence of DTP and measles vaccine and all-cause mortality: simultaneous administration of DTP and measles vaccine compared with DTP before measles vaccine.

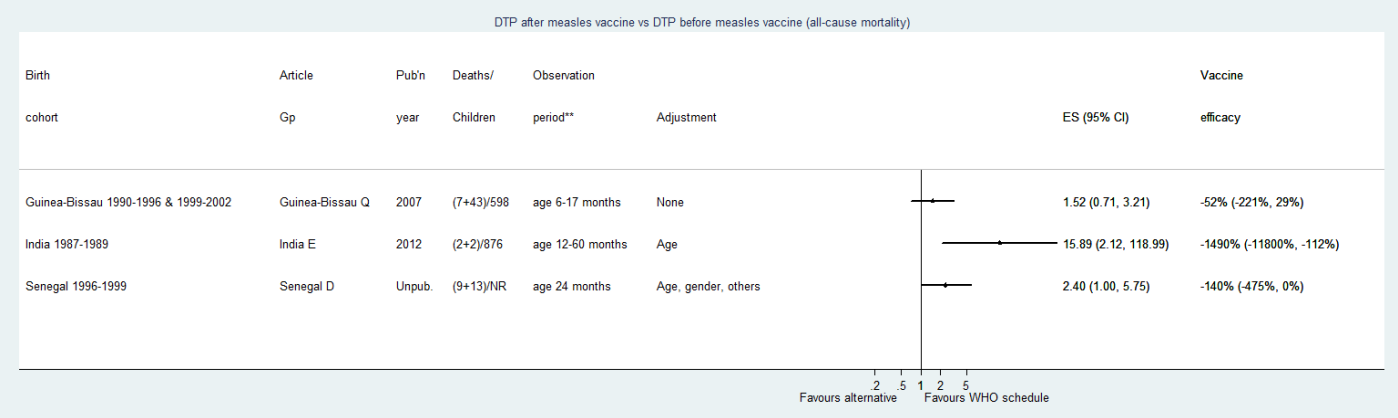


ES = effect size (hazard ratio, rate ratio or risk ratio)
Deaths/Children = (Deaths simultaneous + Deaths WHO recommended)/Total children or Total deaths/Total children
All studies are cohort studies.

9 Does order of DTP and measles vaccine affect all-cause mortality?

Three studies reported results for the comparison of DTP given *after* measles vaccine against the current WHO recommendation of DTP before measles vaccine [combined analysis of Guinea-Bissau 1990-1996 and 1999-2002, #2218 (47); India 1987-1989, #8996 (14); Senegal 1996-1999, #9433 (18)]. We present these results in Figure 22. The three results would suggest that giving DTP after measles vaccine may be associated with higher mortality.

Figure 22. Sequence of DTP and measles vaccine and all-cause mortality: administration of DTP after measles vaccine compared with DTP before measles vaccine.



ES = effect size (hazard ratio, rate ratio or risk ratio)
Deaths/Children = (Deaths reverse order + Deaths WHO recommended)/Total children or Total deaths/Total children
All studies are cohort studies.

10 Summary of the evidence

Here we present GRADE assessments, including summary conclusions, for the seven comparisons addressed in the report. Because in each case a large majority of the included evidence is from non-randomized studies, the starting point for each assessment is a score of 2 (equivalent to the interpretation 'Our confidence in the estimate of the effect on the health outcome is limited'). The score can be decreased or increased according to specific factors. In no instance did we regard it appropriate to increase the score, and in most instances we had less confidence so assigned a score of 1 (equivalent to the interpretation 'We have very little confidence in the estimate of the effect on the health outcome').

Does administration of BCG vaccine in infancy affect all-cause mortality?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		14 studies (5 trials, 9 observational)[1]	2
	Factors decreasing confidence	Limitation in study design	Serious[2]	(0)
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1
		Imprecision	None serious	0
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Large effect[5]	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			1
Summary of findings	**Statement on quality of evidence**			We have very little confidence in the evidence about the effect of BCG vaccine on all-cause mortality.
	Conclusion			BCG vaccine may reduce risk of all-cause mortality.

[1]Excluding studies assessed to be at very high risk of bias.
[2]Addressed by starting score of 2.
[3]Large proportion of studies from one region in West Africa; short follow-up used in randomized trials.
[4]Many confidence intervals were compatible with higher, unchanged and lower risk of mortality. [5]Typical rate ratio in the region of 50% reduction.

Does administration of DTP* vaccine in infancy affect all-cause mortality?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		10 observational studies[1]	2
	Factors decreasing confidence	Limitation in study design	Serious[2]	(0)
		Inconsistency	Very serious[3]	–1
		Indirectness	Serious[4]	(0)
		Imprecision	Serious[5]	(0)
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Not demonstrated	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			1
Summary of findings	**Statement on quality of evidence**			We have very little confidence in the evidence about the effect of DTP vaccine on all-cause mortality.
	Conclusion			Insufficient evidence to draw a conclusion about the effect of DTP vaccine on all-cause mortality.

*DTP was nearly always administered with OPV.
[1]Excluding studies assessed to be at very high risk of bias.
[2]Addressed by starting score of 2.
[3]Inconsistent directions of effect.
[4]Large proportion of studies from one region in West Africa.
[5]Many confidence intervals were compatible with higher, unchanged and lower risk of mortality.

Does simultaneous administration of DTP and BCG vaccine in infancy affect all-cause mortality (compared with BCG followed by DTP)?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		3 observational studies	2
	Factors decreasing confidence	Limitation in study design	Serious[1]	(0)
		Inconsistency	None serious	0
		Indirectness	Serious[2]	(0)
		Imprecision	Serious[3]	-1
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Large effect[4]	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			1
Summary of findings	**Statement on quality of evidence**			We have very little confidence in the evidence about the effect of simultaneous administration of DTP and BCG vaccines on all-cause mortality.
	Conclusion			Simultaneous administration of DTP and BCG vaccines may reduce risk of all-cause mortality compared with BCG followed by DTP.

[1]Addressed by starting score of 2.
[2]Two of the three studies from one region in West Africa.
[3]Only three studies (135 deaths).
[4]Typical rate ratio in the region of 50% reduction.

Does administration of DTP before BCG vaccine in infancy affect all-cause mortality (compared with BCG followed by DTP)?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		4 observational studies[1]	2
	Factors decreasing confidence	Limitation in study design	Serious[2]	(0)
		Inconsistency	None apparent	0
		Indirectness	Not apparent	0
		Imprecision	Serious[3]	–1
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Not demonstrated	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			1
Summary of findings	**Statement on quality of evidence**			We have very little confidence in the evidence about the effect of ordering of DTP and BCG vaccines on all-cause mortality.
	Conclusion			Insufficient evidence to draw a conclusion about the effect of order of administration of BCG and DTP vaccines on all-cause mortality.

[1]Including one study with DTP vaccine given *before or with* BCG, for which we presented two time periods in the forest plot.
[2]Addressed by starting score of 2.
[3]Only five studies (116 deaths); confidence intervals were compatible with higher, unchanged and lower risk of mortality.

Does administration of measles vaccine in infancy affect all-cause mortality?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		22 studies (4 trials, 18 observational)[1]	2
	Factors decreasing confidence	Limitation in study design	Serious[2]	(0)
		Inconsistency	None serious	0
		Indirectness	None serious[3]	(0)
		Imprecision	None serious	0
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Large effect[4]	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			2
Summary of findings	**Statement on quality of evidence**			Our confidence in the effect of measles vaccine on all-cause mortality is limited.
	Conclusion			Measles vaccine may reduce risk of all-cause mortality (an effect that appears stronger in girls than boys).

[1]Excluding studies assessed to be at very high risk of bias.
[2]Addressed by starting score of 2.
[3]We have some concerns, however, about the large proportion of studies from one region in West Africa, and about the short follow-up available in randomized trials.
[4]Typical rate ratio in the region of 50% reduction.

Does <u>simultaneous</u> administration of DTP and measles vaccine in infancy affect all-cause mortality (compared with DTP followed by measles vaccine)?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		5 observational studies	2
	Factors decreasing confidence	Limitation in study design	Serious[1]	(0)
		Inconsistency	None serious	0
		Indirectness	Serious[2]	(0)
		Imprecision	Serious[3]	–1
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Large effect[4]	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			1
Summary of findings	**Statement on quality of evidence**			We have very little confidence in the evidence about the effect of simultaneous administration of DTP and measles vaccines on all-cause mortality.
	Conclusion			Simultaneous administration of DTP and measles vaccines may be associated with higher risk of all-cause mortality compared with DTP followed by measles vaccine.

[1]Addressed by starting score of 2.
[2]Three of the five studies are from one region in West Africa.
[3]Only five studies (125 deaths).
[4]Typical rate ratio compatible with more than two-fold higher mortality rate.

Does administration of measles before DTP vaccine in infancy affect all-cause mortality (compared with DTP followed by measles vaccine)?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		3 observational studies	2
	Factors decreasing confidence	Limitation in study design	Serious[1]	(0)
		Inconsistency	None serious	0
		Indirectness	Serious[2]	(0)
		Imprecision	Serious[3]	–1
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Large effect[4]	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			1
Summary of findings	**Statement on quality of evidence**			We have very little confidence in the evidence about the effect of ordering of DTP and measles vaccines on all-cause mortality.
	Conclusion			Reversing the order of administration of DTP and measles vaccines compared with the WHO recommended strategy may be associated with a lower risk of all-cause mortality.

[1]Addressed by starting score of 2.
[2]Two of the three studies are from one region in West Africa.
[3]Only three studies (76 deaths).
[4]Typical rate ratio compatible with more than two-fold higher mortality rate..

10.1 Closing remarks on risk of bias

Some of the biases described in our assessment were related to the decisions we made in selecting data to best address the policy questions set forth for this review; however in no case was there a relevant result with a lower risk of bias. Different biases were considered likely to operate in different directions. Baseline confounding, if ignored, would tend to lead to bias towards a beneficial effect of the vaccine, because children with a worse prognosis generally tended to be vaccinated later or not vaccinated at all (sometimes described as 'frailty bias'). Some selection biases were expected to operate in the opposite direction: if children are recruited some time after vaccination then early deaths among unvaccinated children – that might have been prevented had they been vaccinated – are not counted and the bias works against the vaccine and can switch the direction of effect. Misclassification of vaccinated children as unvaccinated would lead to bias towards the null (no effect), as occurs when a 'landmark' approach is taken to the analysis (23). Previous receipt, co-administration and subsequent administration of other vaccines (e.g. DTP or measles vaccine when examining BCG) would lead to biases that depend on the effects of these vaccines and combinations, which we cannot infer in the context of this review. Therefore we do not predict the direction of bias for individual studies or for the accumulated body of evidence. A further potential source of bias, which is very difficult to assess, is the selective reporting (and non-reporting) of results, both through mechanisms that lead papers to be written and published, and through decisions about what results to present in papers. There is not a single approach to design and analysis of studies in this research area, leaving open the possibility that investigators may have tried multiple ways to select and analyse the data, thereby putting the accessible literature as a whole at risk of bias.

11 Methods

The final version of our *a priori* protocol is available in Appendix 1. Due in part to the complexity of the material, a number of modifications and additional steps were made, and these are described below.

Key differences between the planned and implemented methods are as follows:

- **Outcomes of interest**: we focus in the report on all-cause mortality, for several reasons. First, there were considerably more data for this outcome, particularly for BCG and DTP (fewer than 20% of included articles contribute data on non-targeted mortality). Second, we had important concerns about the ability to determine cause of death, particularly among very young children. Third, incidence of the diseases being targeted would be low in many of the populations studied, so most deaths would be from other causes. Finally, there is a technical concern about how the deaths from the targeted infections should be addressed in the analysis. For example, a standard analysis of death counts from the causes other than the infection the vaccine is designed to prevent would not be appropriate, since it would combine the deaths from the targeted infection with the children staying alive. Censoring follow-up time is one option, but the exact implications of this for risk of bias are unclear. See Annex D for details of the included studies providing data on non-targeted mortality.
- **Vaccines of interest**: since polio vaccine is usually administered with DTP, we could not separate the effects of these vaccines. Our results for DTP should therefore be interpreted as results for the combination of vaccines.
- **Organization of articles and data**: we had to devise processes to manage the overlap of children in multiple articles reporting on different subsets of children from the same area.
- **Selection of results**: we had to devise processes to select one key result from each birth cohort of children, from among multiple results within an article and from among multiple articles covering the same birth cohort.
- **Risk of bias assessment**: we had made it clear in the protocol that development work would take place on the approach to assessing risk of bias in non-randomized studies, and we summarize our method below. We changed the labels we use to describe our judgements (from 'critical' and 'serious' risk of bias to 'very high' and 'high' risk of bias).
- **Statistical synthesis**: the Working Group requested that meta-analyses not be done, so none of the statistical syntheses are included in the report.

11.1 Study eligibility

As per protocol, we considered for inclusion studies with the following designs: (i) randomized controlled trials; (ii) quasi-randomized controlled trials; (iii) cohort studies (prospective, historical and ambi-directional); and (vi) case-control studies. We excluded animal or laboratory studies, and studies with the following designs: (i) ecological studies, (ii) uncontrolled studies (i.e. case reports, case series studies and studies in which all children received the same vaccine(s)), (iii) studies including only individuals with the outcome of interest in the analyses ["case only" studies], and (iv) self-controlled case series studies. Studies containing data related to the vaccination of children up to 5 years with BCG, DTP or measles-containing vaccine were eligible for inclusion if they compared one of the vaccines with no vaccination (BCG, DTP or measles vaccine) or with simultaneous administration of another vaccine. Since DTP is usually administered with polio vaccine, the effects cannot be separated and they are considered here together. Comparisons of different sequences of vaccine administration were also included.

To facilitate an assessment of the risk of bias in each study, we included (i) primary research papers (published or unpublished), (ii) re-analyses of primary studies with full articles describing methodology; (iii) follow-up commentaries and letters about studies written by the authors of the original article; and we excluded (i) results available only in reviews and meta-analyses and (ii) commentaries or letters about studies not performed by their authors.

11.2 Study selection

The search strategies are provided in Appendix 2. Search results were uploaded to a web-based system (DistillerSR®, www.systematic-review.com). The 5,600 identified titles and abstracts were inspected independently by two reviewers from among four (Michelle Beam, Emi Han, Emma Smith, Paul Zhang), coordinated by one co-principal investigator (Arthur Reingold). The full-text versions of 846 articles were obtained (six articles could not be located), and were again independently inspected by two of the same four reviewers (MB, EH, ES, PZ). Any discrepancies were resolved by the co-principal investigator (Arthur Reingold).

After the completion of the full-text screening, 238 potentially relevant references were cross-checked for eligibility by two reviewers from the Enhance Reviews team (Artemisia Kakourou, Maria Christou). Any disagreements between the two reviewers were discussed with the co-principal investigator Karla Soares-Weiser who took the final decision on inclusion. Justifications for excluding articles from the review were documented.

A flow chart of all screened articles is presented in Section 12, the table of characteristics of the included articles is presented in Annex 1, and a list of references of excluded articles (and articles that could not be located) is provided in Appendix 3.

11.3 Data collection

As per protocol, the data collection took place at article level. In the main round of data extraction, information on study characteristics extracted for each article separately were: study design, demographic and participant characteristics, methods of collecting outcome data and vaccination status, sequence of vaccine, age of vaccination, follow up, co-administration of vaccines or vitamin A, and main outcome data or results. The data extraction forms are provided in Appendix 4.

A second stage of data collection was undertaken by a statistician, with a focus on extraction of all-cause mortality outcome data. The main results collected in the first stage were checked, and supplemented with other findings, such as for different age groups, time points, genders or vitamin A statuses. Where effects could be computed from available data, we extracted the data and computed the effect sizes (see below). The approach at this point was still liberal: we extracted any comparison in which (i) child-time after vaccination of BCG, DTP or measles vaccine was compared with child-time after the vaccine had not been administered; (ii) different vaccination sequences had been compared (e.g., DTP3 before vs. after measles vaccine). The resulting compilation of results (included in Appendix 5) includes a large degree of overlap in samples, repetition, strong biases and extreme comparisons (e.g. children who received all three versus children who received none).

Adjusted and unadjusted effect estimates were collected where available; the estimate providing the most reliable evidence would usually be that including adjustment for one or more potential confounders. We collected all available effect measures stratified by gender (or computed them where the needed information was reported). We also collected all effect measures stratified by receipt or not of Vitamin A supplementation (or computed them if the needed information was available).

Effect metrics

The hierarchy for selection or computation of effect metrics was as follows.

a) Cohort studies:
   1) Hazard ratio (HR) in preference to
   2) Mortality rate ratio (MRR) in preference to
   3) Mortality ratio (MR) in preference to
   4) Odds ratio (OR).
b) Case-control studies: odds ratios.

Computations

Adjusted effect estimates could be computed manually in a few cases where the comparison of interest was to be made between two exposures groups that had been compared to a common reference category (and reference category was not of interest to us). For example, to compare DTP (after BCG) vs. No DTP (BCG only) we might extract the comparison of each to an unvaccinated reference group. In such cases, the effect was computed as a ratio between the two effects reported in the article, and the standard error was computed based on the methods described by Greenland and Longnecker (49).

In some instances we combined results across subgroups to obtain an adjusted estimate of main effect. For example, combining mortality ratios within boys and within girls, or combining mortality ratios estimated within different age groups. Such combination was performed using fixed-effect meta-analysis methods on the log scale (50).

Most of the effect estimates manually computed were unadjusted. These could be calculated where the article reported the required information per group: deaths and person-time for MRRs; deaths and group size for MRs; cell frequencies for ORs. None of the articles included provided the needed information to compute a HR. We followed standard formulae to compute rate ratios, risk ratios and odds ratios and their standard errors on the log scale (50, 51). If there were no deaths on one group, we added 0.5 to the number of deaths in both groups and added 1 to the denominator (either total children or total children-years).

11.4 Organization of articles and data

Grouping related articles

After each included article had been fully data extracted, information about country, location within a country, design, vaccine comparisons, years of enrolment, and years of birth dates were tabulated. Articles were informally grouped to assist in the identification of results from the same children and hence to avoid double-counting of participants. One of the challenges we encountered with this process was that half of the included articles were from a single country (Guinea-Bissau) and many of the birth dates from different articles overlapped. We therefore plotted the different birth dates against the year of publication for all articles from countries on which more than one study was reported (Bangladesh, Ghana, Guinea-Bissau, India, and Senegal) and attempted to identify details of a given study that would make a particular group of articles unique. As an example, seven articles from Guinea-Bissau published since 2006 (or unpublished) in birth dates from 1999 to 2010 were divided into two groups: *Guinea-Bissau A* reported on a randomized trial conducted in low-birth weight infants in the Bandim area on which the main objective was the impact of vitamin A supplementation; however, these children also received the recommended vaccines and data on BCG and measles vaccine were reported; *Guinea-Bissau C* reported on a randomized trial conducted to evaluate the impact of two vs. one dose of measles vaccine in the same area. These groups of articles are used to organize the articles in Annex A. They also appear on the forest plots in the earlier part of this report to aid location of further information relating to the results plotted.

Birth cohorts

After the process of organizing articles into related groups had been completed, it became clear that it was still not possible to discard considerable overlaps across some of these groupings. For example, although *Guinea-Bissau A* and *Guinea-Bissau C* clearly related to different studies, it is likely that part of the population receiving BCG at birth (*Guinea-Bissau A*) later on participated in the measles vaccine trial (*Guinea-Bissau C*). Therefore, in order to prevent double-counting of participants in the analyses, we further organized the article groups into 'birth cohorts' based on geographical area and time period. In some instances there was more than one independent data set within a birth cohort. Information about overlap of studies was obtained from study authors (specifically, for studies in Guinea-Bissau and Senegal).

Details of final groupings of studies for analyses are provided in Annex B.

11.5 Selection of results

Selection of one result

Having determined the (broadly) non-overlapping birth cohorts, we needed to select one result from each cohort to avoid double counting of children. We devised the following algorithm (which evolved iteratively) to achieve this:

1. Select comparison with vaccination sequence according to the WHO recommendations (e.g., BCG, DTP1-3, MCV). We depict 'BCG before DTP' as 'BCP<DTP'
2. Select estimates from randomized trials.
3. Select estimates adjusted for age and other vaccines.
4. Estimates of primary interest
   - BCG
     A. BCG at birth vs. no BCG in preference to
     B. BCG vs. no BCG
   - DTP
     A. BCG<DTP (any number of doses) vs. BCG in preference to
     B. BCG<DTP (1 or 1-2 doses) vs. BCG in preference to
     C. BCG<DTP (2 or more doses) vs. BCG in preference to
     D. DTP (any number of doses) vs. no DTP in preference to
     E. DTP (1 or 1-2 doses) vs. no DTP in preference to
     F. DTP (2 or more doses) vs. no DTP
   - MCV
     A. BCG<DTP<MCV vs. BCG<DTP in preference to
     B. BCG<MCV vs. BCG in preference to
     C. DTP<MCV vs. DTP in preference to
     D. MCV vs. no MCV

5. Select comparison with least co-administration of other vaccines, particularly when vs. unvaccinated children
6. Select comparison involving children from the same area (e.g. #7108)
7. Select estimate obtained using landmark (rather than retrospective) approach
8. Select estimate obtained from general population children rather than subgroups (e.g., hospitalized children)
9. Select comparison including the most comprehensive adjustment for potential confounders.
10. Select result for the shortest period of follow-up
11. Select result with the largest sample size
12. Select comparison with vaccination strategies according to the WHO recommendations (e.g., BCG at birth, MCV vaccine at 9 months)
13. Select estimate using the methodological approach claimed to be superior or more correct (e.g. #9014)
14. Select result from more recent article

We discarded studies in which all children in one of the comparison groups had two of the vaccines administered simultaneously. The sources of data used in the forest plots are described in the first column of the tables in Annex C.

11.6 Risk of bias assessment

As per protocol, we used the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (52). For non-randomized studies, we used a version of a tool under development by the team that developed the randomized trials tool (led by Jonathan Sterne and Julian Higgins at the University of Bristol), informed by methodological consideration specific to this research area (23, 53).

Assessment of risk of bias in non-randomized studies was highly iterative. This was partly because the tool itself was evolving in its development, partly because iteration is inherent in the evaluation of non-randomized studies (with the need to return to papers to consider potential problems, biases, confounders and co-interventions identified in other studies) and partly to respond to refinements to the research questions posed by this particular review. Details of data extracted to assess risk of biases in the included articles, and the judgements reached, are provided in Annex C.

11.6.1 Preliminary considerations for risk of bias in non-randomized studies

We pre-specified potential confounders in four domains:

- Age of child
- Gender of child
- Child's health (including nutritional status and birth weight)
- Socioeconomic status (including poverty, education, health insurance, urban/rural, hygiene conditions)

We pre-specified potentially important co-interventions:

- Malaria interventions
- De-worming
- Micronutrient supplements
- Breast feeding
- Hygiene programmes
- Other vaccines (Hepatitis B, yellow fever. Polio vaccine not considered as a co-intervention for assessing risk of bias, instead being considered an integral part of the DTP vaccination exposure.)

11.6.2 Process of assessing risk of bias

The assessment was informed by thinking about a hypothetical 'target trial' that makes the same comparison as the result being evaluated. Specific information about potential confounders and co-interventions was collected where available. Risks of bias were assessed in seven domains, facilitated by considering pertinent questions about the conduct of the study and analysis. Within each domain, risk of bias was to be rated as 'low' (meaning comparable to a well-performed randomized trial); 'moderate' (meaning sound for an observational study); 'high' (meaning there are some important problems); or 'very high' (meaning the study is too problematic to provide useful evidence). A short explanatory note outlining the reason for any 'high' or 'very high' risk-of-bias judgement is provided. The overall risk-of-bias judgement was specified as the lowest among the domain-level judgements.

At least two reviewers evaluated the risk of bias for study (Katherine Chaplin, Julian Higgins, Hannah Christensen, Natasha Martin), and face-to-face consensus discussions were held for each result.

1. Bias due to confounding (including frailty bias)

Issues for consideration: (i) Did the authors conduct an appropriate analysis that controlled for all the critically important confounding domains?; (ii) If yes, were all of the confounding domains measured validly and reliably by the variables adjusted for in this study?; (iii) Did the authors avoid adjusting for post-intervention variables?

A very high risk of bias would arise if the vaccine groups being compared had very little overlap in distributions of the confounders, particularly if no adjustment was made for this, which was sometime the case for age.

2. Bias in selection of participants into the study (including inception bias)

Issues for consideration: (i) Are all eligible children included in the analyses (and was selection unrelated to intervention or outcome)?; (ii) Do start of follow-up and start of intervention coincide?

A very high risk of bias would arise if follow-up started somewhat after vaccines were administered in such a way that vaccines had potential to affect mortality rates before the start of follow-up.

3. Bias in measurement of interventions (including survival bias)

Issues for consideration: (i) Were the methods of assessment of vaccination status comparable for participants with different outcomes?; (ii) Was the approach to analysis 'landmark' or 'retrospective'?; (iii) If a retrospective approach was used, is it unlikely that substantial numbers of dead children have been assigned to the wrong vaccination status?

A high risk of bias would arise if vaccination status was assumed rather than measured. A (possibly very) high risk of bias might arise if time of vaccination was assigned using information collected at a later time point, since the information may be missing differentially in dead compared with living children. The seriousness of this depends on the interval between attempts to collect vaccination data.

4. Bias due to departures from intended interventions (performance bias)

Issues for consideration: Were the critical co-interventions balanced across intervention groups?

A very high risk of bias would arise if there were high rates of co-administration (or subsequent administration) of the vaccines of interest. If *all* children received a co-administered vaccine (other than polio vaccine with DTP) then the study would be excluded from the analysis altogether.

5. Bias in measurement of outcome (detection bias)

Issues for consideration: (i) Were outcome assessors unaware of the intervention received by study participants?; (ii) Were the methods of outcome assessment comparable across intervention groups?

Because all-cause mortality is an objective measure, we did not consider there to be important problems in this domain.

6. Bias due to missing outcome data (attrition bias)

Issues for consideration: Are outcome data reasonably complete?

We did not consider there to be important problems in this domain.

7. Bias in selection of the reported result (reporting bias)

Issues for consideration: Is the reported effect estimate unlikely to be prone to selective reporting (on the basis of the results) from among multiple analyses?

This is a particularly challenging domain to assess in the absence of *a priori* analysis plans, and for all studies we defaulted to an assessment of 'moderate risk of bias'.

11.7 Analyses

11.7.1 Main effects

All results are presented in forest plots as effect estimates along with 95% confidence intervals, following hierarchies for choice of effect size and selection of data described above. In these plots, a null effect of one would suggest that the vaccine had no effect on infant mortality and arrows at the base of the plot indicate directions of effect. Effects are presented separately for the three vaccines (evaluated in the context of existing WHO policy). Studies assessed as being at very high risk of bias are presented separately at the bottom of the plots, and do not contribute to the main findings or GRADE tables. We also address various sequences of vaccines. In the investigation of sequences, our main goal was to retrieve data points where the sequences recommended by WHO had been compared with alternatives (specifically simultaneous administration of BCG and DTP, DTP before BCG, simultaneous administration of DTP and measles vaccine, DTP after measles vaccine).

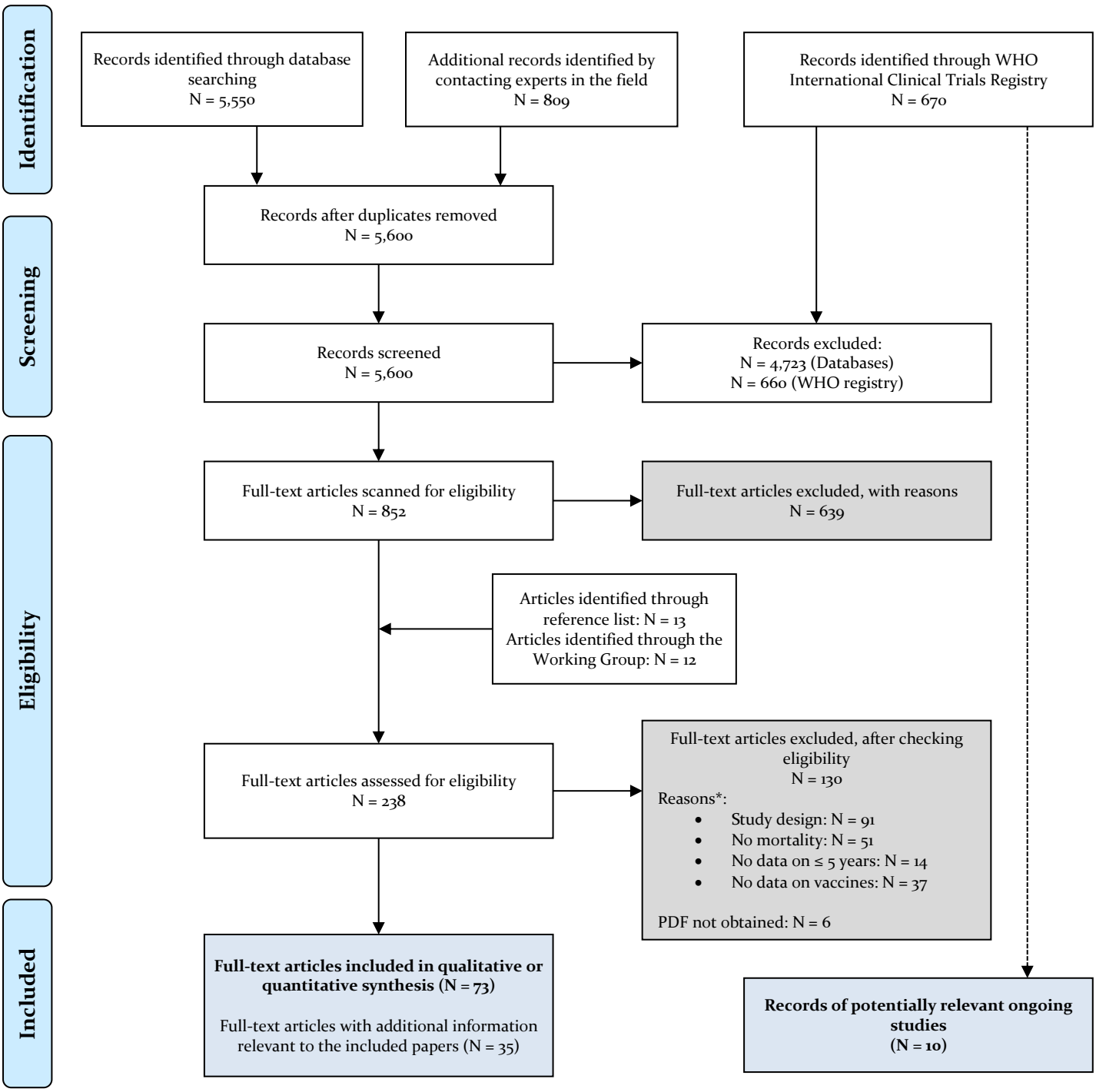
11.7.2 Gender

Results were displayed using separate forest plots for each vaccine with data points presented in two different ways. First, the estimates for each vaccine were grouped in the forest plot by gender to provide an overview of the vaccine effect for boys and girls across birth cohorts. In these plots, a null effect of one would suggest that the vaccine had no effect on infant mortality. Second, we computed the differences between the vaccine effects for boys and girls in each birth cohort, and presented these differential effects for to facilitate assessment of whether one subgroup experienced a higher decrease on mortality than the other. In these plots, a null effect of one would suggest that there was no interaction, i.e. that the vaccine effect on overall mortality was identical for both genders. The sources of data used in the forest plots are described in Appendix 6.

11.7.3 Vitamin A

We also collected all effect measures stratified by receipt or not of vitamin A supplementation (or computed them if the needed information was available). Analyses followed the strategy describe above for gender. The sources of data used in the forest plots are described in Appendix 6.

12 Flow diagram for articles identified in the review



13 Contributors and acknowledgements

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The actual order in which vaccines are given in the EPI: analysis of data from 102 national surveys.

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1 Introduction

Aaby and different groups of co-workers have suggested that there are adverse effects of DTP vaccine on the overall health of young children, but that these are moderated if DTP is followed by a dose of BCG or measles vaccine[1]. A number of more specific hypotheses have been proposed, with one recent formulation as follows:

1. BCG vaccine reduces mortality from infections other than tuberculosis until an inactivated vaccine is given.
2. Measles vaccine reduces mortality from infections other than measles until an inactivated vaccine is given; this effect may be stronger if the child still has maternal antibody when receiving measles vaccine.
3. Whole-cell diphtheria-tetanus-pertussis vaccine (DTP) increases mortality from infections other than diphtheria, tetanus and pertussis until a live vaccine is given; this effect is stronger in females than in males.
4. Live and killed vaccines may interact to produce good or bad non-specific effects when given simultaneously or when the sequence is changed, and the effects may be modified by vitamin A.

At its meeting in November 2011, the SAGE requested a review of the evidence relating to these hypotheses. This paper reviews evidence from nationally representative survey data on the extent to which different vaccines are given out of order or on the same day.

Objectives

This analysis uses existing nationally representative survey data for a preliminary examination of the following questions:

1. What % of children were given a first dose of DTP with or before BCG?
2. What % of children were given a last dose of DTP with or after MCV?
3. For how many child weeks before age 24 months was DTP the last vaccine given?
4. What % of children were given live (BCG or MCV[1]) and killed (DTP) vaccines on the same day?
5. What % of children were given MCV and vitamin A on the same day?

2 Data

The data used were from the Demographic Health Surveys (DHS) rounds 5 and 6, and the Multiple Indicator Cluster Surveys (MICS) round 3. Background information about each survey, and on the completeness of the survey data, are given in Table 1 and Appendix Tables 1.0 to 1.8. Table 1 provides a summary in the form of median values overall and for each WHO Choice/burden-of-

[1] The first dose of measles vaccine.

disease sub-region. Tables A1.0 to A1.7 provide more detail and data for each survey grouped by WHO Region. Table A1.8 shows differences for countries surveyed more than once.

From Table 1 it can be seen that largest numbers of surveys were in Africa. In the Eastern Mediterranean, South East Asian and Western Pacific Regions there were relatively few. Median vaccination periods covered by the surveys were from 2004 to 2007 overall, but the studies in the high adult mortality countries in Africa (sub-region E) tended to be more recent (2006-2009). The median number of children in each survey aged between 24 and 59 months at the time of interview was 3,401.

The DHS series includes a question to mothers on how many of their children have died. In Tables 1 and A1.1 to 1.7, mortality rates estimated from the survey data are compared to the UNPOP infant mortality estimates. It can be seen that for surveys in some regions the DHS-based rates are a little lower than the UNPOP estimates, but in general they are broadly similar.

Table 1: Preliminary examination of the data

		Median values for the group of countries										
		Children	*Year of vaccination*		*Infant mortality*			*Infant*	*Died before*	*% of MCV*	*% of vaccinated*	
WHO	*Surveys*	*in survey*	*earliest*	*latest*				*mortality*	*interview*	*given after*	*children that have*	
sub-Region	*available*	*aged 24m +*	*BCG*	*MCV*	*1995*	*2000*	*2005*	*UNPOP*	*DHS*	*age 24m*	*age*	*median*
Overall	102	3,401	*2004*	*2007*	*7%*	*7%*	*6%*	*6%*	*5%*	*3%*	*24-35m*	*73%*
											24-59m	*68%*
AFR D	22	4,076	2003	2007	9%	9%	9%	9%	7%	3%	24-35m	59%
											24-59m	50%
AFR E	27	4,165	2006	2009	9%	9%	8%	8%	6%	2%	24-35m	71%
											24-59m	65%
AMR	14	3,871	2003	2007	4%	3%	3%	3%	3%	6%	24-35m	78%
											24-59m	75%
EMR	8	6,094	2003	2006	4%	4%	3%	3%	2%	0%	24-35m	53%
											24-59m	50%
EUR	11	1,297	2001	2005	3%	2%	2%	2%	2%	2%	24-35m	94%
											24-59m	94%
SEAR	11	5,132	2004	2007	5%	3%	2%	4%	3%	1%	24-35m	85%
											24-59m	82%
WPR	7	2,248	2003	2006	7%	6%	5%	7%	5%	4%	24-35m	74%
											24-59m	68%

In both DHS and MICS surveys, exact dates of vaccination are copied from vaccination cards if they are available; otherwise the mother is asked whether or not their child has had each vaccination. To determine the order of vaccine administration, only data from children with dates for all the relevant vaccines can be used. The proportion with data from cards ranged from over 90% in surveys in the EURO B & C sub-regions down to about 50% in the AFR D and EMR B & D sub-regions, and in some surveys the percentage of vaccinations with dates was very low indeed (eg Georgia 4%, Pakistan 12%, Nepal 13%, Mauritania 15%). Only surveys with at least 20% with dates were included in the rest of the tables. Data from surveys with between 20% and 40% were included in the tables but excluded from calculation of the 'overall' figures at the top of each table. Also in countries

with more than one survey, only the most recent data were included in the summary figures. These inclusion criteria also required of any country-specific figures mentioned in the text. For all the children aged 24-59m at interview in included studies, dates from cards were available for 67% of vaccinations (median across included surveys), ie 33% of reports were based on mother's recall or an undated record.

There were 102 surveys in all. Of these 92 were included in the tables, and 56 were used for calculating summary statistics: 14 from the AFR D sub-region, 14 from AFR E, 11from AMR B & D, 3 from EMR B & D, 7 from EUR B & C, 3 from SEAR B & D, and 4 from WPR B.

From Table A1.8 it can be seen that in the 17 countries with two or more eligible surveys, in the more recent years the % of doses of MCV given after age 24m have tended to be lower, and the % of data from vaccination cards rather than mother's recall have tended to be higher.

3 Analysis

The survey data were taken from interviews with mothers about children that were less than 5 years old. To achieve the same length of follow-up for each child, the analysis was restricted to vaccinations in the first 24 months of life. This meant that: i) children aged less than 24m at the time of the mother's interview were excluded (about 40% of the children surveyed); and ii) any vaccinations given after age 24m were ignored. Typically the percentage of the first doses of the measles vaccine given after age 24 months (and so not taken into account in these analyses) was around 3%. This proportion was generally higher in the Americas Region (6%) and much higher in some specific surveys, the highest being Guinea-Bissau 2002-6 (14%)[2].

The following results were reported for first DTP before, with or after BCG; last BCG before with or after MCV, child-weeks with DTP as the most recent vaccine ('DTP weeks'), and for vaccines given on the same day:

- *for each survey*: % overall, for boys v girls, for urban v rural, and by wealth quintile.
- *overall and for each sub-region*: medians, upper quartiles and deciles overall, and medians for boys v girls, for urban v rural, and by wealth quintile.

'DTP weeks' were calculated for each child as the number of weeks before age 24m for which any dose of DTP was the most recent vaccine received. Thus if doses were complete and in order, this was from the date of DTP1 to the date of MCV. If eg BCG was given between DTP1 and DTP2, the total DTP weeks were from date of DTP1 to BCG plus date of DTP2 to MCV. If the child was given DTP but no MCV, usually the total DTP weeks would be from date of first DTP to age 24m, but an out-of-

[2] These were some higher figures than this in some of the surveys excluded because of missing vaccine dates

order dose of BCG would reduce this. If a child received BCG and a dose of DTP on the same day, no DTP weeks were accrued until after the first subsequent dose of DTP.

It was found that both the numbers of DTP weeks and the completeness of recording of vaccination dates were related to the numbers and combinations of vaccines received. In particular, children who had had all five vaccines were more likely than the others to have complete sets of dates, and of the children with complete dates, those who had had all five vaccines tended to have lower values for DTP weeks than children who had missed MCV. Thus simply using the data from children with complete dates would have given a biased estimate of DTP weeks. For children with incomplete dates, the combinations of vaccines that they had received were used to impute values for DTP weeks using the distributions for children with the same combinations of vaccines but known dates.

In calculating summary figures such as medians, no attempt was made to weight different survey results by eg population size, or to interpolate for missing countries. Thus the summary figures in the tables, overall and for the surveys in each region, should not be interpreted as global and regional estimates.

When specific surveys are mentioned in the text, the relevant ranges of vaccine years are given, defined as follows: at least 90% of doses of BCG were given during or after the start of the range, and at least 90% of the doses of BCG were given before the end of it.

Details of the calculations are given in footnotes to the tables.

4 Results

What % of children were given a first dose of DTP before or with BCG?

Overall, for about 99% of children there were data on whether they had had BCG and DTP or not. Of these, about 5% of children had received neither, 2% had had BCG but no DTP, and 1% DTP but no BCG. In these children the question of order did not arise. This was most common in the AFR D sub-region (Table A2.1a col 2+ col 3 +col 4 = 18%), especially in the poorest groups (30%: Table A2.1b), although there is substantial within-region variation, with high levels in eg Niger 2001-5 (59%) but much lower levels in Gambia 2001-4, Ghana 2004-7 and Senegal 2006-9 (5 to 7%). There were also high levels in Lao PDR (48%). In EUR B & D by contrast, the corresponding figure was less than 1%.

Apart from two countries (Suriname 2002-5 and Trinidad & Tobago 2002-5) that do not include BCG in their survey, the percentage of children recorded as having DTP but not BCG was unusually high in Jordan 2003-6 (19%).

Table 2 shows the percentages of children who received their first dose of DTP before BCG. The overall figure was 2%. In most countries the figure was less than 5%, but it was more common in specific countries such as Jordan 2003-6 (17%), Zambia 2003-6 (12%) and Haiti 2007-12 (11%).

Table 2: Percentage of children with their first dose of DTP before BCG

Median values for surveys in each group of countries; data for children aged 24-59m

Region	Median	Upper quartile	Boys	Girls	Urban	Rural	Wealth quintile top	Wealth quintile bottom
Overall	**2%**	4%	2%	2%	1%	3%	1%	2%
AFR D	**3%**	4%	3%	3%	2%	4%	1%	4%
AFR E	**1%**	5%	1%	1%	1%	1%	1%	1%
AMR	**3%**	4%	2%	3%	2%	4%	1%	5%
EMR	**5%**		6%	5%	6%	4%	4%	3%
EUR	**2%**	3%	2%	2%	1%	3%	1%	1%
SEAR	**1%**		0%	1%	1%	1%	1%	1%
WPR	**2%**	2%	2%	2%	1%	2%	2%	2%

Table 3 shows the percentage of children who had BCG and their first dose of DTP on the same day. The overall figure was 5%, but in general it was much common in the poorest quintile (13%) than the richest (4%), and much more common than this in some countries. Bangladesh 2003-6 was an outlier at over 60%, but figures of 20% or more were seen in eg Guinea-Bissau 2002-6, Madagascar 2004-7, Malawi 2006-9, Jamaica 2001-4 and Lao PDR 2002-5. In the countries with 2 or more surveys, the proportions of children with first doses of DPT given before or on the same day as BCG tended to be smaller in the more recent data (Table 2.8), even though the proportions of children receiving at least one dose of DPT had increased.

Table 3: Percentage of children with BCG and their first dose of DTP on the same day

Median values for surveys in each group of countries; data for children aged 24-59m

Region	Median	upper quartile	Boys	Girls	Urban	Rural	Wealth quintile top	Wealth quintile bottom
Overall	5%	15%	5%	6%	4%	7%	3%	9%
AFR D	9%	17%	10%	9%	6%	11%	4%	15%
AFR E	7%	20%	6%	7%	3%	9%	3%	10%
AMR	4%	8%	4%	4%	3%	7%	1%	7%
EMR	5%		5%	5%	4%	5%	1%	4%
EUR	1%	1%	1%	1%	0%	1%	0%	1%
SEAR	6%		6%	6%	4%	7%	3%	9%
WPR	10%	14%	10%	9%	6%	11%	4%	16%

What % of children were given their last dose of DTP with or after MCV?

Overall 6% of children had had at least one dose of DPT but no MCV (Appendix Table 2, which also shows the percentages of children who had missing data for DTP or MCV, the % who had neither or only one of these vaccines).

Table 4 shows that overall about 4% of children had their last dose of DTP after the MCV[3]. Table 5 shows that about 2% had both doses of vaccine on the same day. The potential problems were greatest in the AFR D sub-region (4% and 5% respectively) and WPR B (5% and 5%), but again the summary figures conceal a good deal of country-to-country variation. At least one country in each region had high percentages, examples being Gambia (16% , 7%), Guinea-Bissau (14%, 12%), Sierra-Leone (4%,8%), Uganda 2007-10 (3%, 10%) and Lao PDR 2002-5 (7%, 13%).

Table 4: Percentage of children who had their last dose of DTP after MCV

Median values for surveys in each group of countries; data for children aged 24-59m

Region	Median	Upper quartile	Boys	Girls	Urban	Rural	Wealth quintile top	Wealth quintile bottom
Overall	**4%**	6%	3%	4%	3%	3%	2%	3%
AFR D	**4%**	6%	4%	4%	3%	3%	4%	4%
AFR E	**2%**	4%	2%	2%	1%	2%	1%	3%
AMR	**5%**	9%	4%	5%	3%	5%	3%	6%
EMR	**1%**		1%	1%	1%	1%	0%	1%
EUR	**3%**	4%	2%	3%	4%	2%	4%	2%
SEAR	**3%**		3%	2%	1%	3%	0%	4%
WPR	**5%**	6%	4%	5%	3%	5%	4%	5%

In the countries with more than one survey, the proportions of children with last doses of DPT given after or on the same day as MCV again tended to be smaller in the more recent data (Appendix Table 2.8).

Table 5: Percentage of children who had MCV and their last dose of DTP on the same day

Median values for surveys in each group of countries; data for children aged 24-59m

Region	Median	upper quartile	Boys	Girls	Urban	Rural	Wealth quintile top	Wealth quintile bottom
Overall	**2%**	6%	2%	3%	1%	3%	1%	4%
AFR D	**5%**	7%	5%	5%	4%	6%	2%	7%
AFR E	**3%**	5%	3%	3%	2%	3%	1%	4%
AMR	**2%**	4%	2%	2%	2%	2%	1%	2%
EMR	**1%**		1%	1%	1%	1%	1%	1%
EUR	**1%**	1%	1%	0%	0%	1%	0%	0%
SEAR	**1%**		1%	1%	1%	1%	1%	1%
WPR	**5%**	8%	5%	6%	1%	6%	1%	8%

[3] or first dose of MCV if there was more than one. Data on MCV2 were not routinely collected in these surveys.

For how many child weeks before age 24 months was DTP the last vaccine given?

Table 6 and section 5 of Appendix Table 2 (cols 17-20) give the estimated median, upper quartile and 90th percentile values of total 'DTP weeks' Appendix Table 2 also gives the number of cases that the estimates are based on. Overall around 50% of children spent 35 weeks or more of their lives with DTP as their most recent dose of vaccine. However for about 10% of children the number of DTP weeks was 78 or more. Results for AFR D and E, and WPR B were close to the overall, but the figures were higher for surveys in AMR (45 and 80 weeks), and lower in EMR (31 and 39 weeks) and SEAR (32 and 45 weeks). At least part of the explanation lies in the different schedules used in different regions. For much of the period concerned, the scheduled ages were [6w, 10w, 14, 9m] in AFR but [2m, 4m, 6m 12m] in AMR, with mixtures elsewhere, so the scheduled gap between DTP1 and MCV was largest in AMR.

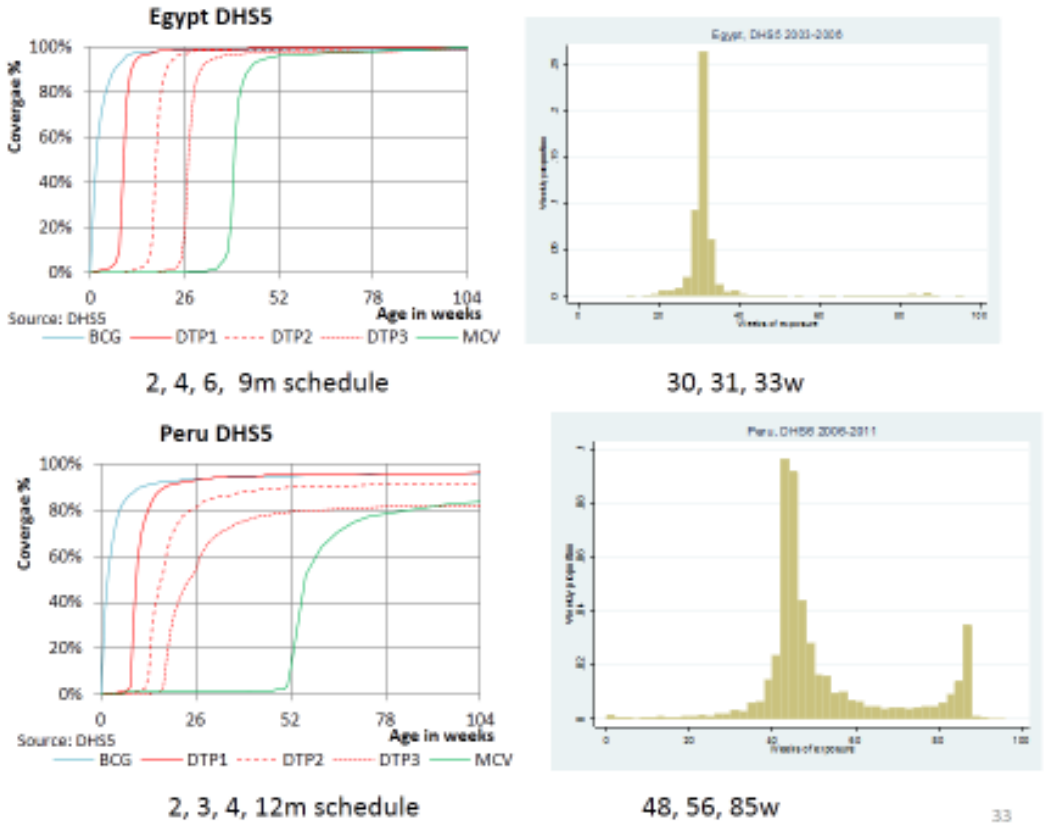
Table 6: DTP weeks before age 24 months

Median values for surveys in each group of countries.

Region	*Median*	*upper quartile*	*upper decile*	*Boys*	*Girls*	*Urban*	*Rural*	*Wealth top*	*Wealth bottom*
Overall	**35**	46	78	35	35	35	35	34	36
AFR D	**34**	51	85	34	34	34	34	34	35
AFR E	**34**	40	76	34	34	34	34	34	35
AMR	**45**	55	80	45	45	45	45	45	45
EMR	**31**	34	39	31	31	31	31	31	30
EUR	**44**	46	57	43	44	44	44	43	43
SEAR	**32**	36	45	32	32	32	32	33	32
WPR	**35**	57	83	37	34	34	36	34	35

This relationship between DTP weeks and the schedule is shown in Figure 1, with data from Egypt and Peru. In each case there is a diagram on the left showing age-specific coverage for BCG, DTP1-3 and MCV, and the vaccine schedule underneath; and on the right there is a histogram showing the probability distribution of DTP weeks, with the 50th, 75th and 90th percentiles underneath. Egypt 2003-6 is an example of a country with high coverage for all five vaccine doses, with most given on time or close to it. The histogram for DTP weeks has a single sharp peak and around 30 weeks, close to the scheduled difference between DTP1 and MCV. Vaccination in Peru is slightly less prompt, particularly for DTP3, and also there is a marked difference in coverage between DTP1 and MCV. The histogram has one main peak which is later than in Egypt (at around 48 weeks, reflecting the longer gap between DTP1 and MCV in the schedule) and more spread out (reflecting the somewhat less timely programme). It also has a secondary peak at around 90 weeks. This is the result of children having had DTP but not MCV, and reflects the length of time between DTP1 in the schedule and the end of the follow-up period at age 24 months.

Figure 1: Vaccine coverage and DTP weeks: Egypt and Peru

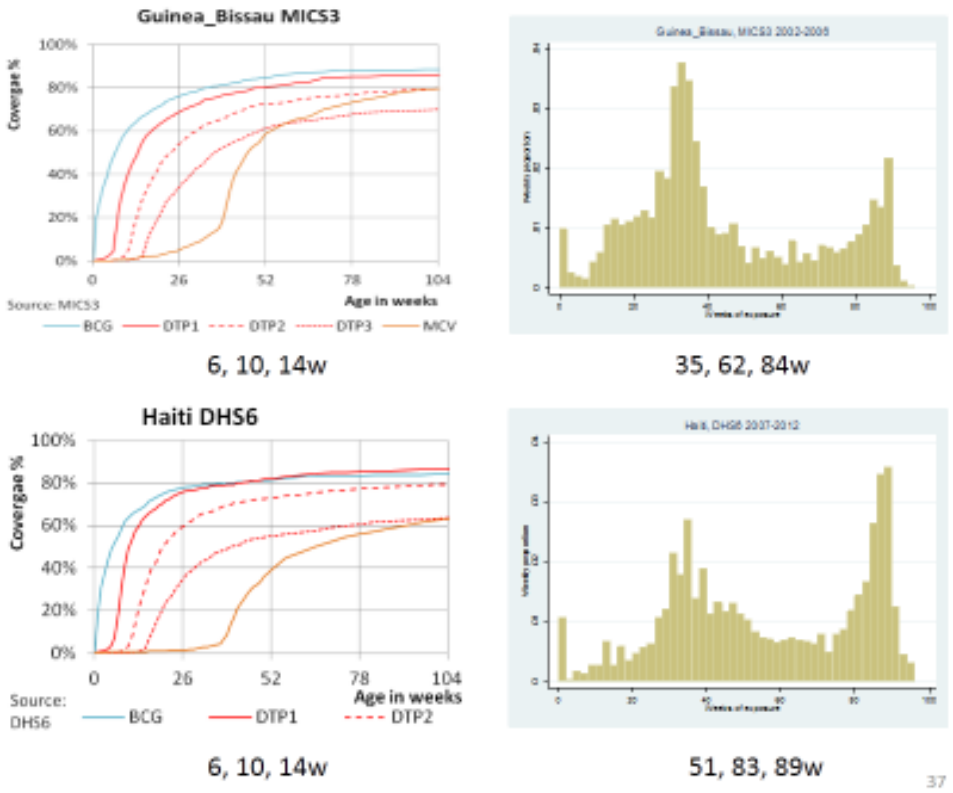


Similar diagrams for Guinea-Bissau 2002-6 and Haiti 2007-12 are shown in Figure 2. The histograms for DTP weeks extend towards zero, indicating some children with small gaps between DPT1 and MCV, and both have the second peak at the right characteristic of lower coverage for MCV than for DTP. Both countries have relatively low coverage for scheduled vaccinations, and in the DHS and MICS reports on these two surveys it was mentioned that in both countries there had been vaccination campaigns during the period covered by the data.

What % of children are given different vaccines on the same day?

The results of this analysis are given in Table 7, with results for each survey in Appendix Table 3. These tables cover some of the same ground as earlier sections but in a different way and with more detail. For each pair of vaccines or vaccine plus vitamin A, the denominator is the number of children who had both, and the numerator is the number of children who had both on the same day. Also instead of the first and last doses of DTP, figures are given for DTP1, DTP2 and DTP3 specifically.

Figure 2: Vaccine coverage and DTP weeks: Guinea-Bissau and Haiti



For pairs of vaccines, BCG with DPT1 was far the most common combination; overall, about 6% of children who had had both were given them on the same day. The corresponding figures were 1% for DTP2 and MCV, and 2% for DTP3 with MCV and DTP3. In general the figures for combinations were higher in the AFR and WPR regions and lower in the EMR and EUR regions. Overall, DTP1 with BCG was far more common in rural than in urban areas (8% vs 4%), and in the poorest wealth quintile than in the richest (9% vs 3%). This gradient was seen in all regions except EUR, where the combination was rare. In the countries with two or more surveys, the overall figure for DTP1 given on the same day as BCG fell from around 11% in the earlier surveys to 6% in more recent ones.

The question on Vitamin A was not asked in a number of surveys, and this is shown as blanks in the relevant sections of Appendix Table 3. The summary figures are based only on the surveys that included the question. Eleven percent of children had vitamin A and MCV on the same day, and 1% had vitamin A with DTP3.

Table 7: For vaccines and vitamin A, % of children who had both given them on the same day.

Median values for surveys in each group of countries.

Region	*BCG + **DTP1***	*BCG+ DTP2*	*DTP1+ MCV*	*DTP2 + MCV*	*DTP3+ MCV*	*BCG + vitA*	*DTP3+ vitA*	*MCV+ vitA*
Overall	**6%**	0%	0%	1%	2%	0%	1%	11%
AFR D	**9%**	1%	1%	1%	3%	1%	1%	13%
AFR E	**7%**	0%	0%	0%	2%	0%	1%	21%
AMR	**6%**	0%	0%	1%	2%	0%	2%	5%
EMR	**5%**	1%	0%	0%	1%	0%	0%	1%
EUR	**1%**	0%	0%	0%	1%	0%	0%	0%
SEAR	**6%**	0%	0%	0%	1%	0%	0%	38%
WPR	**10%**	1%	1%	2%	4%	7%	1%	6%

5 Discussion

From the evidence of these surveys, giving vaccines out of order or on the same day has been quite a common occurrence in some countries, but very rare in others. As a generalisation, these phenomena appear to have been more common in Africa, particularly in sub-region D, and less common in the European and East Mediterranean regions. However every region has countries where they are seen to a significant extent. Numbers of 'DTP weeks' are highly variable, and partly dependent on the local schedule.

How robust is this evidence? The data are from well-established surveys, designed to be nationally representative. The broad similarity of the survey-based and the UNPOP estimates of infant mortality is reassuring although it appears that in some surveys either respondents are relatively healthy or very young deaths are under-reported. Also it is not safe to generalise from these surveys to whole regions, particularly those with few surveys to go on. The countries that are included may well not be representative, because the focus of both survey series is on poorer and higher-mortality countries. On the other hand their high mortality makes them the countries of greatest public health interest.

In some surveys the proportion of children for whom the vaccination card, and hence data on vaccination order, are unavailable is clearly a matter for concern when interpreting these results. An arbitrary threshold of at least 40% of vaccinated children with cards was chosen as the basis for including surveys in the calculation of summary medians and comments in the text, but results are given for all surveys with over 20%, so that readers with knowledge of particular countries can use their own judgement. The method used for imputation was simple, but will have resulted in less bias than assuming that children without vaccine dates would have had the same distribution of DTP weeks as children with dates.

Use of this kind of survey data involves a trade-off between excluding large numbers of children and truncating the length of follow-up. In this case the focus on children aged 24-59 months at the time of

their mother's interview involved discarding about 40% of the data, but also excluding any vaccinations given after age 24m. Extension of the follow-up period to say 36m would have involved sacrificing another 20% of the data. Also this would have meant limiting the analysis to data from older children, and the proportion of children with vaccination cards available drops off with age. Thus recording would have been more complete (72% rather than 67%) if the analysis had been restricted to children aged 24-35m at mothers' interview, but at the expense of sample size. The effect of excluding vaccinations after age 24m will be to overestimate the proportion of children for whom DTP is the last dose, but arguably a final dose of MCV after age 24m would be too late to provide protection against any adverse effects of DTP during the period of highest risk.

How do these results compare with other community-based studies? In an analysis of surveillance data from 1986 to 2001 for the Matlab area of Bangladesh[2], children were given BCG on the same date as DTP1, DTP2 and DTP3 in 55%, 10% and 5.5% of cases respectively. The very high total of 70% is below the estimate of 63% found in the DHS data covering vaccinations in 2007-10, but the DHS study was rather later. In a community-based 3-monthly surveillance study of children born between 1987 and 1989 in 45 contiguous villages in India[3], of the 2015 children who had had both DTP1 and BCG, in 27% the two vaccines were given together and in 32% BCG was given after DTP1. The corresponding figures in the DHS data for 2001-05 were 15% and 29%. Of 893 who had been given DTP and MCV, 9% had them at the same time and 5% had DTP after MCV (DHS: 1% and 23%).

In a report by Welaga et al[4] on data from trial of vitamin A supplementation in Ghana in 1989-91, on enrolment to the placebo group 76% of the children with vaccination cards had had BCG with DTP, and 86% had had a dose of DTP either with or after MCV (14% and 17% respectively in the DHS data for 2004-07). In a community-based cohort study in Malawi by Aaby et al[5] of children born in 1995-97, 22 (about 4%) children were given DTP and MCV on the same day (DHS 2006-09: 2%, MICS 2002-05: 5%). The actual number for whom DTP3 was the last given was not reported, but appears from a figure to be about 16%. This compares with 6% in DHS for 2006-09 and 10% in MICS for 2002-05. In surveillance data for 1998 and 2000 from one area in the Gambia[6] with a population of about 17,000, 6% of children had had DTP after, or at the same time as, measles vaccine (MICS 2001-04: 30%).

Two more recent reports on this question from Guinea-Bissau give contrasting results. In data gathered between 2003 and 2009 from biannual surveillance of randomly selected villages[7], in 5806 children given BCG by age 12m, 54% had received DTP before or with the BCG (MICS 2002-6: 33%). Among those given MCV by age 12m, 28% had received DTP with or after MCV (MICS 2002-6: also 28%). But the most recent data (2008-9) are from a health and demographic surveillance system covering a population of about 78,000. Of the children with vaccination cards, about 5% had BCG with or after DTP1, and about 4% had DTP with or after MCV[8].

Most of these studies are in specific areas of the countries concerned, and quite substantial local variations around a national figure can be expected. However one point that does stand out is that much of the published data on out-of-order vaccination are from around twenty years ago or more. Some of the national surveys were also done some ago, but at least part of any apparent discrepancies between the results of national surveys and of more focussed studies can be attributed to the passage of time. It does appear that out-of-order, and same-day vaccinations are on the decline. As Ouédraogo et al point out, 'correct sequencing of childhood vaccinations has significantly improved in recent years in West Africa', and the limited information on trends from the survey data suggest that has also been happening elsewhere. Also the survey data are improving.

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Technical Brief No.1, 2008

INTEGRATED HEALTH SERVICES – WHAT AND WHY?

Main Messages

This Technical Brief is intended as a practical aid for people involved in discussions about "integrated health services".

Integration is not a new topic – in the past it has been the subject of a rather polarized debate. It is once again a topical issue, largely because of the rise of single-disease funding and recognition of the fact that the health Millennium Development Goals (MDGs) will not be met without improving health *systems.*

"Integrated health services" means different things to different people – it is important to be clear about how the term is being used. Six common uses of the term are described in this Brief.

Integration is best seen as a continuum rather than as two extremes of integrated/not integrated. Integration is about the organization of various tasks which need to be performed in order to provide a population with good quality health services.

An overall working definition of integrated service delivery is **"The management and delivery of health services so that clients receive a continuum of preventive and curative services, according to their needs over time and across different levels of the health system."**

The evidence base about integration is limited, though a systematic review was published in 2007 (15). We have learned 3 important lessons:

- Supporting integrated services does not mean that everything has to be integrated into one package. In reality, there are many possible permutations.
- Integration isn't a cure for inadequate resources.
- There are more examples of policies in favour of integrated services than examples of actual implementation. Managing change may require action at several levels. It requires engagement of health workers and managers, plus a sustained commitment from senior management and policy-makers.

World Health Organization

Introduction

This Technical Brief is intended as a practical aid for people involved in discussions about "integrated health services". The term "integrated health services" has several usages and can refer to a number of different health service issues. This Brief aims to demonstrate both the importance of clarity and the fact that "integration" is an important and topical issue.

The Brief outlines the various definitions of "integrated health service" and proposes one overall working definition. It then briefly describes key questions around integration – is it a good thing? How is it achieved? In the past, discussions about integration have been rather polarized – this Brief aims to show that integration is best seen as a continuum and is about the organization of various tasks which need to be performed in order to provide a population with good quality health services.

The length of this Brief obviously means that it cannot describe the full complexities of the subject – references are provided for interested readers who want to explore the subject in more depth.

Context

"We need a comprehensive, integrated approach to service delivery. We need to fight fragmentation." ***WHO Director-General, 2007 (1)***

Why has the Director-General of WHO called so unequivocally for integrated health services? There are a number of reasons for the current interest in integrated services:

- Recent years have seen a dramatic rise in funding for single-disease or population-group-specific programmes, such as HIV/AIDS, immunizations, malaria and polio eradication. For example, funding for HIV/AIDS as a proportion of total health Official Development Assistance (ODA) has risen from less than 10% in the 1990s to around 30% currently. (2) There are concerns about potentially adverse effects on less well-funded health priorities.
- Health services face resource constraints. Of particular concern are human resource shortages in low income countries. Available resources have to be used as efficiently as possible.
- The MDGs – with their simultaneous focus on child and maternal health, HIV/AIDS and malaria – have highlighted the fact that some constraints to effective scaled-up service delivery are common to several technical programmes. For example all the health-related MDGs rely on the existence in a country of a well-functioning workforce of nurses and an efficient pharmaceutical distribution system – it thus makes no sense to tackle the three relevant Goals separately. (3, 4)

Talk of integration can arouse fears that specialist functions will be compromised. One example is technical supervision: efforts to introduce more integrated supervision, to reduce demands on local health workers' time and generate economies of scale with limited resources, raise fears about reduced quality of supervision. This fear should be baseless in a properly designed system, but must be addressed: such a system might well include specialist oversight of - for example - surveillance for a package of infectious diseases.

The idea of integrated health services is not new. Indeed it was the basis for the focus on primary health care in the 1980s. For some people this renewed interest is not surprising, as they regard integrated services as the most logical way to organize a health system – indeed the only way that does not compromise universal access to a broad range of services. The current challenge is to be specific about what integrated services look like – what are the key functions which need to be delivered?

Multiple Meanings

"Integrated health services" means different things to different people. There are six main usages, but many nuances within these. Inevitably these overlap somewhat, particularly definitions 1 and 2.

1. "Integrated" is frequently used to refer to **a package of preventive and curative health interventions for a particular population group –** often (but not always) this group is distinguished by its stage in the life cycle. (5) Examples are the Integrated Management of Childhood Illness (IMCI), Integrated Management of Pregnancy and Childbirth (IMPAC), Integrated Management of Adolescent and Adult Illness (IMAI) and (not specifically related to life cycle) Integrated Management of Cardiovascular Risk. The aim of this form of integration is for individuals in the target group to receive all appropriate interventions, ideally from the client's perspective at a "one-stop shop". This can be very important – for example, TB services need to deal with the fact that many of their clients may be HIV positive; be malnourished, smoke or have diabetes. Key questions under this definition are: exactly what interventions should be packaged together? How are management support systems best organized to service these interventions? [1]

2. "Integrated health service" can refer to **multi-purpose service delivery points –** a range of services for a catchment population is provided at one location and under one overall manager. Examples are multi-purpose clinics, multi-purpose outreach visits and a hospital with the management of all its services consolidated under one Board and one Chief Executive. A feature of this form of integration from the client's perspective is the opportunity to receive co-ordinated care, rather than having separate visits for separate interventions. Again key issues are: exactly what functions should be included in "multi-purpose"? How can management systems best support these service delivery points?

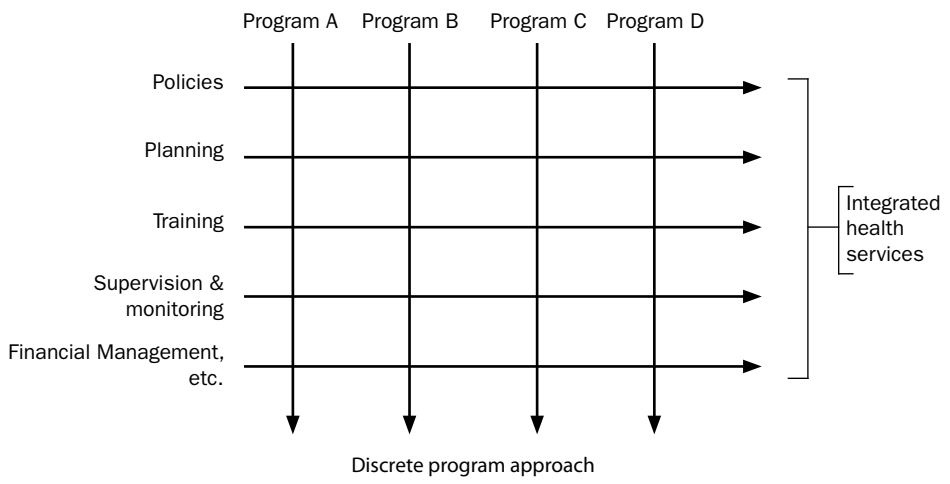
3. "Integrated services" to some means achieving continuity of care **over time.** This may be about life-long care for chronic conditions such as HIV/AIDS, or a continuum of care between more specific stages in a person's life-cycle – for example antenatal, postnatal, newborn and child care.

4. Integration can also refer to the **vertical integration of different levels of service –** for example a district hospital, health centres and health posts. In this form of integrated health services, an overall manager is in charge of a network of facilities and personal and non-personal health services – for example a District or Provincial Medical Officer of Health, who in turn supervises the work of the managers of individual facilities. Ideally, s/he should be able to rise above day-to-day concerns and take a strategic overview of issues such as which services should be provided at which level(s) of the system. From the clients' perspective, a key feature of this type of integrated health service is well-functioning procedures for referrals up and down the levels of the system, and between public and private providers. Key issues are: what services should be provided where, and how to ensure that clients are efficiently referred? Realistically, to what extent can private and voluntary providers be integrated with the public system?

5. Integration can also refer to **integrated policy-making and management** which is organized to bring together decisions and support functions across different parts of the health service. For example a management team in an integrated system may have overall responsibility for the health status of a given population and may be able to simultaneously contract services from the public, voluntary and private sectors. An integrated district service would conduct integrated supervision – supervisory visits to health centres, for example, would look at all aspects of the centre's work, ideally using a standardized checklist. This definition is illustrated by the horizontal arrows in Figure 1. Key issues include how best to provide an all-round good service for clients and how to solve problems such as a lack of co-ordination or gaps in the service.

1 People speaking from a particular technical area also use this definition, but in a narrower sense to mean the combination of some services which were previously separate – for example the integration of HIV/AIDS and sexual/reproductive health activities or an integrated strategy for preventive chemotherapy for four neglected tropical diseases (lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminthiasis).

Figure 1 – Integrated Policy and Management



6. Integration can mean **working across sectors.** It occurs when there are institutionalized mechanisms to enable cross-sectoral funding, regulation or service delivery. In industrialized countries, this concept is frequently applied to the co-ordination of health and social services, such as for long term care for the elderly. It may refer to work with education services to develop effective school health promotion campaigns. The key issue here is to identify the most appropriate sector(s) to deal with a particular health issue and establish linkages between them.

In addition, there is a seventh, less common, usage, used in countries dominated by health insurance. In this context, integration can mean that **the insurance function and health care provision are provided by the same organization.** According to this definition, Health Maintenance Organizations are an example of integration. (6)

Definitions 1-6 are best seen as continuums, rather than in terms of "integrated" or "not integrated". For example, a fully integrated service has one set of management support systems (financial and human resource management, logistics and supplies etc.) supporting the service as a whole. In reality, various arrangements can exist under any of these definitions. In practice, separate management support systems often exist when a particular area is (or has been) supported financially by an external development partner. This means that there are many hybrid versions of "integrated health services" – an example is a district TB officer who reports to the District Medical Officer and participates fully in district health team activities, but who receives TB drug supplies through a separate supply system and sends TB surveillance data through a stand-alone information system.

One working definition

The most common use of "integration" – and the meaning implied in the WHO quotation on page 2 – is a combination of definitions 1 - 5.[2] This can be summarized as:

> **"The management and delivery of health services so that clients receive a continuum of preventive and curative services, according to their needs over time and across different levels of the health system."**

2 This is less true for industrialized countries, where "integration" tends to be used more in the contexts of (a) links with social services and/or (b) insurance.

There are clearly many issues going on "behind" this general definition and it is useful to look at "integration" from various perspectives. (7)

For the ***user,*** integration means health care that is seamless, smooth and easy to navigate. Users want a co-ordinated service which minimizes both the number of stages in an appointment and the number of separate visits required to a health facility. They want health workers to be aware of their health as a whole (not just one clinical aspect) and for health workers from different levels of a system to communicate well. In short, clients want continuity of care.

For ***providers,*** integration means that separate technical services (and their management support systems) are provided, managed, financed and evaluated either together, or in a closely co-ordinated way.

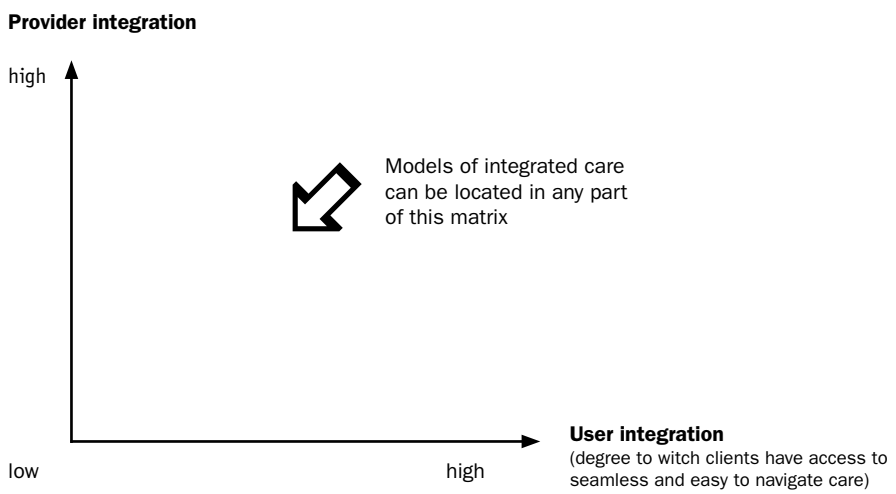
At the macro level of ***senior managers and policy-makers,*** integration happens when decisions on policies, financing, regulation or delivery are not inappropriately compartmentalized. This means bringing together different technical programmes, but also considering the whole network of public, private and voluntary health services, rather than looking at the public sector in isolation.

Organizational integration happens when there are mergers, contracts or strategic alliances between different institutions.

Professional integration happens when different health professions or specialties work together to provide joined-up services. An obvious example is co-ordinating the timings of ante-natal and child health clinics. The first challenge in professional integration is to have the appropriate range of skills available in the health service; the second challenge is to ensure that different professional groups collaborate effectively. Skill mix can be tackled by employing a number of different types of professional; it can also be improved by assigning a broad range of tasks to one specific cadre – this is what is meant by a multi-purpose health worker.

Many permutations of integration from the users' and providers' perspectives are possible. In some models of care, despite high levels of provider integration, users may experience low levels of integration in their access to care - or vice versa. These ideas are portrayed visually in Figure 2, below (7), which reinforces the idea of a continuum. Reference (7) also provides a practical example: "Imagine a primary care centre that has organized its professionals in a network, but where communication between them is poor. Though this centre may appear integrated from a provider perspective, for the user, navigating the system has not been made any easier. From his perspective, care is still fragmented".

Figure 2 – The Integrated Care Matrix (7)



Integration – key considerations

In the past, discussions about integration have been rather polarized – this Brief aims to show that integrated service delivery is best seen as a continuum and that it involves technical discussions about the various tasks that need to be performed in order to provide a population with good quality health services.

1. Arguments for and against integration

Many benefits are claimed for integrated health services – they can be cost-effective, client-oriented, equitable and locally owned. The "cost" part of cost-effectiveness is based on the idea that it is more economically efficient to share resources (particularly human resources) than have them devoted to one particular disease. The "effectiveness" is based on the idea that it makes sense to deal with a whole person (plus his or her family, sexual contacts etc.), rather than focussing separately on just one health problem in an individual.

An integrated health service is not *necessarily* equitable – one can imagine a well-integrated but very inequitable system, because of, for example, a strong urban bias. The idea here is that an integrated service has more chance of ensuring more equitable access across the spectrum of priority conditions than do a series of single-issue programmes.

Integration has its critics, who deploy the following arguments:

- Especially in countries where the wider health system does not function well, it makes no sense (or is too risky) to change a separate programme which works well. The high quality work of a programme which provides a rather narrow range of services to an excellent standard is jeopardized by integration. There are also concerns that the allocation of financial resources to a particular health priority may be reduced.
- The desire for integrated services ignores realpolitik, which is currently dominated by an interest in targets, short time-frames and sound-bites. If the health sector is to attract attention and financial support, it needs to be able to show significant reductions in specific diseases. (8)
- AIDS exceptionalism – i.e. the argument that the nature of the HIV epidemic means that it is important to regard HIV/AIDS services as a special case which needs to be well-resourced, expanded quickly and "protected" from the inefficiencies of the broader health system. As with all these supposedly yes/no arguments, the reality is more nuanced, along a continuum of integration. AIDS exceptionalism does not imply that no HIV/AIDS services can be integrated.

In practice, an "always good" versus "always bad" debate about integration is not helpful. On the ground, integration is about practical issues of how to deliver health services to those who need them.

2. Lessons for successful integration

Three main lessons emerge from the literature about successfully developing integrated health services:

(a) Supporting integrated services does not mean that everything has to be integrated into one package. It is best regarded as a continuum. There are also arguments in favour of some "single-issue-style" provision:

- as a short-term measure in fragile states
- for the control of some epidemics and the management of some emergencies (9)
- so that appropriate services can be provided for specific client groups such as sex workers, drug addicts or prisoners. (10)

(b) Integration isn't a cure for inadequate resources. Integrating two separate programmes may provide some savings, but integrating new activities into an existing system can't continue indefinitely without the system as a whole being better resourced. For example, a given workforce of nurses cannot be expected to add more and more duties to their workload without expanding the overall workforce at some point. Quality of care can also be affected by integration and hence needs to be regularly monitored. Moreover, integration is not a cure for something that simply doesn't work. A public system with no track record of regulating the quality of private providers may decide to "integrate" private provision of priority services – but this will not change the underlying problem of non-existent regulation of private provision.

(c) There are many more examples of policies in favour of integrated services than there are of actual implementation. (8). Developing integrated health services requires a full-scale "hearts and minds" commitment, backed up by guidance, such as that from the South African Department of Health. (11) Activities at the operational level often rely too heavily on training alone and need to be complemented by changes at the management level. Otherwise there are situations such as new working practices for health workers (who may be asked to change their hours of work, for example, to better meet clients' needs) which are not reflected in the documents and procedures of the Human Resources Division.

3. A weak empirical base

The empirical base for many of the above arguments is weak. Most research work has focussed on reproductive health and integration. (12, 13) We know, for example, that integrating services does not automatically lead to an uptake of family planning – indeed it can have the reverse effect. We also know that STI treatments for women can increase significantly when the treatment is integrated into broader health service delivery. (14) So we know that the move from disease- or population-specific programmes to integrated services has risks as well as benefits and needs to be managed carefully. There is little empirical evidence, at least from low and middle-income countries, for the more basic question – as we develop and expand service delivery, is it right to assume that concentrating on integrated services is the best approach? This conclusion about a weak evidence base is confirmed by a 2007 Cochrane systematic review of integration, which concluded:

> "Few studies of good quality, large and with rigorous study design have been carried out to investigate strategies to promote service integration in low and middle income countries. All describe the service supply side, and none examine or measure aspects of the demand side. Future studies must also assess the client's view, as this will influence uptake of integration strategies and their effectiveness on community health." (15, page 1)

More empirical evidence from low-income countries is needed. At the same time experience from high-income countries should not be ignored - provided it is carefully interpreted.

Conclusion

"Integration" is used by different people to mean different things. Combined with the fact that this is an issue which arouses strong feelings, there is clearly much scope for misunderstanding and fruitless polarization.

Integration can be broken down into a series of practical questions about who does what at what levels of a health system. Being clear about these questions can be the basis for constructive discussions about the development of integrated health services.

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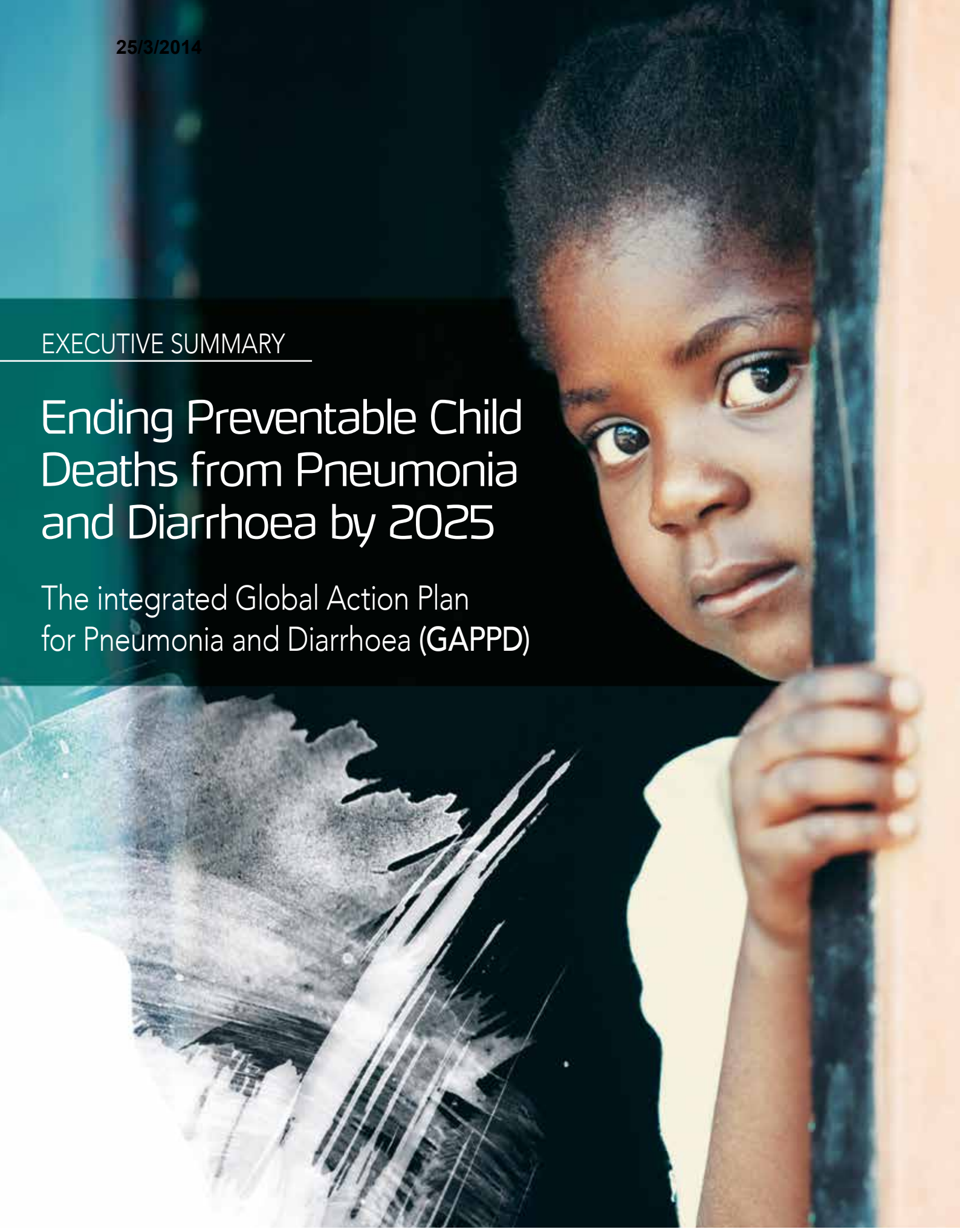
This brief has been prepared by Catriona Waddington of HLSP and Dominique Egger of the WHO Department of Health Policy, Development and Services and has been through a peer review process.

See www.who.int/healthsystems for additional resource materials on health systems.



EXECUTIVE SUMMARY

Ending Preventable Child Deaths from Pneumonia and Diarrhoea by 2025

The integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD)

unicef

World Health Organization

Ending two major preventable causes of child death

Stopping the loss of millions of young lives from pneumonia and diarrhoea is a goal within our grasp. The *integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD)* proposes a cohesive approach to ending preventable pneumonia and diarrhoea deaths. It brings together critical services and interventions to create healthy environments, promotes practices known to protect children from disease and ensures that every child has access to proven and appropriate preventive and treatment measures.

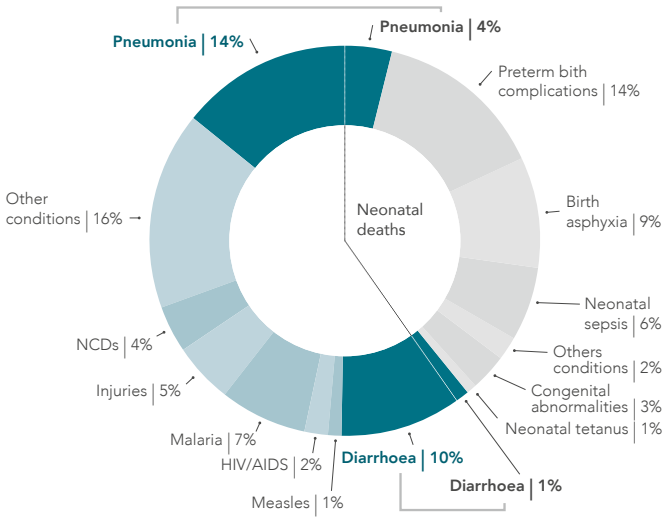
The goal is ambitious but achievable: to end preventable childhood deaths due to pneumonia and diarrhoea by 2025.

The momentum needed to achieve this goal exists already. The world has achieved substantial gains in child survival over the past 20 years and extensive work has been done to not only meet the Millennium Development Goal for 2015 on child survival, but also go beyond. The United Nations *Global Strategy for Women's and Children's Health*, launched in 2010, calls for a "continuum of care" approach to services, aiming to save 16 million lives. With the Every Woman Every Child movement, efforts have continued. In 2012, the call to action *Committing to Child Survival: A Promise Renewed* challenged the global community to reduce child mortality to 20 or fewer child deaths per 1000 live births in every country by 2035.

Other contributing initiatives include the *Global Vaccine Action Plan*, which sets out a strategy for preventing childhood disease through vaccination; the comprehensive implementation plan to improve maternal, infant and young child nutrition endorsed by WHO Member States; and the United Nations *Sustainable Energy For All* initiative which is a public-private commitment to universal access to modern energy services by 2030. Moreover, the United Nations *Commission on Life-Saving Commodities* made important recommendations to strengthen access to and use of life-saving commodities including treatment for pneumonia and diarrhoea, while the United Nations *Commission on Information and Accountability* paved the way for improved monitoring of programmes to protect women's and children's health.

Closing the gap: reaching all children with existing interventions

Pneumonia and diarrhoea remain major killers of young children. Together, these diseases account for 29% of all deaths of children less than 5 years of age and result in the loss of 2 million young lives each year.

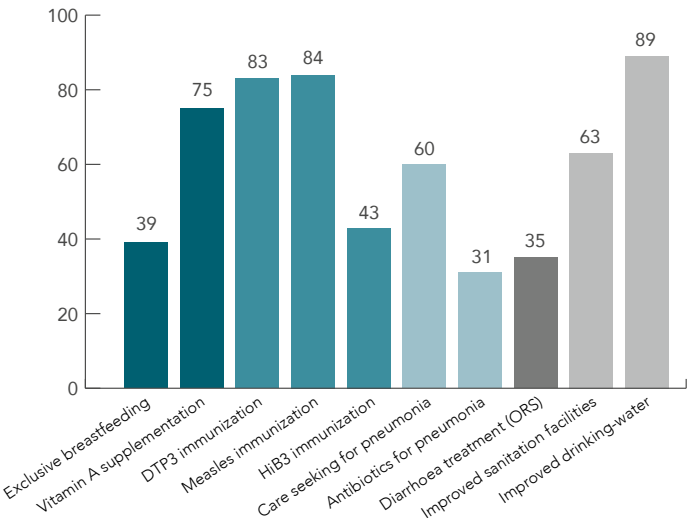


Thirty-five percent of deaths in children less than five years of age are associated with malnutrition.'

Sources: WHO Global Health Observatory (http://www.who.int/gho/child_health/en/index.html) and 'Black R et al. *Lancet*, 2008, 371:243-260

Children who are poor, hungry and living in remote areas are most likely to be visited by these "forgotten killers" and the burden placed by pneumonia and diarrhoea on families and health systems aggravates existing inequalities.

The solutions to tackling pneumonia and diarrhoea do not require major advances in technology. Proven interventions exist. Children are dying because services are provided piece-meal and those most at risk are not being reached. Use of effective interventions remains too low; for instance, only 39% of infants less than 6 months are exclusively breastfed while only 60% of children with suspected pneumonia access appropriate care. Moreover, children are not receiving life-saving treatment; only 31% of children with suspected pneumonia receive antibiotics and only 35% of children with diarrhoea receive oral rehydration therapy.



Source: UNICEF's State of the World's Children 2013

Identifying those children at greatest risk, hardest to reach and most neglected, and targeting them with **interventions of proven efficacy** will enable us to close the gap, ultimately ending the heavy toll of preventable child deaths.

Using interventions that work

Research shows that these interventions and activities work:

- Exclusive breastfeeding for six months and continued breastfeeding with appropriate complementary feeding reduces the onset and severity of diarrhoea and pneumonia.
- Use of vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, the two most common bacterial causes of childhood pneumonia, and against rotavirus, the most common cause of childhood diarrhoea deaths, substantially reduces the disease burden and deaths caused by these infectious agents. In response, an increasing number of countries are introducing these vaccines.
- Use of vaccines against measles and pertussis substantially reduces pneumonia illness and death in children.
- Use of simple, standardized guidelines for the identification and treatment of pneumonia and diarrhoea in the community, at first-level health facilities and at referral hospitals, such as those for integrated management of childhood illness (IMCI), substantially reduces child deaths.
- Oral rehydration salts (ORS), and particularly the low-osmolarity formula, are a proven life-saving commodity for the treatment of children with diarrhoea.
- Innovative demand creation activities are important for achieving behaviour change and sustaining long-term preventive practices.
- Water, sanitation and hygiene interventions, including access to and use of safe drinking-water and sanitation, as well as promotion of key hygiene practices provide health, economic and social benefits.
- Reduction of household air pollution with improved stoves has been shown to reduce severe pneumonia. Safer and more efficient energy in the home prevents burns, saves time and fuel costs, and contributes to better development opportunities.

An integrated approach for saving lives

The GAPPD provides an integrated framework of key interventions proven to effectively prevent and treat childhood pneumonia and diarrhoea. Although effective interventions have been well established, they are not always promoted together to achieve maximum benefit. It is now clear that pneumonia and diarrhoea must be addressed in a coordinated manner. The determinants are often the same, hence preventive strategies and delivery platforms via health care facilities, families, communities and schools are similar.

Engaging all sectors and actors

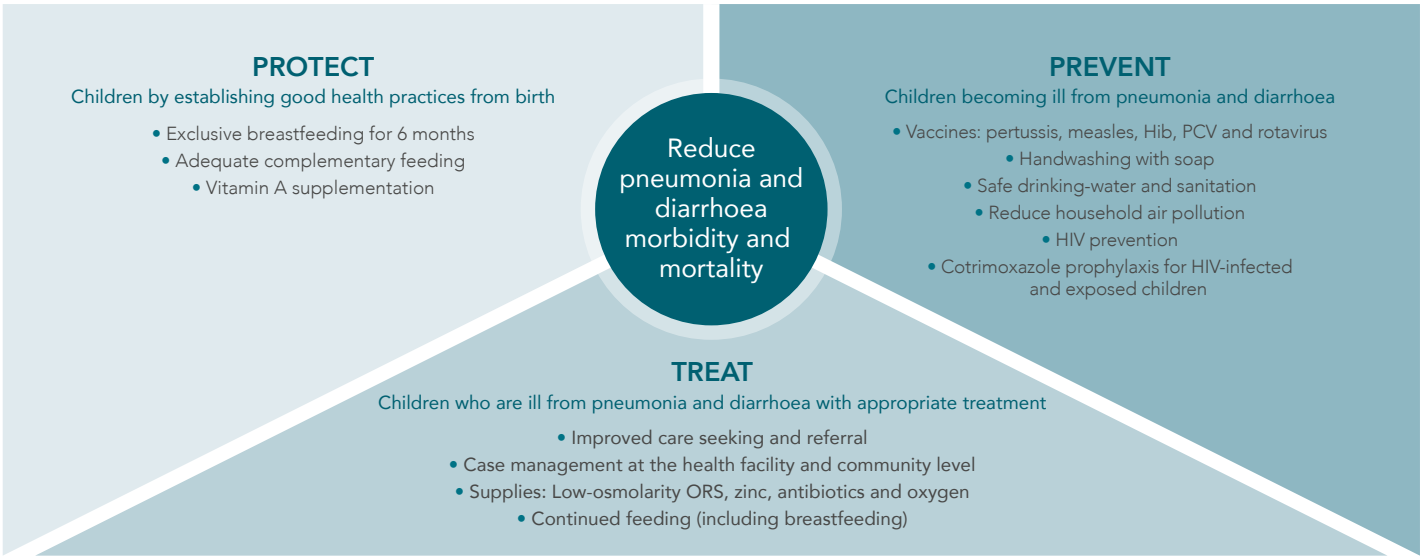
The GAPPD provides a roadmap for national governments and their partners to plan and implement integrated approaches for the prevention and control of pneumonia and diarrhoea. It recognizes that for successful implementation, the effective engagement of all relevant stakeholders is key, and it pays special tribute to front-line health care providers, especially those at the most peripheral levels, as well as communities.

The strategy at a glance

The GAPPD identifies opportunities to better integrate activities as well as capture synergies and efficiencies.

It envisions the various interventions for controlling pneumonia and diarrhoea in children less than five years of age as:

- *protecting* children by establishing and promoting good health practices;
- *preventing* children from becoming ill from pneumonia and diarrhoea by ensuring universal coverage of immunization, HIV prevention and healthy environments;
- *treating* children who are ill from pneumonia and diarrhoea with appropriate treatment.



A focus on country impact

The Integrated Global Action Plan aims to help countries achieve impact by analysing local data, acting on the results and monitoring their progress towards clear, achievable goals.

Goals by 2025:

- reduce mortality from pneumonia in children less than 5 years of age to fewer than 3 per 1000 live births;
- reduce mortality from diarrhoea in children less than 5 years of age to fewer than 1 per 1000 live births;
- reduce the incidence of severe pneumonia by 75% in children less than 5 years of age compared to 2010 levels;
- reduce the incidence of severe diarrhoea by 75% in children less than 5 years of age compared to 2010 levels;
- reduce by 40% the global number of children less than 5 years of age who are stunted compared to 2010 levels.

Coverage targets: to achieve these goals, the following targets will need to be maintained or reached by the end of 2025:

- 90% full-dose coverage of each relevant vaccine (with 80% coverage in every district);
- 90% access to appropriate pneumonia and diarrhoea case management (with 80% coverage in every district);
- at least 50% coverage of exclusive breastfeeding during the first 6 months of life;
- virtual elimination of paediatric HIV.

By the end of 2030:

- universal access to basic drinking-water in health care facilities and homes;
- universal access to adequate sanitation in health care facilities by 2030 and in homes by 2040;
- universal access to handwashing facilities (water and soap) in health care facilities and homes;
- universal access to clean and safe energy technologies in health care facilities and homes.

Action at country level

In order to reach the goals, the GAPPD recommends that governments and partners:

Develop a clear country-level strategy and work plan, with key responsibilities assigned:

- generate political will;
- develop/update a situation analysis for pneumonia and diarrhoea;
- prioritize interventions;
- develop/update a costed plan for accelerated action;
- identify areas of harmonization and collaboration between programmes and sectors, including the private sector, academia and civil society;
- use data to identify groups at greater risk or missed by services and develop targeted approaches to reach them;
- develop a set of common indicators for tracking progress.

Coordinate implementation of interventions:

- designate a national working group for pneumonia and diarrhoea prevention and control or review membership of an appropriate existing group;
- mobilize resources;
- apply lessons from other integrated disease prevention and control efforts;
- track execution and progress;
- take and/or assign accountability for action.

Engage and embed critical partners in the overall work plan/ approach:

- involve other programmes and sectors;
- involve the private sector and nongovernmental organizations;
- engage the United Nations agencies and development partners.

Other actions:

- promote innovations, especially for overcoming barriers to service delivery;
- generate demand and ensure supply;
- focus on implementation research and identify optimal modes of delivery of existing interventions in order to reach those most in need.

Conclusion

The targets in the *integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea* will not be achieved without urgent action in the areas listed above from national governments as well as supporting partners at the global level. Focused, coordinated and integrated international, national and sub-national action on pneumonia and diarrhoea control is needed to continue sustaining and increasing the gains in the reduction of child mortality. This document calls on all concerned groups to demonstrate their commitment, allocate the required resources, and work together to make preventable child deaths due to pneumonia and diarrhoea a tragedy of the past.

GAPPD Key Messages

1. Working together, we can end preventable deaths of young children around the world from two of the leading child killers, pneumonia and diarrhoea.
2. The *integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD)* from WHO and UNICEF goes to the heart of the challenge: recognizing that prevention and control of pneumonia and diarrhoea cannot be adequately dealt with separately but only through integrated programmes.
3. Without these urgent accelerated and coordinated efforts, each year more than two million of the world's most vulnerable children will continue to die from these two diseases. We must close this equity gap.
4. Successfully reducing pneumonia and diarrhoea deaths requires engagement by a wide range of actors and sectors, and first and foremost, it requires national political will.
5. These diseases must be addressed if we are to move the needle significantly in achieving the Millennium Development Goal to save the lives of children under the age of five (MDG4), as well as successful implementation of the UN Global Strategy for Women's and Children's Health, and the Promise Renewed commitment to child survival.

SUPPLEMENT ARTICLE

Experiences Integrating Delivery of Maternal and Child Health Services With Childhood Immunization Programs: Systematic Review Update

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Background. The World Health Organization and the United Nations Children's Fund promote integration of maternal and child health (MCH) and immunization services as a strategy to strengthen immunization programs. We updated our previous review of integrated programs and reviewed reports of integration of MCH services with immunization programs at the service delivery level.

Methods. Published and unpublished reports of interventions integrating MCH and immunization service delivery were reviewed by searching journal databases and Web sites and by contacting organizations.

Results. Among 27 integrated activities, interventions included hearing screening, human immunodeficiency virus services, vitamin A supplementation, deworming tablet administration, malaria treatment, bednet distribution, family planning, growth monitoring, and health education. When reported, linked intervention coverage increased, though not to the level of the corresponding immunization coverage in all cases. Logistical difficulties, time-intensive interventions ill suited for campaign delivery, concern for harming existing services, inadequate overlap of target age groups, and low immunization coverage were identified as challenges.

Conclusions. Results of this review reinforce our 2005 review findings, including importance of intervention compatibility and focus on immunization program strength. Ensuring proper planning and awareness of compatibility of service delivery requirements were found to be important. The review revealed gaps in information about costs, comparison to vertical delivery, and impact on all integrated interventions that future studies should aim to address.

The Expanded Programme on Immunization (EPI), begun in 1974, is considered one of the world's most successful public health programs, as measured by equity and coverage of its intended target population, infants <12 months of age [1–3]. EPI is a platform from which it is possible to deliver additional health interventions, and this concept has received widespread support. In 2005, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) introduced the Global Immunization Vision and Strategy, a 10-year framework for guiding immunization programs worldwide. The strategy promotes integration of primary healthcare services with immunization as a strategy to increase coverage with other maternal and child health (MCH) interventions and sustain immunization programs [4].

In 2005, we conducted a systematic literature review of experiences integrating additional services into immunization programs in order to document lessons learned for future integration activities [5]. Our review of 27 articles that were published prior to 2005 identified key benefits, such as quick scale-up of coverage for the linked intervention and increased user satisfaction, in addition to concerns about overburdening health workers and difficulty planning in the face of increased logistical requirements. Although reported outcomes were primarily positive across all studies, few used rigorous comparison groups or documented the costs associated with integration.

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This review provides an update on experiences integrating health interventions with immunization programs at the point of service delivery. We identify the linked interventions and the reported results by service delivery method and discuss implications for research and practice.

METHODS

Literature Search

We used the same methodology described in our previous review of experiences integrating health interventions with immunization services to conduct the literature search to preserve consistency and enable us to compare findings [5]. In our previous review, we reviewed gray and peer-reviewed literature from 1970 to 2005 on experiences in operationally integrating immunization services with other health interventions at the point of service delivery.

For this review, we used 48 keywords, alone and in combination, to search gray and peer-reviewed online literature databases and organizations' Web sites and to conduct Internet searches using Google (Table 1). Gray literature was defined as material not published in a peer-reviewed journal; it was collected through contact with field experts, Internet searches, and requests to organizations known to conduct integrated services projects. Organizations and individuals with experience conducting integrated projects were e-mailed with requests for information on projects they had conducted. We included articles published in English and Spanish from January 2001 through February 2011 that reported experiences operationally integrating immunization services with additional maternal or child health interventions at the service delivery level in any low- or middle-income country, as defined by the World Bank [6]. We purposely overlapped our review dates with the review dates of the previous review in the event that additional gray literature from the 2001–2005 time frame had become available since 2005. We excluded expert opinions, other systematic reviews, studies describing integration of immunization services with general primary healthcare, studies that did not focus on the operational impact of integrated service delivery, studies that focused primarily on the biological interactions of drugs administered rather than the operational aspects of integration interventions, and studies included in our previous review [5].

Systematic Review Method

We updated the data extraction form used in our previous review to systematically collect information from each article including intervention and evaluation details, outcomes, costs, and lessons learned. Two researchers extracted data from each article. Extractions were compared, and if there were discrepancies, the articles were discussed until both researchers reached agreement. To assist in interpretation of each study's results, the following scientific components were also extracted: (1) presentation of target population data, (2) use of a randomized study design, (3) presence of well-defined research outcomes, (4) extent of data analysis, (5) discussion of study limitations, and (6) comparison of findings to published literature. Articles were grouped according to the type of immunization service delivery. *Routine immunization* (RI) services were defined as those provided on an ongoing basis through fixed or outreach locations, and *immunization campaigns* were defined as time-limited events usually focused on specific disease elimination or eradication targets [3]. *Enhanced routine activities* (ERAs) include services such as child health weeks (CHWs), which are structured like campaigns but with the aim of increasing RI coverage. In many countries, ERAs occur at least 1–2 times each year [3]. Fully immunized coverage was defined as 1 dose of BCG vaccine, 3 doses of diphtheria-tetanus-pertussis (DTP) vaccine, 3 doses of polio vaccine, and 1 dose of measles vaccine.

RESULTS

The initial search yielded 86 articles, 32 of which met our criteria for inclusion in the review. Of these 32 articles, 24 (75%) were from peer-reviewed journals and 8 (25%) were from the gray literature. These 32 articles covered 27 distinct integration activities/studies. In some instances, articles reported on the same integration activity (Table 2). Of the 27 activities, 24 (89%) were based in African countries, 1 in India, 1 in Mexico, and 1 in the Philippines. Sixteen (59%) projects described integrated routine services, 5 (19%) enhanced routine activities, and 6 (22%) campaigns.

The articles reporting integration with RI programs were conducted in countries where WHO/UNICEF estimated that coverage with the third dose of DTP vaccine (DTP3) ranged from 68% (South Africa) to 99% (Malawi), with a nonweighted mean of 78% (Table 2) [7, 8]. In countries where integration occurred with enhanced routine activities, DTP3 coverage ranged from 72% (Ethiopia) to 91% (Mexico), with a nonweighted mean of 81%. Countries with integrated campaign studies had estimated DTP3 coverage ranging from 39% (Niger) to 90% (Tanzania), with a nonweighted mean of 70%. These integrated campaigns reached >85% coverage for vaccinations and other linked interventions, including in countries where DTP3 coverage was <50%, as measured by WHO/UNICEF coverage estimates. We identified no studies published on integration of interventions with routine services in countries where estimated DTP3 coverage was <68% (Table 2).

Characteristics of Methods

The 32 articles we reviewed reported a variety of methods to describe and assess integration activities. Twenty-six (81%) included a formal evaluation and 6 (21%) only provided a description of the integrated activity. Eighteen of the 26 evaluative articles used quantitative methods, 5 used qualitative methods, and 3 used mixed methods. Three (9%) of the 32 articles included control groups and 8 (25%) reported implementation

Table 1. Keywords and Data Sources Used for a Systematic Literature Review of Maternal and Child Health Interventions Integrated With Immunization Services in Developing Countries

Keywords (used singly or in combination)	Africa
	Asia
	Bednet
	Campaign
	Child health week
	Collaborate[a]
	Collaboration
	Combination
	Combine
	Deworming
	Disease[a]
	EPI
	Expanded Programme
	Family planning
	Filariasis
	Health
	Immunization plus
	Immunization[a]
	India
	Integrate
	Integration
	Intermittent preventative
	IPTi
	ITN
	Joint
	Link[a]
	Linkage
	Malaria
	Maternal
	Measles
	Net[a]
	Onchocerciasis
	Partner
	Partnership[a]
	Polio
	Reproductive
	Routine
	Shistosomiasis
	Synergies
	Synergy
	Trachoma
	Vaccination[a]
	Vitamin A
Literature databases used	Access UN
	AccessScience
	AGRICOLA
	Bioline International
	BioMed Central
	BIOSIS
	CAB Abstracts
	CHID Online
	CINAHL
	Cochrane Library
	CSA-Illumina Databases
	Dissertation Abstracts
	EMBASE
	Expanded Academic ASAP
	Global Health
	IBSS
	IndMed
	LexisNexis Academic
	LILACS
	Ovid MEDLINE
	PAIS
	POPLINE
	Population Index
	Proquest Research Library
	PubMed (Medline)
	SIGLE
	UNDP Project Reports
	Web of Science
	WHOLIS
Websites visited (using the Google search engine)	www.basics.org
	searchbeta.bl.uk
	www.care.org
	www.fhi.org
	www.filariasis.org
	www.gavialliance.org
	www.greynet.org
	www.hki.org
	www.ifrc.org
	www.msh.org
	www.nyam.org/library/greylitorgs.shtml
	www.paho.org
	www.path.org
	www.pathfind.org
	www.psi.org
	www.redcross.org
	www.savethechildren.org
	www.savethechildren.org.uk
	www.trachoma.org
	www.un.org
	www.undp.org
	www.who.int/library
Organizations contacted (by e-mail or telephone)	London School of Hygiene and Tropical Medicine
	International Federation of Red Cross & Red Crescent Societies
	World Health Organization
	Liverpool School of Tropical Medicine
	Centers for Disease Control and Prevention
	World Bank
	Rollins School of Public Health, Emory University

Table 1 continued.

[a] Keyword search included singular and plural versions.

Table 2. Strategies and Characteristics of Activities Integrating Immunization Services With Additional Health Interventions Documented in 32 Reviewed Articles

Delivery Method	Country	Study Year	Linked Intervention(s)	Vaccine(s) Provided	Primary Integration Strategy	DTP3 Coverage[a]	Vaccine Coverage Assessed	Linked Intervention Coverage Assessed	Primary Indicator(s) Measured in Study	Literature Type and Citation
Routine	Ghana	2004	Infant malaria treatment	DTP, measles	IPTi delivered to infants at DTP2, 3, and measles vaccination visits	80	No	No	Cost-effectiveness of delivery strategy	Peer-reviewed [10]
Routine	Mozambique	2002	Infant malaria treatment	DTP, measles, polio	Infants at immunization visits were referred to IPTi services	72	No	No	Caretaker opinions of integrated delivery	Peer-reviewed [9]
Routine	Ghana	2006	Infant malaria treatment	DTP, measles, polio	IPTi delivered to infants at routine vaccination visits	84	No	Yes	Comparison of 2 delivery strategies for IPTi	Peer-reviewed [11]
Routine	Tanzania	2005	Infant malaria treatment	DTP, measles, polio	IPTi delivered to infants at routine vaccination visits	90	No	No	Description of how IPTi was integrated into routine services	Peer-reviewed [12]
Routine	Mozambique; Tanzania	2002; 1999	Infant malaria treatment	DTP, measles, polio	IPTi delivered to infants at routine vaccination visits	72; 76	No	No	Cost effectiveness of delivery strategy	Peer-reviewed [13]
Routine	Gabon, Ghana, Kenya, Malawi, Tanzania	NA	Infant malaria treatment	DTP, measles, polio	IPTi delivered to infants at routine vaccination visits	NA	No	No	Key stakeholder opinions of integrated delivery	Peer-reviewed [14]
Routine	Tanzania	2005	Infant malaria treatment	DTP, measles, polio	IPTi delivered to infants at routine vaccination visits	90	No	No	Key stakeholder opinions of integrated delivery	Peer-reviewed [15]
Routine	Zimbabwe	2001	HIV services	DTP, measles, polio	At immunization visits, HIV-positive mothers were referred for follow-up counseling	73	No	No	Description of utilization of EPI clinics for HIV services	Peer-reviewed [17]
Routine	South Africa	2004	HIV services	DTP, measles, polio	Mothers who brought child to immunization services were asked to participate in anonymous HIV testing	67	No	Post only	Utilization of immunization visits for linkage	Peer-reviewed [18]
Routine	South Africa	2007	HIV services	DTP, measles, polio	Mothers who brought child to immunization services were asked to participate in HIV testing	67	No	Post only	Acceptability of offer of infant HIV test during immunization visit	Peer-reviewed [19]
Routine	Nigeria	2005	Infant hearing screening	BCG	Vaccinator referred child to a hearing-screening team in separate testing room	76	No	Post only	Utilization of immunization visits for linkage	Peer-reviewed [23]
Routine	South Africa	2003	Infant hearing screening	DTP, measles, polio	Vaccinator referred child to a hearing-screening team in separate testing room	67	No	No	Utilization of immunization visits for linkage	Peer-reviewed [22]

Table 2 continued.

Delivery Method	Country	Study Year	Linked Intervention(s)	Vaccine(s) Provided	Primary Integration Strategy	DTP3 Coverage[a]	Vaccine Coverage Assessed	Linked Intervention Coverage Assessed	Primary Indicator(s) Measured in Study	Literature Type and Citation
Routine	India	1998	Complementary feeding practices	DTP, measles, polio	Health workers counsel mothers at multiple contacts including immunization visits on complementary feeding practices	74	Post only	Post only	Utilization of immunization visits for linkage	Peer-reviewed [20, 21]
Routine	Philippines	1999	Vitamin A, family planning promotion	DTP, measles, polio	Interventions were offered together at outreach sessions on immunization days	80	Pre and post	Pre and post	Coverage of interventions	Gray [24]
Routine	Zambia	2002–2006	Growth monitoring, vitamin A, deworming, family planning, health education	BCG, DTP, measles, polio	Interventions offered together as part of a package known as Growth Monitoring Programme Plus	84	Pre and post	No	Coverage of interventions	Peer-reviewed [26]
Routine	Malawi	2005	Bednet distribution	DTP, measles, polio	Bednets distributed at immunization visits when child completed third DTP dose	95	Pre and post	Pre and post	Coverage of interventions	Peer-reviewed [16]
ERA[b]	Ethiopia	2006	Vitamin A, deworming tablet, nutritional screening (for latter, only in certain districts)	Measles	Biannual multiday simultaneous distribution from fixed and temporary outreach posts	72	No	No	Cost effectiveness of child health weeks delivery strategy	Peer-reviewed [27]
ERA[c]	Mexico	1993	Deworming tablet	DTP, measles, polio	Deworming tablets integrated into biannual national health week	91	No	Pre and post	Coverage of interventions	Peer-reviewed [28]
ERA[c]	Cameroon	2005	Vitamin A, bednet retreatment, deworming tablet, nutrition promotion, malaria treatment for pregnant women	DTP, polio	Injectable vaccines were given from fixed site; polio vaccine and vitamin A given house to house	82	No	No	Description of intervention	Gray [29]
ERA[c]	Madagascar	2006	Vitamin A, deworming tablet, bednets, IPTi, IEC on breastfeeding, maternal nutrition and safe motherhood, FP counseling, HIV testing	DTP, measles, polio	Interventions simultaneously given at fixed posts	77	No	No	Impact of child health week on immunization coverage	Gray [30]

Table 2 continued.

Delivery Method	Country	Study Year	Linked Intervention(s)	Vaccine(s) Provided	Primary Integration Strategy	DTP3 Coverage[a]	Vaccine Coverage Assessed	Linked Intervention Coverage Assessed	Primary Indicator(s) Measured in Study	Literature Type and Citation
ERA[c]	Ethiopia, Madagascar, Tanzania, Uganda, Zambia, Zimbabwe	2006–2007	Country-dependent. interventions included vitamin A, deworming tablets, malnutrition screening, bednet promotion, supplementary feeding, and health education	DTP, measles, polio, tetanus-toxoid	Mix of methods; some interventions distributed from fixed posts and others distributed house to house	NA	NA[d]	No	Key stakeholder opinions of integrated delivery	Peer-reviewed [31]
Campaign	Republic of Congo	2005	Vitamin A, deworming tablets	Polio	Simultaneous delivery of interventions	56	No	Post only	Coverage of interventions	Gray [32, 41]
Campaign	Niger	2005	Vitamin A, bednets	Polio	Polio vaccine, vitamin A, and bednet voucher given house to house; voucher was redeemed later at fixed post for bednet	39	Post only	Pre and post	Coverage of interventions	Gray and peer-reviewed [33, 37, 40]
Campaign	Tanzania	2005	Bednets, vitamin A, deworming tablets	Measles	Interventions distributed at temporary and fixed posts	90	Pre and post	Pre and post	Coverage of interventions	Peer-reviewed [36]
Campaign	Zambia	2003	Bednets, bednet vouchers	Measles	Bednets were distributed at fixed posts; 1 district distributed bednet vouchers that were redeemed at local shops	80	No	Pre and post	Coverage of interventions	Peer-reviewed [38]
Campaign	Togo	2005	Bednets, deworming tablets	Measles, polio	Bednets distributed at fixed posts; polio vaccine and deworming tablets given house to house	71	Post only	Pre and post	Coverage of interventions	Gray and peer-reviewed [34, 35]
Campaign	Madagascar	2007	Vitamin A, deworming tablet, bednets	Measles	Interventions simultaneously given at fixed and mobile posts	84	No	Post only	Coverage of interventions; equity of coverage	Peer-reviewed [39]

Abbreviations: DTP, diphtheria-tetanus-pertussis vaccine; EPI, Expanded Programme on Immunisation; ERA, enhanced routine activity; FP, family planning; HIV, human immunodeficiency virus; IEC, information, education, communication; IPTi, intermittent preventative malaria treatment of infants; NA, not applicable.

[a] World Health Organization/United Nations Children's Fund national immunization coverage in the year of the study, or when available, the reported regional coverage from the Demographic Health Survey in the year of the study.

[b] Promoted as an enhanced routine activity; however, only measles vaccine was given.

[c] Promoted as an enhanced routine activity where routine injectable vaccinations (DTP, measles) were all given.

[d] Secondary data analysis on health intervention coverage conducted using demographic and health survey data before and after child health weeks.

Table 3. Classification of Integrated Interventions by Delivery Strategy from the 27 Activities Integrating Health Interventions With Immunization Programs in Developing Countries as Documented in a Review of 32 Articles, 2011

Intervention[a]	Routine	Enhanced Routine[b]	Campaign	Total
Total number of activities	16	5	6	27
Bednet distribution/malaria treatment	8	5	5	18
Deworming tablet administration	1	5	4	10
Family planning promotion	2	2	0	4
Hearing-screening referral	2	0	0	2
HIV testing/referral	3	2	0	5
Nutrition promotion	2	4	0	6
Vitamin A distribution	2	4	4	10
Growth monitoring	1	1	0	2

[a] In multiple activities, >1 intervention was delivered along with immunizations.

[b] In 1 article, an assessment of enhanced routine activities in multiple countries was documented; these are counted as a single activity in this table.

costs. Assessed immunization coverage data were reported by 9 (29%); 5 of these 9 reported coverage both before and after integration activities. Pre- and/or postcoverage of the linked intervention was reported in 20 (63%) articles; 6 (19%) reported this information before and after implementation of the integrated activity.

Interventions Integrated With RI Delivery

Sixteen (50%) studies documented integration of other MCH interventions with RI delivery. These interventions included intermittent preventative malaria treatment of infants (IPTi) (N = 7) [9–15], bednet distribution (N = 1) [16], human immunodeficiency virus (HIV) testing and counseling (N = 3) [17–19], promotion of infant feeding practices (N = 2) [20, 21], and referrals for infant hearing screening (N = 2) [22, 23]. Two articles documented assessments of packages of interventions delivered routinely with immunizations. In 1, vitamin A supplementation (N = 1) and family planning (N = 1) [23] were included; in the other, growth monitoring, vitamin A, deworming tablets, promotion of infant feeding practices, and family planning were included [24] (Tables 2 and 3).

Studies from Mozambique [9, 13], Ghana [10, 11, 14], Gabon [14], Kenya [14], Malawi [14], and Tanzania [12–15] reported linkage of IPTi with RI services. In 1 Ghana study, findings from a trial integrating IPTi with RI visits were used to estimate the impact on the prevalence of malaria in infants if integrated service delivery were to be scaled up across West African countries [10]. Due to low RI coverage in these countries, the authors estimated that only 10% of infant malaria cases would be averted using this strategy. In another Ghana study, integration of delivery of IPTi with RI visits was compared with delivery of IPTi by community volunteers. Coverage between the 2 delivery methods was similar, and authors felt that the community-based method could reach those infants who did not attend vaccination visits [11]. In a Tanzania study describing how IPTi was operationally integrated into routine services, IPTi implementers worked collaboratively with immunization and other health managers to develop communication strategies, use immunization management tools for forecasting IPTi drug supply, use immunization supply chain to deliver IPTi drugs, and use the immunization records system to monitor and record IPTi visits [12]. Qualitative results of integrating IPTi with immunization visits included no increases in health worker schedules and time and money savings to the health system versus creating another vertical delivery mechanism.

In a Mozambique study [9], a Tanzania study [15], and a multicountry study in Tanzania, Gabon, Ghana, Kenya, and Malawi [14], authors qualitatively documented community members' attitudes toward integrating IPTi with immunization services and saw similar results. The visible linkage between IPTi, a new service, and immunization, an existing and trusted service, aided acceptance of the new intervention. In the multicountry study [14], health workers at busy clinics had mothers administer the IPTi drug at the facility rather than the worker administering it at the immunization visit; 2% of the 1300 mothers interviewed said IPTi would discourage them from attending immunization visits. Last, in a study in Tanzania and Mozambique, authors found that IPTi was classified as highly cost effective when delivered through RI visits in these countries, at a cost per disability-adjusted life-year averted <$12 [13].

The integration of HIV services with immunization services was reported in studies from Zimbabwe [17] and South Africa [18, 19]. In Zimbabwe, vaccination visits were utilized to provide follow-up counseling to HIV-positive mothers [17]. However, because follow-up counseling was only available at the district hospitals, mothers who normally attended local immunization clinics needed to travel longer distances to get their children vaccinated. This highlighted the need to decentralize HIV follow-up counseling services to all health facilities. In South Africa, mothers and infants at 6 weeks of age who came for RI

were tested for HIV. The prevalence of HIV exposure among tested infants (37%) and among 20- to 29-year-old mothers (47%) was reported to be consistent with local estimates, suggesting that immunization visit integration could serve as a method for monitoring local Prevention of Mother-to-Child Transmission of HIV program performance [18]. In a second study from South Africa, mothers and infants who came for RI at 6, 10, and 14 weeks of age were offered infant HIV testing conducted by HIV counselors; 90% accepted the offer [19]. Of those 90%, 57% returned for test results. Most mothers reported comfort with infant HIV testing and reported its benefits as confirmation of HIV status and opportunity to start HIV treatment if needed. A quarter of mothers reported concerns the test could reveal their HIV status and that the HIV test was "frightening." HIV counselors were supportive of the intervention but felt space and privacy were insufficient.

Two studies, 1 from South Africa [22] and 1 from Nigeria [23], reported on the referral of infants seen at RI visits for hearing screening conducted at the same site in a separate room. In Nigeria, where only BCG vaccination visits were used, 88% of infants <3 months of age were screened; in South Africa, where all infant vaccination visits were used, 93% of infants <12 months of age were screened. These studies also examined the mean age at which hearing loss was confirmed; the Joint Committee on Infant Hearing benchmark is <3 months of age [25]. In the Nigerian study, the mean age was 17.7 days, and in South Africa, it was 105 days. The authors attributed the later age at diagnosis to the enrollment of infants 0–12 months of age.

Two articles described a study from India that examined the impact of training health workers in 1 district to provide infant nutrition counseling to mothers during immunization, home-based health education, and growth monitoring visits. The intervention districts were compared with a control district where no training about providing nutritional counseling was given [20, 21]. Although nutritional counseling was reportedly rare at any contacts before the start of the project, during implementation, immunization visits accounted for 80%–85% of all counseling contacts during the first 9 months of life. In the intervention district, 43% of immunization visits included nutritional counseling messages; in control districts, 0.5% of visits included such messages [20].

In the Philippines, a strategy known as EPI+ integrated family planning and vitamin A supplementation into RI services provided at outreach sites [24]. After 1 year, fully immunized coverage increased from 80% to 90%, utilization of any family planning services by mothers of infants increased from 70% to 80%, and infant vitamin A supplementation coverage increased from 70% to 90%. In a similar study conducted from 2002 to 2006 in 4 urban slums of Zambia, a package of growth monitoring, immunizations, vitamin A, deworming tablets, nutrition counseling, family planning, community referral, oral rehydration salt distribution, and child healthcare education were systematically delivered together during routine child health sessions [26]. Baseline, midterm (9 months postbaseline), and final (33 months postbaseline) surveys of immunization coverage and timeliness were conducted. Results indicated a significant change in baseline to final full immunized coverage at 12 months of age (53%–69%) in 2 slums and significant change in midterm to final full immunization coverage (43%–57%) in the other 2 slums. Timeliness improved from a baseline level of 25% DTP3 coverage to a final level of 63% DTP3 coverage at 5 months of age. Frequency of integrated health visit attendance was the only sociodemographic indicator associated with improved immunization coverage.

Interventions Integrated With Enhanced Routine Delivery

Five of the 32 (16%) articles described interventions integrated with enhanced routine activities. A report from Ethiopia described the cost of providing nutritional screening, vitamin A supplements, and deworming tablets [27]. The estimated total cost of 1 round of enhanced routine activities where measles vaccine, vitamin A, deworming tablet, and nutritional screening were included was $1.04 per eligible child; without the measles vaccine, the cost was half that [27]. In Cameroon, vitamin A, deworming tablets, DTP vaccine, and measles vaccine were provided as part of a district-level CHW [28]. At the end of the 5-day intervention, the number of DTP doses given reached 2 times the monthly administrative target. However, because no costs were reported, it was not possible to determine the cost-effectiveness of this strategy compared with routine services, nor were comparisons with administrative coverage without integrated activities provided [29]. During Mexico's CHW, deworming tablets have been provided along with vaccinations since 1993. Evaluation of parasite prevalence from 1993 to 1998 among all Mexican states' target populations showed prevalence had decreased by 26%–60%; however, no controls were available to determine impact [28]. The 2005 Madagascar health week integrated >9 interventions, including polio, DTP, and measles vaccines; HIV testing; nutrition promotion; family planning counseling; vitamin A supplementation; bednet distribution; and deworming treatment [30]. Program managers reported the length of time needed to deliver this package of interventions impeded the overall implemention of the 2005 CHW. They believed this challenge was a major factor behind the decrease in the number of districts which had vitamin A and deworming tablet coverage >90% from the previous CHW (106 of 111 districts) to the 2005 CHW (91 districts). In a 2006–2007 multicountry assessment of CHWs in Ethiopia, Madagascar, Tanzania, Uganda, Zambia, and Zimbabwe, held between 2000 and 2006, health providers were interviewed about CHW benefits and challenges, and demographic and health survey data were analyzed to compare pre- and post-CHW coverage of interventions [31]. A variety of interventions were given during each country's CHW (Table 2). Health workers viewed CHWs positively, and CHWs were also

seen to raise the profile of child survival among government officials. Key challenges included poor coordination and assignment of responsibilities between implementing agencies, issues with late arrival or lack of commodities, and interruption of routine services because CHW supervisors and workers also were responsible for managing routine healthcare. In some locations, CHW financial incentives were perceived to demotivate health workers into performing routine services.

Interventions Integrated With Campaigns

Ten studies (31%) reported on 6 immunization campaigns. In each campaign, a different package was provided (Table 2) [32–41]. The campaigns occurred in the Republic of the Congo [32, 41], Niger [33, 37, 40], Togo [34, 35], Tanzania [36], Zambia [38], and Madagascar [39]. Vaccinators used house-to-house delivery of polio vaccine to distribute vitamin A (Congo and Niger) and deworming tablets (Congo). The Niger campaign also included distribution of bednets to mothers of vaccinated children a few weeks after the campaign, using finger markings to verify receipt of polio vaccine. The Togo campaign used a 2-phase delivery strategy in which vaccinators provided deworming tablets during house-to-house polio vaccination and then distributed bednets in conjunction with measles vaccine at fixed posts. In Tanzania and Zambia, fixed post–based measles campaigns were utilized to distribute bednets (or vouchers for bednets) from local vendors; vitamin A and deworming tablets were also distributed in Tanzania. In Madagascar, a mix of fixed and mobile posts were utilized for measles vaccine, deworming administration, and vitamin A supplementation; half the country also received long-lasting insecticidal nets (LLINs) targeted at children <5 years of age and pregnant women.

In 4 campaigns, precampaign coverage with the nonimmunization intervention ranged from 5% to 67% (Table 4). One month to 5 months after the campaigns, polio vaccination coverage ranged from 87% to 94%; linked intervention coverage ranges were also high (90% received vitamin A, 90%–93% received deworming tablets, and 84%–91% of households with infants owned a bednet) (Table 4). One month to 5 months after the campaigns, however, bednet usage by children <5 years of age was reported to be markedly lower than postcampaign bednet ownership and/or immunization coverage levels (Table 4), except in Madagascar. In Madagascar, postcampaign household ownership of ≥1 LLIN was 77%, and in 95% of these households, children <5 years of age were using the LLIN. One week after the campaign, recipients were shown how to hang the nets [39]. In the Republic of Congo campaign [32], organizers initially identified weak support from parents, who believed that polio vaccine had few benefits because vaccine effects were not immediately visible to them. However, support and participation reportedly increased with the addition of deworming tablets, as community members reported immediate and visible effects following their receipt.

Reported Impact on Coverage

Two projects— 1 in India [21] and 1 in Malawi [16]—included comparison groups, which allowed for measurement of impact of the integrated service; in both projects, coverage with the intervention linked to immunization services increased markedly. In India, where health workers were trained to provide nutrition counseling during RI visits, the exposure of caregivers to counseling during vaccination visits was 42% higher in intervention locations compared with control locations [20, 21]. Because immunization coverage was not reported, changes to the immunization program could not be determined. In Malawi, where bednet distribution was integrated with RI, bednet usage by 12- to 23-month-olds doubled in intervention districts, from 25% to 28% at baseline to 52% to 69% 18 months later. However, the rate remained constant in the control district [16], although full immunization coverage by 1 year of age was not significantly different between the intervention (63%–79%) and control locations (68%). One explanation for this finding may be the introduction of a major initiative for strengthening the RI program, known as Reaching Every District, in the control location only [42]. In a study in Zambia linking immunization to multiple other child health interventions in a routine setting, fully immunized coverage significantly improved by 16 percentage points in 1 area 33 months after the start of integrated routine visits and improved significantly by 14 percentage points in another area starting from the midpoint (9 months after baseline) to the time of assessment (24 months later) [26].

Other articles contained information on the coverage with immunizations and the linked intervention to illustrate the differences in postintervention performance between the 2 services, although neither controls nor baseline data were available (Table 4). In 12 of 16 instances where postintervention coverage (or equivalent outcome indicator) for the linked intervention was measured and reported, this value was below the reported immunization coverage. In all instances where preintervention coverage was reported, coverage increased after the intervention. In 2 instances, both vitamin A coverage [24] and deworming tablet coverage [34] were equal to immunization coverage. In the remaining 2 instances, vitamin A coverage [36] and bednet ownership [16] were higher than immunization coverage.

Reported Lessons Learned

Authors documented a variety of lessons learned from implementing integrated services. For example, in the Madagascar CHW, HIV testing and family planning counseling, both time-intensive interventions, resulted in noticeable increases in the time for service delivery compared with that required for vaccination delivery alone, which slowed the CHW approach [30]. Logistical issues were noted in multiple integrated activities; for example, in Ethiopia's CHW, 58% of locations reported that campaign supplies did not arrive on schedule and 66% reported

supply shortages [27]. In the multicountry assessment of CHWs, authors felt that CHWs could be most effective in places with weak routine systems, whereas in countries with stronger routine systems, targeted CHWs conducted only in areas with weak systems should be considered due to concern about how CHWs disrupted the routine system [31]. In 2 studies on integrating bednets with routine services, anecdotal reports suggested distribution of bednets disrupted the supply chain and service delivery sites, resulting in lower coverage of other services (eg, immunizations, vitamin A) in at least 1 location [16, 27]. In a polio campaign in Niger, one-third of mothers who had not received a bednet reported that the delivery site had no bednets [33]. Authors in a Tanzania IPTi study noted general issues with IPTi drug stockouts as a key challenge to implementation; however, vaccine stockouts were also a noted problem [9].

Efforts to link provision of insecticide-treated bednets to measles vaccination suggested that such linked interventions may require additional education to change community behavior [38]. For example, although postcampaign bednet ownership and immunization coverage were similar in integrated campaigns, postcampaign bednet usage by children <5 years of age was 17–48 percentage points lower than ownership, and authors described the need for social mobilization activities to increase bednet usage [36, 38, 40].

The impact of low immunization coverage and incomplete overlap of the target populations for immunizations and linked interventions drew concern around efficiency of resource use [10, 34, 40]. An analysis from Ghana concluded that due to malaria seasonality and poor overlap of target age groups between RI services (0–12 months) and IPTi (4–24 months), as well as low immunization coverage (<80% DTP3) in many West African countries, scaling up the linkage between these interventions could lead to inefficient use of IPTi resources [10]. Stakeholder concern that high immunization coverage could be adversely affected may also pose a barrier to linking programs, as seen in India during preparation for a linked nutrition education initiative [21]. Similarly, based on concerns by immunization program managers that the addition of vitamin A and deworming tablets might jeopardize the immunization campaign, a decision was made in Republic of Congo to add only 1 intervention per campaign round [41]. Conversely, in multiple IPTi studies, authors attributed success of integrating IPTi and immunizations to active engagement of key stakeholders through a collaborative partnership between immunization and malaria decision makers to develop and determine how to integrate IPTi into RI visits [12, 15]. In a multicountry study on the acceptance of IPTi alongside immunization visits, the main determinants of acceptance of the approach were mothers' familiarity of the IPTI drug prior to integration, simplicity of delivering the IPTI drug, and caretakers' perceptions that the intervention has a perceived benefit that outweighs any downsides [14].

DISCUSSION

In this review of integration of immunization and other primary healthcare services, we found that the spectrum of interventions linked to immunization delivery increased since our 2005 review [5] and now includes 2 new interventions studied for integration: newborn hearing screening and HIV counseling and treatment services. An indication of the increased interest in integration since our 2005 review was the volume of literature on the topic: The number of reports published during the past 5 years alone was similar to the number published during the previous 20 years, which were covered in the 2005 review. Despite this growth in the number of reports, knowledge gaps identified in the 2005 review are still evident in this review, most notably the absence of comparisons of integrated activities with nonintegrated activities. Without this information, stakeholders cannot measure impact, which in turn limits their ability to appreciate the potential benefits of integration. This may result in ongoing concern over how integration impacts existing immunization programs. Whether resources are more efficiently used in an integrated delivery setting or 2 separate vertical delivery systems is a critical question that was raised in the 2005 review and has yet to be answered by the review of studies included here. Among all studies included in this and our 2005 review, only 1 reported data on resources saved through integration [34]. Rigorous evaluations on the impact and cost of integrated interventions would be useful to filling key knowledge gaps in integrated service delivery.

A number of characteristics of success in integrated service delivery were identified in the reviewed studies. How well a linked intervention's target age group and resource needs (eg, supplies, equipment, and appropriately trained health workers) were compatible with immunization services emerged as an important consideration about whether and how to integrate. In campaigns where immunization service delivery requirements were similar to those of the linked intervention (eg, vitamin A and deworming tablets), coverage for all interventions was similar. Bednet ownership levels also reached the same levels as immunization coverage in both integrated campaigns and routine service delivery; however, the use of bednets by children <5 years of age lagged behind immunization coverage and the need for additional education was frequently recommended. Using immunization programs as a mechanism for referring mothers and infants for additional services such as hearing screening or HIV testing also appeared to be successful, provided that additional health workers were available to offer the referred service. Ensuring the supply chain was sufficient to carry commodities for both immunization and services such as bednets or HIV treatment may have also contributed to successful integrated delivery.

The primary concerns about integration with immunization services we identified were related to immunization programs

Table 4. Reported Outcome Indicators From Studies With Evaluations Where Maternal and Child Health Interventions Were Linked to Immunization Services in Developing Countries

Project Country [Reference]	Delivery Method	Intervention Location Data						Comparison Location Data			Post-intervention Coverage Difference[b]
		Linked Intervention Indicator	Pre[a]	Post[a]	Immunization Indicator	Pre[a]	Post[a]	Indicator	Pre[a]	Post[a]	
South Africa [22]	Routine	Proportion of infants screened in hearing test		95%							
		Mean infant age at hearing screening		105 days							
Nigeria [23]	Routine	Proportion of infants screened in hearing test		88%							
		Mean infant age at hearing screening		17.7 days							
Philippines [24]	Routine	Family planning utilization	70%	80%	Fully vaccinated coverage[c]	80%	90%				−10
		Vitamin A coverage	70%	90%							0
India [20, 21]	Routine	Proportion immunization visits where mother received nutrition counseling		43%	Vaccination card retention rate[c]		87%	Vaccination card retention rate[c]		74%	−44
Malawi [16]	Routine	Bednet ownership[d]	39%	83%	Fully vaccinated coverage[c]	49%	68%	Fully vaccinated coverage[c]	47%	79%	15
		Bednet ownership[d]	65%	86%	Fully vaccinated coverage[c]	33%	63%	Bednet ownership[d]	50%	52%	23
		Slept under bednet previous night[d]	25%	52%				Slept under bednet[d]	29%	28%	−11
		Slept under bednet previous night[d]	28%	69%							7
Ghana [11]	Routine	Coverage of malaria intervention treatment of infants		87%							
South Africa [19]	Routine	Proportion of mothers accepting offer of infant HIV test		90%							
Zambia [26]	Routine				Fully vaccinated coverage[c]	52%	69%				
					Fully vaccinated coverage[c]	48%	57%				
Mexico [28]	Enhanced routine	Geohelminth infection prevalence rate[e]	20%	8%							
Republic of Congo [41]	Campaign	Vitamin A coverage[e]		>90%							
		Deworming tablet coverage[e]		>90%							
Niger [40]	Campaign	Bednet ownership[e]	5%	70%	Polio vaccine coverage[e]	NA	87%				−17
		Slept under bednet previous night[e]		22%							−65
Tanzania [36]	Campaign	Deworming tablet administration[e]	39%	86%	Measles vaccine coverage[e]	77%	91%				−5
		Vitamin A coverage[e]	67%	93%							−2
		Bednet ownership[e]	61%	91%							0
Zambia [38]	Campaign	Bednet ownership[e]	21%	88%							
		Slept under bednet previous night[e]		56%							

Table 4 continued.

Project Country [Reference]	Delivery Method	Intervention Location Data						Comparison Location Data			Post-intervention Coverage Difference[b]
		Linked Intervention Indicator	Pre[a]	Post[a]	Immunization Indicator	Pre[a]	Post[a]	Indicator	Pre[a]	Post[a]	
Togo [34, 35]	Campaign	Bednet ownership[e]	8%	63%	Measles vaccine coverage[e]		93%				−30
		Slept under bednet previous night[e]		44%	Polio vaccine coverage[e]		94%				−49
		Deworming tablet coverage[e]		93%							0
Madagascar [39]	Campaign	Household bednet ownership		84%							
		Slept under bednet previous night[e]		85%							

[a] Time of data collection for postintervention data varies by study, ranging from 1 week to 6 months.

[b] Postintervention linked-intervention indicator minus the postintervention immunization coverage indicator.

[c] Target age group: <1 year.

[d] Target age group: 1–2 years.

[e] Target age group: <5 years.

with low coverage, time-consuming interventions in campaigns, interventions requiring behavior change, and interventions with different target age groups from immunization services. Because campaigns are designed to deliver vaccines quickly and efficiently, any activity that slows delivery may affect overall performance. During campaigns, service integration suffered in situations where substantial time and interaction between provider and patient were required. A number of linked services (eg, hearing screening, HIV services) have unique resource requirements, such as the need for a private room, which may also be limiting simultaneous delivery with vaccinations. This was addressed in some of the reviewed studies by having the vaccinator refer the mother or child to another health worker who delivered the linked service. However, this could pose logistical hurdles and require the need for more cross-worker coordination. Integrating other health interventions with immunization services can result in rapid increases in coverage of the second intervention. However, the integrated method appears to inherit the same challenges that immunization services were likely already faced with prior to integration. For example, challenges often mentioned related to systemic issues such as poor supply chains, infrequent supportive supervision, insufficient planning, and inadequate engagement of community leaders. In integrating a new intervention, a useful preintegration activity may be to identify the key challenges already facing the system and to incorporate strategies to address them rather than only focus on how to integrate.

This review was limited to literature databases we could access by computer and to experts we contacted by e-mail or telephone. Including sources in languages other than English and Spanish and conducting field visits to interview program managers experienced in integrated service delivery may provide additional information. Few reviewed studies reported pre- and postintervention coverage data for all integrated services from both intervention and comparison settings; this information would help strengthen our understanding of various integration strategies.

In this review, the most successful integration efforts appeared to be those that included an easy-to-administer intervention, such as malaria treatment, vitamin A, and deworming tablets, which were added to existing immunization services with little additional effort. Due to challenges identified in integrating complex interventions that require time or behavior change, such as HIV and family-planning services, more data are needed from programs that have first outlined the resource needs for each intervention to ensure that commodities are consistently available. In light of the recent WHO policy to identify all HIV-exposed infants by 6 weeks of age and subsequent calls for using immunization visits to do so, further research linking HIV care to immunizations visits is vital [43, 44]. A comprehensive approach to integrated service delivery that ties together researchers with programmatic implementers and provides evidence across multiple countries on community impacts, biologic impacts, cost effectiveness of different delivery approach, and best practices for planning of integrated service delivery as exemplified by the work of the IPTi consortium may be a critical model for yielding substantial data for each major intervention that uses immunization services [45]. Reviewing integration strategies outside immunization services can also be beneficial; these include reviews of packages of maternal and child health services and expert opinions proposing frameworks for integrated services [46–50]. Although gaps remain, the acceleration of research and the diversity of interventions linked to immunization indicate a strong interest in identifying successful ways to link services and to determine best practices for integrated services involving immunization programs.

Notes

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